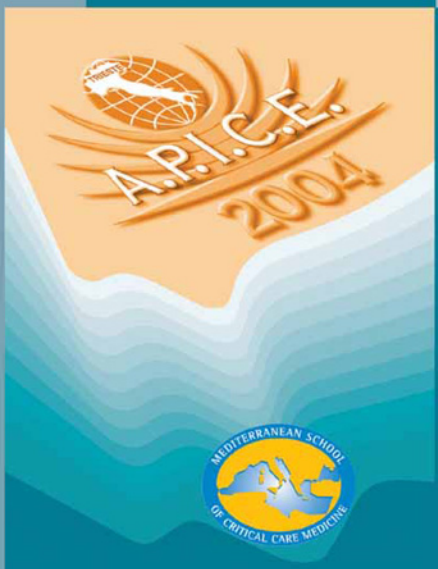
A. Gullo (Ed)

A.P.I.C.E. 19

Anaesthesia Pain Intensive Care and Emergency Medicine



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Proceedings of the
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Abbreviations

ABRs	Auditory Brainstem Responses
AC/VT	Assist Control/Volume-Targeted
ACCI	Acceleration Index
ACLS	Advanced Cardiac Life Support
ACS	Acute Coronary Syndrome
AD	Antiarrhythmic Drug
ADP	Adenosine
AHA	American Heart Association
ALI	Acute Lung Injury
ALIVE	Amiodarone versus Lidocaione in Prehospital Ventricular Fibrillation Evaluation
ALS	Advanced Life Support
AMI	Acute Myocardial Infarction
AMP	Adenosine Monophosphate
AP	Augmented Pressure
APACHE	Acute Physiology and Chronic Health Evaluation
APRV	Airway Pressure Release Ventilation
APS	Acute Pain Service
AR	Adaptive-Rate
ARDS	Acute Respiratory Distress Syndrome
ARR	Absolute Risk Reduction
ARREST	Amiodarone in the Resuscitation of Refractory Sustained Ventricular Tachyarrhytmias
ASA	American Society of Anaesthesiology
ATLS	Advanced Trauma Life Support
ATP	Antitachycardia Pacing
ATPase	Adenosine Triphospatase
AV	Atrioventricular
AVO_2	Arterial-Venous Oxygenation
AVP	Arginine Vasopressin
BAL	Broncho Alveolar Lavage
BBB	Bundle-Branch Block
BIPAP	Biphasic Positive Airway Pressure
BMI	Body Mass Index
BNP	B-Type Natriuretic Peptide
BP	Blood Pressure
BPD	Broncho Pulmonary Dysplasia
BPI	Brief Pain Inventory
BSD	Berkley Software Distribution

CAA	Cerebral Amyloid Angiopathy
CAAH	Haemorrhage with Cerebral Amyloid Angiopathy
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
cAMP	Cyclic Adenosine Monophosphate
CaO_2	Oxygen Content
CARD	Caspase Recruiting Domain
CBF	Cerebral Blood Flow
CBV	Cerebral Perfusion Blood Volume
CCO	Continuous Cardiac Output
CCP	Cerebral Perfusion Pressure
CCT	Central Conduction Time
CCTR	Cochrane Controlled Trials Register
CDSR	Cochrane Database of Systematic Reviews
CF	Cardiac Function
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
CHEOPS	Children's Hospital of Eastern Ontario Postoperative Scale
CHF	Congestive Hearth Failure
CI	Cardiac Index
CK-MB	Creatine Kinase MB isoenzyme
C-LQTS	Congenital Long QT Syndrome
CMV	Conventional Mechanical Ventilation
CNS	Central Nervous System
CO	Cardiac Output
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous Positive Airway Pressure
CPB	Cardiopulmonary Bypass
CPE	Cardiogenic Pulmonary Oedema
CPP	Coronary Perfusion Pressure
CPR	Cardiopulmonary Resuscitation
CPU	Chest Pain Unit
CRMD	Cardiac Rhytm Management Device
CRP	C-Reactive Protein
CRRT	Continuous Renal Replacement Therapy
CRT	Cardiar Resynchronisation Therapy
CSF	Cerebrospinal Fluid
CT	Computed Tomography
CV/DF	Cardioversion/Defibrillation
CVP	Central Venous Pressure
CX	Chest X-Ray
DARE	Database of Abstracts of Reviews of Effectiveness
DB RTC	Double Blind Randomized Controlled Trial
DCA	Dichloracetat
DeltaP	Pressure Amplitude
DNA	Deoxi-ribonucleic Acid
DO_2	Oxygen Delivery
DPL	Diagnostic Peritoneal Lavage
DVT	Deep Vein Thrombosis

Ea	Arterial Elastance
EAD	Early Afterdepolarizations
EBM	Evidence-Based Medicine
ECC	Extracorporeal Circulation
ECF	Extracellular Fluid
ECG	Electrocardiography
ECMO	Extracorporeal Membrane Oxigenation
ECT	Electroconvulsive Therapy
ED	Emergency Department
EDV	End-Diastolic Volume
EEG	Electroencephalography
EELV	End-Expiratory Lung Volume
EF	Ejection Fraction
EIT	Electrical Impedance Tomography
ELSO	Extracorporeal Life Support Organization
Emax	Maximal Elastance
EMD	Electromechanical dissociation
EMEA	European Agency for the Evaluation of Medical Products
EMI	Electromagnetic Interference
EPAP	Expiratory Positive Airway Pressure
ER	Emergency Room
ERBF	Effective Renal Blood Flow
ERC	European Resuscitation Council
Ers	Respiratory System Elastance
ES	Endotoxin Shock
ESICM	European Society of Intensive Care Medicine
Estat L	Static Lung Elastance
ESWL	Extracorporeal Shock Wave Lithotripsy
ET	Ejection Time
EVLW	Extravascular Lung Water
FAST	Focused Assessment with Sonography for Trauma
FDA	Food and Drug Administration
FDL	Free Documentation License
FEV_1	Forced Expiratory Volume in One Second
FL	Flow Limitation
FRC	Functional Residual Capacity
FTc	Corrected Flow Time
FV	Flow Velocity
FVC	Forced Vital Capacity
Fvmean	Mean Flow Velocity
GABA	Gamma-Aminobutryc Acid
GCP	Good Clinical Practice
GEDV	Global End Diastolic Volume
GFR	Glomerular Filtration Rate
GIK	Glucose-Insulin-Potassium
GIMBE	Gruppo Italiano per la Medicina Basata sulla Evidenza
GNU	GNU's Not Unix
GP	Ground Plate
GPL	GNU General Public License

GSC	Glasgow Coma Scale
HCMV	Human Cytomegalovirus
HFJV	High Frequency Jet Ventilation
HFOV	High Frequency Oscillatory Ventilation
HFPV	High Frequency Percussive Ventilation
HFV	High Frequency Ventilation
HGF	Hepatocyte Growth Factor
HR	Heart Rate
HS	Haemorrhage Shock
hs-CRP	High-Sensitivity C-Reactive Protein
HSD	Hypertonic Saline/DextraneBaker
HT	Haemothorax
IAPB	Intraaortic Balloon Pump
ICD	Implanted Cardioverterdefibrillator
ICF	Informed Consent Form
ICG	Indocyanine Green
ICH	Intracranial Haemorrhage
ICP	Intracranial Pressure
ICU	Intensive Care Unit
IL	Interleukin
ILCOR	International Liaison Committee on Resuscitation
IMV	Intermittent Mandatory Ventilation
INO	Inhaled Nitric Oxide
IP	Intracranial Pressure
IPAP	Inspiratory Positive Airway Pressure
IPM	Intraperitoneal microdialysis
IPN	Interpeduncular Nucleus
IPPV	Intermittent Positive Pressure Ventilation
ISF	International Sepsis Forum
ISF	Interstitial Space Fluid
ISS	Injury Severity Score
ITBV	Intrathoracic Blood Volume
KGF	Keratinocyte Growth Factor
LAD	Left Anterior Descending Coronary Artery
LGPL	Lesser GNU General Public License
LIDCO	Lithium Dilution System
LIDO	Levosimendan-Dobutamine Study
LILACS	Latin American and Caribbean Health Science Information Database
LIMA	Left Internal Mammaria Artery
LIP	Lower Inflection Point
LP ratio	Lactate to Pyruvate Ratio
LQTS	Long QT Syndrome
LT	Lithotripsy
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
LVSWI	Left Ventricular Stroke Work Index
MAC	Minimum Alveolar Concentration
MAP	Mean Arterial Pressure
MCP	Mean Circulatory Pressure

MEAC	Minimum Effective Analgesic Concentration
MeSH	Medical Subject Heading
MI	Myocardial Infarction
MIC	Minimal Inhibitory Concentration
MIS	Modified Injury Score
MODS	Multiple Organ Dysfunction Score
MPAP	Mean Pulmonary Artery Pressure
MPQ	McGill Pain Questionnaire
MPT	Mitochondria permeability transition
MRI	Magnetic Resonance Imaging
mRNA	messenger Ribonucleic Acid
MTT	Mean Transit Time
MV	Mechanical Ventilation
nAChRs	Nicotin Receptors
NASCIS	National Acute Spinal Cord Injury Studies
NCA	Nurse or Parent Controlled Analgesia
NCPE	Non-Cardiogenic Pulmonary Oedema
NE	Norepinephrine
NEP	Negative Expiratory Pressure Method
NFCS	Neonatal Facial Coding System
NHE-1	Sodium-Hydrogen Exchanger Isoform-1
$NICO_2$	CO2 Partial Rebreathing System
NICU	Neonatal Intensive Care Unit
NIPPV	Non-Invasive Positive Pressure Ventilation
NIRS	Near Infrared Spectroscopy
NISS	New Injury Severity Score
NMR	Nuclear Magnetic Resonance
NNT	Number Needed to Treat
NPPV	Noninvasive Positive Pressure Ventilation
NRS	Numerical Rating Scale
NSAID	Non-Steroideal Anti-Inflammatory Drugs
NSCLC	Non-Small Cell Lung Cancers
NSE	Neuron Specific Enolase
O_2ER	Oxygen Extraction Ratio
OA	Oleic-Acid Group
OP	Operative System
OPS	Orthogonal Polarisation Spectral
OR	Odds Ratio
OSA	Obstructive Sleep Apnea
PAC	Pulmonary Artery Catether
$PaCO_2$	Partiarl Arterial Carbon Dioxide Pressure
PaO_2	Oxygen Pressure
PACU	Post Anaesthesia Care Unit
PAOP	Pulmonary Artery Occlusion Pressure
PAV	Proportional Assisted Ventilation
Paw	Airway Pressure
PC	Phosphatidylcholine
PCA	Patient-Controlled Analgesia
PCBF	Pulmonary Capillary Blood Flow

PCM	Pulse Contour Method
PCR	Polymerase Chain Reaction
P_{CRIT}	Critical Closing Pressure
PCT	Procalcitonin
PCV	Pressure Control Ventilation
PCWP	Pulmonary Capillary Wedge Pressure
PEA	Pulseless Electrical Activity
PEEP	Positive End Expiratory Pressure
$PEEP_I$	Intrinsic Positive End Expiratory Pressure
PEP	Ejection Period
Pes	Oesophageal pressure
PET	Positron Emission Tomography
PG	Pulse Generator
PG	Phospatidylglycerol
PGF	Placental Growth Factor
PGI2	Prostacyclin2 pedice
P-gp	P-Glycoprotein
PI	Phosphatidylinositol
PK/PD	Pharmacokinetic/Pharmacodynamic
Plip	Lower Inflection Point of PV Curve
PM	Pacemaker
Pms	Mean Systemic Pressure
PMT	Pacemaker-Mediated Tachycardia
PNX	Pneumothorax
PONV	Post-Operative Nausea and Vomiting
PPB	Plasma Protein Binding
PPC	Postoperative Pulmonary Complications
PPHN	Persistent Pulmonary Hypertension of the Newborn
Ppl	Pleural pressure
PPV	Pulse Pression Variation
PRAM	Pressure Recording Analytical Method
PRMD	Postresuscitation Myocardial Dysfunction
PRT	Pacemaker Reentry Tachycardia
PRVC	Pressure Regulated Volume Controlled
PS	Pressure Support
PSV	Pressure Support Ventilation
PTA	Percutaneous Transluminal Angioplasty
$PtcCO_2$	Transcutaneous Partial Arterial Carbon Dioxide Pressure
$PtcO_2$	Transcutaneous Partial Arterial Oxygen Pressure
Ptp	Transpulmonary Pressure
PTP	Pressure Time Product
PTS	Paediatric Trauma Score
PTV	Patient-Triggered Ventilation
PV	Pressure-Volume
PVI	Pressure-Volume Index
PVR	Pulmonary Vascular Resistance
PWV	Pulse Wave Velocity
rAAV	Recombinant Adeno-Associated Viruses
RAP	Right Atrial Pressure

rAV	Recombinant Adenoviruses
rCBF	Regional Cerebral Blood Flood
rCMRglc	Regional Cerebral Metabolic Rates for Glucose
RDS	Respiratory Distress Syndrome
RFA	Radiofrequency Arrhythmia Ablation
rFVIIa	Recombinant Human Factor VIIa
RM	Recruitmen Manoeuvre
RNA	Ribonucleic Acid
RNAi	Ribonucleic Acid Interference
ROS	Reactive Oxygen Species
ROSC	Return of Spontaneous Circulation
RPA	RNase Protection Assay
RR	Recovery Room
RT	Radiation Therapy
RTC	Routine Thermal Care
RV	Right Ventricular
RVEDV	Right Ventricular End-Diastolic Volume
RVEDVI	Right Ventricular End-Diastolic Volume Index
RVEF	Right Ventricle Ejection Fraction
RVSWI	Right Ventricular Stroke Work Index
SA	Sinoatrial
SAH	Subarachnoid Haemorrhage
SaO_2	Oxygen Saturation
SAPS	Simplified Acute Physiology Score
SB	Spontaneous Breathing
SBP	Systolic Blood Pressure
SCCM	Society of Critical Care Medicine
SCI	Spinal Cord Injury
SCIWORA	Spinal Cord Injury Without Obvious Radiographic Abnormality
SCLC	Small Cell Lung Cancers
$ShvO_2$	Hepatic Venous Oxygen Saturation
SIMV	Synchronised Intermittent Mechanical Ventilation
SOFA	Sequential Organ Failure Assessment
SOO	Single-Chamber Pacing
SP	Surfactant Proteins
SPECT	Single Photon Emission Computed Tomography
SpO_2	Pulse Oximetry
SSC	Surviving Sepsis Campaign
ST	Simple Thoracostomy
SV	Stroke Volume
SVC	Superior Vena Cava
SvO_2	Oxygen Venous Saturation
SVR	Systemic Vascular Resistance
SVV	Stroke Volume Variation
SW	Saline Washout Group
TBI	Traumatic Brain Injury
TCD	Transcranial Doppler Ultrasonography
TCO	Total Cost Ownership
TdP	Torsade de Pointe

TEB	Thoracic Electrical Bioimpedance
TEE	Transoesophageal Echocardiography
TENS	Transcutaneous Electric Nerve Stimulation
TF	Tissue Factor
TG	Triglycerides
T_I	Inspiratory Duration
TIVA	Total Intravenous Anaesthesia
TLC	Total Lung Capacity
TNF	Tumor Necrosis Factor
TREM-1	Triggering Receptor Expressed in Myeloid Cells
TTP	Thrombotic Thrombocytopenic Purpura
UIP	Upper Inflection Point
V/Q	Ventilation-Perfusion Ratio
VALI	Ventilator-Associated Lung Injury
VAPS	Volume Assured Pressure Support
VAS	Visual Analogue Scale
VCV	Volume-Controlled Ventilation
V_E	Minute Ventilation
VE	Volume Expansion
VF	Ventricular Fibrillation
VILI	Ventilator-Induced Lung Injury
VR	Venous Return
VRS	Verbal Rating Scale
VT	Ventricular Tachycardia
V_T	Tidal Volume
vWF	von Willebrand Factor
WPW	Wolff-Parkinson-White Syndrome
ZEEP	Zero End-Espiratory Pressure

ADVANCES IN CRITICAL CARE

Chapter 1

Effects of body position on ventilation/perfusion matching

G. Hedenstierna

A new interest in body positioning emerged when it was shown that placing the ARDS patient in the prone position frequently improved arterial oxygenation over that observed in the supine patient. Thus, body positioning can be used as a tool for improving oxygenation in severely ill patients. A lateral position with the 'good lung down' is a frequent component of treatment in unilateral lung disease, and a combination of lateral position and selective PEEP to the lower lung has been tried in bilateral lung disease. The improvement in oxygenation frequently seen raises the question of what the mechanisms underlying potential improvement are?

The awake, healthy subject

Ventilation distribution

The air that is inspired is not then evenly distributed in the lung. During quiet breathing, most air goes to the lower, dependent regions, i.e. to basal, diaphragmatic areas for patients in the upright or sitting position and to dorsal units for those in the supine position [1]. This also means that the lower lung will receive most of the air if the subject is in the lateral position. When the patient is in the prone position, more of the air will presumably go to anterior than to dorsal regions. The reason for this seemingly gravitational orientation of something as light as gas is the combined effect of the curved shape of the pressure-volume curve for the lung and the decreasing transpulmonary pressure (Ptp) down the lung (Ptp = airway minus pleural pressure). In the upright position, apical lung regions are exposed to a higher transpulmonary pressure than dependent, basal ones. Thus, upper and lower lung regions are positioned at different levels of the pressure-volume curve (Fig. 1). During an inspiration, pleural pressure is lowered and causes lower lung regions to inflate more than upper ones for a similar change in transpulmonary pressure. (It is assumed that pleural pressure changes uniformly in the pleural space [1].)

When the body position is changed from upright to supine, lateral or prone, FRC is reduced by 0.7–0.8 l, down to an average of 2.5 l (there is considerable variation between subjects, depending on sex, age and body configuration). The fall in FRC promotes airway closure in dependent lung regions. This is a normal phenomenon that occurs during expiration, with reopening of airways during the

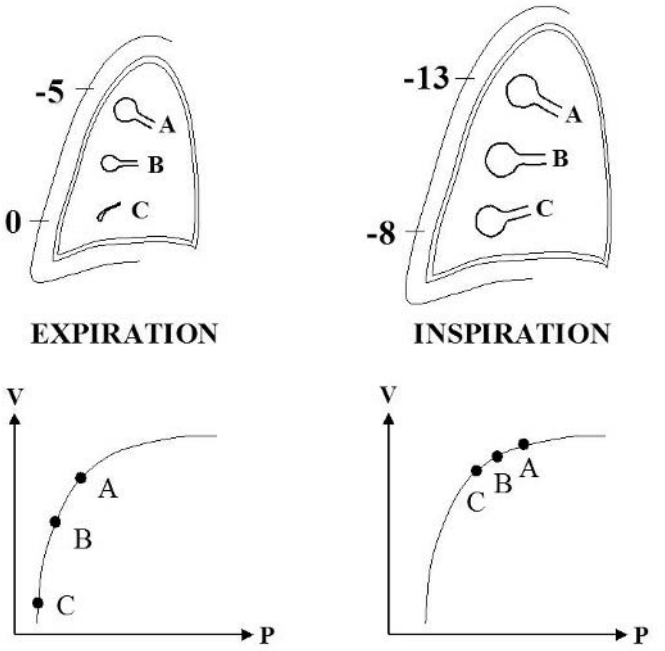

Fig. 1. Alveolar expansion at three vertical levels of the lung (*A* upper lung, *B* midlung, *C* lower, dependent, lung) and pressure–volume curves at end–expiration and end–inspiration. Note the pleural pressure difference with more markedly subatmospheric values at upper parts. Since alveolar pressure is the same from top to bottom, the distending, transpulmonary pressure is higher in the upper regions, which is why alveoli at the bottom are less highly aerated and may even be collapsed during expiration. During inspiration the pressure differences between alveoli remain, but all regions have been expanded and are higher up, on the flatter part of the pressure–volume curve

succeeding inspiration. The older the subject is the more likely it is that airways will close during breathing [2]. It can be expected during normal breathing in 65- to 70-year-old subjects when they are upright, and even in 50-year-old subjects when in the horizontal position. Airway closure will thus decrease ventilation in the dependent regions. Since lung blood flow passes preferentially to dependent regions, matching between ventilation and perfusion is impeded.

The most marked decrease in FRC can be seen in the Trendelenburg position and head-down positions, the decrease in FRC being caused by cranial displacement of the diaphragm. These body positions may also be accompanied by more severe decreases in arterial oxygenation than others.

Lung blood flow

The blood flow through the lung is governed by the driving pressure and the vascular resistance. Pulmonary artery pressure increases from top to bottom in the lung, an effect of the hydrostatic pressure that builds up on the way from top to bottom of the lung. There is therefore less driving pressure at the top of the lung. It may approach zero in the apex of the lung in persons in the upright position. Moreover, if alveolar pressure is increased, as it is during positive pressure ventilation, it may exceed that in the pulmonary artery and compress the pulmonary capillaries. No blood will then flow through the vessels (zone I, according to the nomenclature introduced by West et al. [3]. Further down, arterial pressure exceeds alveolar pressure (zone II), and still further down both arterial and venous pressures exceed alveolar pressure (zone III). The increasing driving pressure from top to bottom of the lung increases perfusion, and most of the blood flow passes through the dependent regions. This gravitational orientation of blood flow results in a preference for caudal regions in persons in an upright position, for dorsal regions in those lying supine, for the lower lung in persons lying in a lateral position and for anterior regions when those lying prone. Blood flow thus has a roughly similar distribution to ventilation.

In dog experiments, groups at the Mayo Clinic and subsequently in Seattle noted that the vertical lung blood flow distribution was rather even and did not change when position was altered between supine and prone [4]. This led the Seattle group to conclude that gravity was of minor importance in determining perfusion distribution. The same group also showed that perfusion at a given vertical level was unevenly distributed on that horizontal plane, with an inhomogeneity that far exceeded that in the vertical direction [5]. This suggests that there are morphological and/or functional differences between lung vessels that are also involved in determining blood flow distribution, and perhaps to a more significant degree than gravity. In their hypothesis, they postulate that blood flow in the lung varies between lung regions, and that the variation becomes larger with decreasing size of the lung unit under scrutiny. Moreover, there may be regional differences in vascular resistance. Thus, vascular resistance seems to be lower in dorsal regions of horse lungs than in the anterior part [6]. This will also affect the distribution of blood flow, opposing the effect of gravity. To what extent this phenomenon may exist in the human lung is not known.

Ventilation-perfusion match

Since both ventilation and perfusion increases from top to bottom in the lung, the ventilation-lung blood flow match is fairly similar in the gravitational direction, with a ventilation-to-perfusion ratio (V/Q) close to 1. In the upper regions V/Q may approach 4–5; that is to say that ventilation exceeds perfusion by a factor of 4–5. At the bottom of the lung the V/Q is typically 0.6–0.8, indicating relative underventilation. The former situation with excess of ventilation over perfusion causes a dead-space-like effect ('wasted' ventilation), while relative underventilation causes

some impairment of the oxygenation of blood. There is also a mismatch at an isogravitational level, which may be larger than that in the gravitational direction. However, the mechanisms are not known.

The anaesthetised subject

Ventilation distribution

In addition to the fall in FRC with adoption of the horizontal position, anaesthesia causes further reduction of 0.4-0.5 l in FRC. This brings FRC close to the waking residual volume. This is an abnormal lung volume to breathe at, as can be experienced by expiring to the maximal degree and then trying to breathe at that level. The reduction in FRC occurs with spontaneous breathing and regardless of whether the anaesthetic is inhaled or given intravenously [7]. Muscle paralysis and mechanical ventilation cause no further decrease in FRC. Thus, anaesthetics in general reduce tonic muscle activity even though they allow spontaneous breathing. This loss of tonic activity is the cause of reduced FRC.

The fall in FRC during anaesthesia promotes airway closure. It can be expected in almost all adult patients when in the supine position (from 30–35 years of age onward). Moreover, atelectasis appears in 90% of all patients who are anaesthetised [8].

Ventilation is distributed more to the upper half of the lung than to the lower, which is the opposite of the distribution in the awake subject. Major causes of this shift must be airway closure and atelectasis. Moreover, with small lung volume airway resistance increases, and especially in dependent regions that are less inflated than upper regions.

There are few studies on atelectasis formation and distribution in the lateral position during anaesthesia. Atelectasis that was seen in both lungs in the anaesthetised patient in the supine position decreased in size in the upper, nondependent lung when the patient was turned into a lateral position [9]. However, the atelectasis remained in the dependent lung. The resolution in the upper lung is a consequence of the increase in the upper lung volume when the patient is rotated. This is similar to a PEEP applied to the upper lung, but without the need for external pressure. When anaesthesia was induced in the lateral position, atelectasis appeared in the lower, dependent lung whilst no collapse was seen in the upper, nondependent lung (Fig. 2). When the patient was turned to the supine position no atelectasis appeared in the previously upper lung, whereas it remained in the other lung [9]. The absence of atelectasis formation in the lung that had previously been the upper lung may appear surprising. However, atelectasis formation is promoted by ventilation with high inspiratory oxygen fraction at decreased lung volume (FRC), the decrease being caused by most anaesthetics [10, 11]. If lung volume is maintained during the induction of anaesthesia, as is the case in the upper lung, no atelectasis need be produced. Subsequent ventilation with lower oxygen fractions (FiO_2: 0.3–0.4 in the present case) will not promote atelectasis within a reasonable time even though the volume of that lung has been reduced by turning the patient into the supine

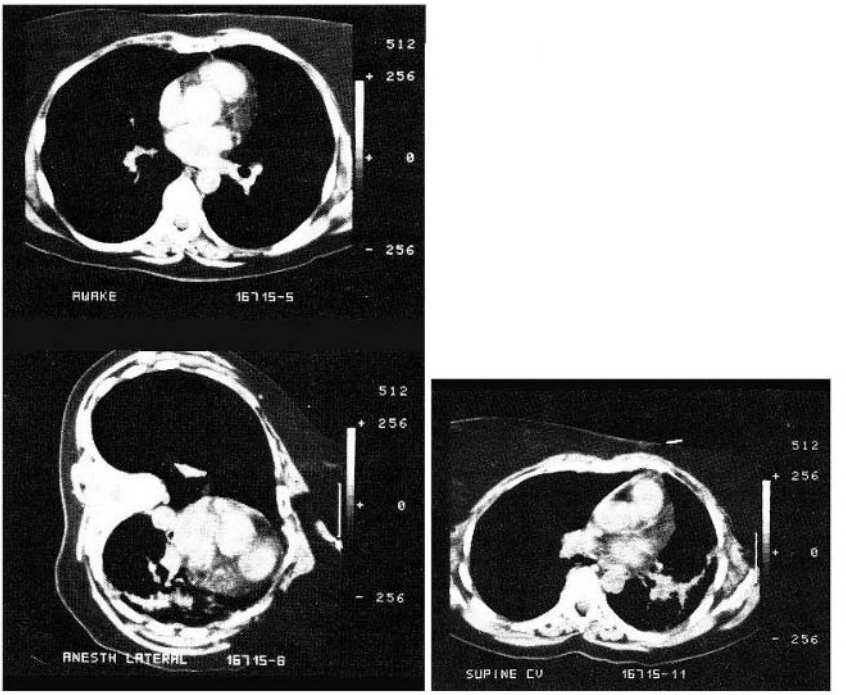

Fig. 2. CT scan of a patient awake in the supine position (*upper panel*), after induction of anaesthesia in the lateral position and, finally, when turned to lie in the supine position during anaesthesia (*lower right*). Note the well-aerated lung while patient is awake and the formation of atelectasis in the dependent lung, whereas no atelectasis can be seen in the upper, nondependent lung during anaesthesia. Finally, when the patient is turned to supine there is still no atelectasis in the lung that was previously higher. For further details and explanations, see text. (From [9], with permission from the publisher)

position. If ventilation had been continued with 100% O_2 after the change to the supine position, it is most likely that atelectasis would also have been produced in the lung that had formerly been above.

There are no reports of atelectasis in prone, anaesthetised patients. However, the vertical pleural pressure gradient seems to be smaller in the prone than in the supine position [12]. This difference may be due to the weight of the heart, which compresses the dependent parts of the lung in the supine position and enables the nondependent regions to expand. In the prone position, the heart is resting on the sternum with little or no effect on the shape of the lung. We can therefore speculate that there is less atelectasis in patients in the prone position.

Lung blood flow distribution

In the anaesthetised, spontaneously breathing patient, blood flow distribution will be much the same as in the waking subject. However, lung blood flow will be affected by mechanical ventilation, and with increasing ventilation pressure the reduction in lung blood flow will become more pronounced because venous return will be impeded and it is possible that pulmonary vascular resistance will be increased. Moreover, perfusion is forced down in the lung so that more blood flow goes to lower lung regions and less to higher regions [3]. With PEEP, it is possible to reduce atelectasis but this forcing of blood flow down the lung may result in a larger fraction of blood flow passing through the remaining atelectasis than without PEEP [8]. Hewlett et al. gave a warning against the indiscriminate use of PEEP in routine anaesthesia as much as 30 years ago, because they had observed that the oxygenation sometimes became worse with PEEP [13]. Today we also know why.

In the lateral position most of the blood flow goes to the lower lung, which will receive 60–65% of the total lung blood flow (Fig. 3). With PEEP, blood flow is forced down to the lower lung, in a similar way to that described above. A PEEP of 10 cmH_2O can almost eliminate blood flow to the upper lung in an individual case and causes a shift so that on average 20% goes to the upper lung and 80% to the lower lung [14].

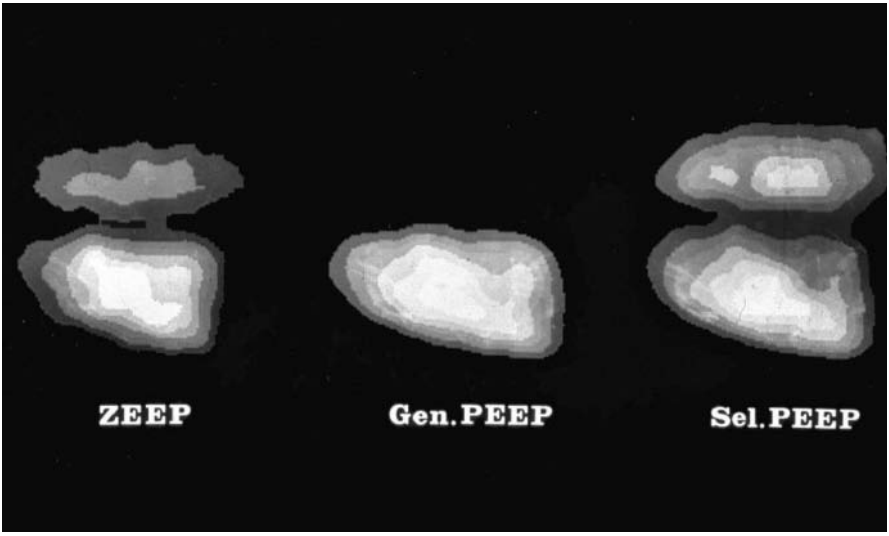

Fig. 3. Perfusion scintigrams of an anaesthetised subject in the lateral position. Note the perfusion in the upper lung during mechanical ventilation without end-expiratory pressure (ZEEP), the almost complete elimination of blood flow through the upper, nondependent lung during ventilation with PEEP of 10 cmH_2O to both lungs (*Gen.PEEP*). Finally, a selective PEEP of 10 cmH_2O was applied solely to the dependent lung and both lungs were ventilated with a similar tidal volume via double-lumen endobronchial catheter (*Sel.PEEP*). This resulted in a more even distribution of perfusion between the two lungs. (From [14], with permission from the publisher)

Ventilation-perfusion match

Venous admixture, as calculated according to the standard oxygen 'shunt' equation, is increased during anaesthesia, from the 1–3% that can be seen in the awake, healthy subject to approximately 10% of cardiac output.

There is a good correlation between the amount of atelectasis and pulmonary shunt. Thus,

$$\text{Shunt} = 0.8 \times \text{Atelectasis} + 1.7 \ (r = 0.81, p.01)$$

with atelectasis expressed as a percentage of the lung area just above the diaphragm on the CT scan and shunt as a percentage of cardiac output. Anaesthesia also causes an increased V/Q mismatch as a consequence of the changes in ventilation and perfusion distributions [8].

Lateral position may worsen the V/Q match, ventilation going mainly to the upper lung and perfusion to the lower one. In some patients PaO_2 falls by more than 30–50%. In some, on the other hand, oxygenation improves when they are placed in the lateral position [15]. This may depend on regional no gravitational differences between the lungs.

Prone position has been shown to reduce the V/Q mismatch to some extent [16].

The patient in acute respiratory failure

In acute respiratory failure, a gravitational distribution of collapse and consolidation can be seen; this can be plausibly explained by the greater weight of the oedematous lung causing compression of the underlying tissue [17]. In addition, fluid, pus and debris can fill air spaces without shrinkage of alveolar dimensions [18].

Several studies have shown an improvement in oxygenation in both adult and paediatric patients with acute lung injury and in patients who have undergone cardiac surgery when they are turned from the supine to the prone position [19–24] (see Table 1). The mechanisms are not fully clear. A list of proposed mechanisms is shown in Table 2 [25–34]. As can be seen, a more even vertical distribution of both perfusion and ventilation has been shown in the prone position. It has been suggested that the more even ventilation is related to a smaller vertical pleural pressure gradient, increased FRC, more even gas volume distribution and less marked lung compression by the heart, which will be resting directly on the sternum. It is the opinion of the present author that these mechanisms may contribute to the improved oxygenation but that a smaller amount of lung tissue will be collapsed in the prone position and that this might be a more important cause of the improved gas exchange.

Table 1. Improved oxygenation in prone position

Condition	Reference
Adult ALI	[19–23]
Cardiac surgery	[23]
Paediatric ALI	[24]

ALI = acute lung injury

Table 2. Potential mechanisms of improved oxygenation in the prone position

Proposed mechanism		Reference
1	More even vertical distribution of perfusion	[25]
2	Improved V/Q match	[26, 27]
3	More even ventilation distribution	
	a) Smaller vertical pleural pressure gradient	[28]
	b) Increased FRC and more even gas volume distribution	[29]
	c) Less lung compression by the heart	[30, 31]
4	Less lung consolidation/atelectasis	[33, 34]

The distribution of ventilation will be affected by the collapse and consolidation, and a major feature is redistribution away from the dependent to the higher lung regions that are still aerated. The macroscopic pathology, seen for example as densities on a CT, will change location on a change in body position. Thus, when a subject is in the prone position densities are seen in the anterior part and dorsal regions are aerated [32]. Similarly, in the lateral position densities should be expected in the dependent lung and less in the upper lung.

In early papers on lung collapse in the prone position published by the Cationic group, reduced atelectasis was not an explicit conclusion [32, 33]. In a more recent study, Lim et al. [34] showed less atelectasis/consolidation in patients suffering from extra pulmonary ARDS when in the prone position, whereas pulmonary ARDS was less affected by changes in the body position.

Why atelectasis may be less marked in the prone position is not fully clear. The difference may be related to the factors that cause more even ventilation distribution (Table 2). Interestingly, chest wall compliance is lower in the prone position [29]. A possible explanation for this reduced compliance is that rib cage motion is restricted when the patient is resting prone. In these circumstances, inflation of the lung will push the diaphragm further caudally than in a supine patient. Displacement of the diaphragm requires a similar displacement of the abdominal wall. Abdominal movement seems to be less restricted than movement of the chest. Since the major share of collapse and consolidation is in regions close to the diaphragm, preferential displacement of the diaphragm may improve aeration and recruitment of collapsed regions (see Fig. 4, panels MV, supine and MV, prone). This beneficial effect by forcing the diaphragm to move, although passively during mechanical ventilation, is similar to what has been demonstrated recently during spontaneous breaths added to mechanical ventilation. Spontaneous breaths improve the aeration and recruit collapsed lung tissue better than mechanical ventilation alone [35].

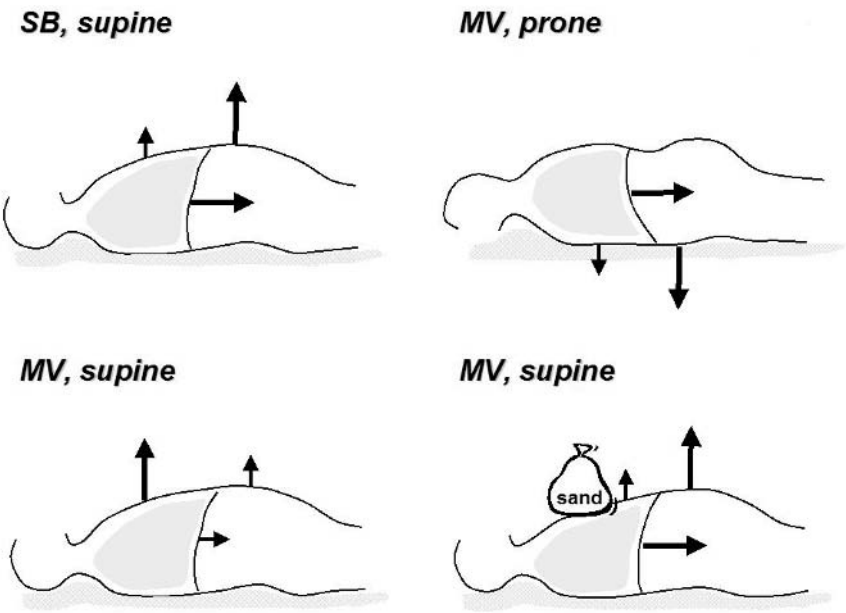

Fig. 4. Movements of the rib cage, diaphragm and abdomen. Size of *arrows* indicates degree of displacement. Note that in supine, spontaneously breathing (*SB*) subject diaphragm excursion with subsequent abdominal movement is larger than rib cage excursion (*upper left panel*). During mechanical ventilation (*MV*) rib cage displacement is larger than the diaphragm/abdominal movement (*lower left panel*). When the subject is turned to the prone position rib cage movement may be reduced during MV, with increased displacement of the diaphragm (*upper right panel*). Finally, if a heavy weight is placed on the rib cage, MV will cause the diaphragm to move more than without the weight applied (*MV, supine, lower right*)

Cationic et al. proposed that heavy weights placed on a supine patient's ribcage might improve oxygenation. This is another way of limiting ribcage excursion (Fig. 4, right lower panel).

It might be stressed that the alert anaesthetist may observe a change in the movement of the ribcage and abdomen when inducing anaesthesia in the supine position. During spontaneous breathing, the abdominal movement reflecting displacement of the diaphragm is greater than the corresponding movement of the ribcage. This reflects the greater importance of the diaphragm as a respiratory muscle than of the intercostals expanding the ribcage. During induction of anaesthesia, when the patient is being ventilated mechanically, displacement of the ribcage increases and that of the abdomen decreases, giving a pattern that is the opposite of that seen during spontaneous breathing. This reflects the higher compliance of the ribcage than of the abdomen (Fig. 4, left upper and lower panels).

In patients with ARDS who were treated according to a concept proposed almost 20 years ago PEEP was applied exclusively to the dependent lung via a double-lumen end bronchial catheter and both lungs were ventilated with similar

tidal volumes [36]; these patients were all treated in the lateral position. The underlying hypothesis (this was before the era of CT scan studies in ARDS patients) was that the pathology of the lung was localised in dependent lung regions and that efforts to re-expand lung tissue therefore should be directed at the dependent lung. It was also assumed that application of PEEP solely to the dependent lung would force blood flow upwards so that when patients were in the lateral position perfusion of each lung would be similar, which was the reason for the similar tidal volumes to both lungs (see Fig. 3). The technique, known as independent lung ventilation with selective PEEP, led to impressive improvement in the oxygenation of blood in anaesthetised subjects and patients with early acute lung insufficiency [37] (see Fig. 5). However, the results were modest in severe and long-standing ARDS. The poor effect can reasonably be attributed to the presence of nonrecruitable consolidated tissue in the dependent lung with the selective PEEP.

Conclusion

In conclusion, body position plays a major role in the distribution of ventilation and lung blood flow. This means that body position is also an important determinant of gas exchange. There are a number of mechanisms. One is gravity, which

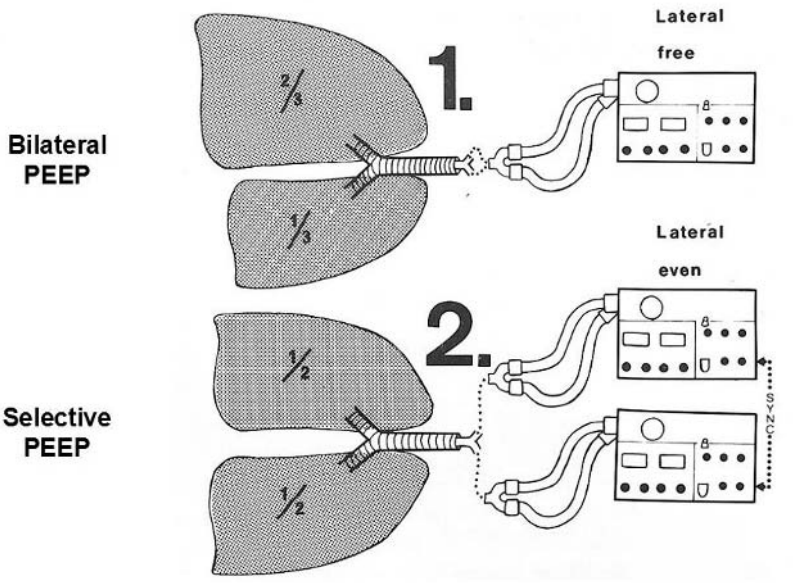

Fig. 5. Ventilation with a single-lumen endobronchial catheter and by lateral PEEP (*1*) and ventilation with an endobronchial double-lumen catheter with equal distribution of ventilation and selective PEEP to the lower lung only (*2*). For further details see text

forces blood flow to dependent lung regions irrespective of body position. There is also 'gravitationally' oriented distribution of ventilation as a consequence of the vertical pleural pressure gradient and a curved pressure–volume relationship of the lung. Moreover, ventilation and blood flow are unevenly distributed at an isogravitational level, with inhomogeneity of ventilation and blood flow that is larger than the vertical unevenness. Body position also has a considerable impact on lung volume, which will affect airway calibre, airway closure and atelectasis formation. Body position will also affect the movement of the ribcage and the abdomen, prone position limiting ribcage movement. This affects the degree of diaphragm displacement. Finally, techniques are available to distribute ventilation to poorly aerated and even collapsed lung regions without overstretching aerated lung regions. However, this requires separate ventilation of lung regions. At present this can be achieved by positioning the patient in the lateral position and then ventilating the two lungs separately via a double-lumen endobronchial catheter. By applying PEEP to the dependent lung and less or no PEEP to the upper lung while distributing ventilation equally between the lungs an improved V/Q match can be obtained. It should also be emphasised that spontaneous breathing has beneficial effects on aeration and recruitment of collapsed lung, with improvement in V/Q match and oxygenation of blood.

References

1. Milic-Emili J, Henderson JAM, Dolovich MB et al (1966) Regional distribution of inspired gas in the lung. J Appl Physiol 21:749-759
2. Leblanc P, Ruff F, Milic Emili J (1970) Effects of age and body position on "airway closure" in man. J Appl Physiol 28:448-451
3. West JB (1977) Blood flow. In: West JB (ed) Regional differences in the lung. Academic Press, New York, pp 85-165
4. Glenny RW, Lamm WI, Albert RK et al (1991) Gravity is a minor determinant of pulmonary blood flow distribution. J Appl Physiol 71:620-629
5. Glenny RW, Bernard S, Robertson HT et al (1999) Gravity is an important but secondary determinant of in regional pulmonary blood flow in upright primates. J Appl Physiol 86:623-632
6. Hlastala MP, Bernard SL, Erickson HH et al (1996) Pulmonary blood flow distribution in standing horses is not determined by gravity. J Appl Physiol 81:1051-1061
7. Wahba RWM (1991) Perioperative functional residual capacity. Can J Anaesth 38:384-400
8. Hedenstierna G (1995) Ventilation-perfusion relationships during anaesthesia. Thorax 50:85-91
9. Klingstedt C, Hedenstierna G, Lundquist H et al (1990) The influence of body position and differential ventilation on lung dimensions and atelectasis formation in anaesthetized man. Acta Anaesthesiol Scand 34:315-322
10. Rothen HU, Sporre B, Engberg G (1995) Prevention of atelectasis during general anaesthesia. Lancet 345:1387-1391
11. Edmark L, Kostova-Aherdan K, Enlund M et al (2003) Optimal oxygen concentration during induction of general anesthesia. Anesthesiology 98:28-33

12. Ganesan S, Lai-Fook SJ (1989) Finite element analysis of regional lung expansion in prone and supine positions: effect of heart weight and diaphragmatic compliance. Physiologist 32:191
13. Hewlett AM, Hulands GH, Nunn IF et al (1974) Functional residual capacity during anesthesia. III. Artificial ventilation. Br J Anaesth 46:495-503
14. Hedenstierna G, Baehrendtz S, Klingstedt C et al (1984) Ventilation and perfusion of each lung during differential ventilation with selective PEEP. Anesthesiology 61:369-376
15. Klingstedt C, Hedenstierna G, Baehrendtz S et al (1991) Ventilation-perfusion relationships and atelectasis formation in the supine and lateral positions during conventional mechanical and differential ventilation. Acta Anaesthesiol Scand 34:421-429
16. Mure M, Domino KB, Lindahl SGE et al (2000) Regional ventilation-perfusion distribution is more uniform in the prone position. J Appl Physiol 88:1076-1083
17. Gattinoni L, Pesenti A, Bombino M et al (1988) Relationships between lung computed tomographic density, gas exchange and PEEP in acute respiratory failure. Anesthesiology 69:824-832
18. Hubmayr RD (2002) Perspective on lung injury and recruitment. A skeptical look at the opening and collapse story. Am J Respir Crit Care Med 165:1647-1653
19. Piehl MA, Brown RS (1976) Use of extreme position changes in acute respiratory failure. Crit Care Med 4:13-14
20. Douglas WW, Rehder K, Beynen FM (1977) Improved oxygenation in patients with acute respiratory failure: the prone position. Am Rev Respir Dis 115:559-566
21. Mure M, Martling CR, Lindahl SG (1997) Dramatic effect on oxygenation in patients with severe acute lung insufficiency treated in the prone position. Crit Care Med 25:1539-1544
22. Gattinoni L, Tognoni G, Pesenti A (2001) Prone-Supine Study Group. Effect of prone positioning on the survival of patients with acute respiratory failure. N Engl J Med 345:568-573
23. Brussel T, Hachenberg T, Roos N (1993) Mechanical ventilation in the prone position for acute respiratory failure after cardiac surgery. J Cardiothorac Vasc Anesth 7:541-546
24. Murdoch IA, Storman MO (1994) Improved arterial oxygenation in children with the adult respiratory distress syndrome: the prone position. Acta Paediatr 83:1043-1046
25. Nyren S, Mure M, Jacobsson H et al (1999) Pulmonary perfusion is more uniform in the prone than in the supine position: scintigraphy in healthy humans. J Appl Physiol 86:1135-1141
26. Pappert D, Rossaint R, Slama K et al (1994) Influence of positioning on ventilation-perfusion relationships in severe adult respiratory distress syndrome. Chest 106:1511-1516
27. Mure M, Domino KB, Lindahl SG et al (2000) Regional ventilation-perfusion distribution is more uniform in the prone position. J Appl Physiol 88:1076-1083
28. Mutoh T, Guest RJ, Lamm WJ et al (1992) Prone position alters the effect of volume overload on regional pleural pressures and improves hypoxemia in pigs in vivo. Am Rev Respir Dis 146:300-306
29. Pelosi P, Croci M, Calappi E et al (1995) The prone positioning during general anesthesia minimally affects respiratory mechanics while improving functional residual capacity and increasing oxygen tension. Anesth Analg 80:955-960
30. Albert RK, Hubmayr RD (2000) The prone position eliminates compression of the lungs by the heart. Am J Respir Crit Care Med 161:1660-1665
31. Broccard AF (2003) Prone position in ARDS: are we looking at a half-empty or half-full glass? Chest 123:1334-1336

32. Gattinoni L, Pelosi P, Vitale G et al (1991) Body position changes redistribute lung computed-tomographic density in patients with acute respiratory failure. Anesthesiology 74:15-23
33. Langer M, Mascheroni D, Marcolin R et al (1988) The prone position in ARDS patients. A clinical study. Chest 94:103-107
34. Lim CM, Kim EK, Lee JS et al (2001) Comparison of the response to the prone position between pulmonary and extrapulmonary acute respiratory distress syndrome. Intensive Care Med 27:477-485
35. Wrigge H, Zinserling J, Neumann P (2003) Spontaneous breathing improves lung aeration in oleic acid-induced lung injury. Anesthesiology 99:376-384
36. Baehrendtz S, Santesson J, Bindslev L (1983) Differential ventilation in acute bilateral lung disease. Influence on gas exchange and central hemodynamics. Acta Anaesth Scand 27:270-227
37. Baehrendtz S, Hedenstierna G (1984) Differential ventilation and selective positive end-expiratory pressure. Effects on patients with acute bilateral lung disease. Anesthesiology 61:511-517

Chapter 2

Chest pain

F. Schiraldi

Owing to the growing pressure on emergency department (ED) personnel for hospital admissions, a particular clinical challenge is linked with chest pain syndromes. It is generally accepted that the acute coronary syndromes (ACS) are heterogeneous with respect to pathophysiology, clinical presentation, response to therapy and outcomes. The body of evidence on the benefits of reperfusion therapy strongly support an evolving strategy aiming to reduce the 'door-to-needle time', at the same time allowing early risk stratification to optimise 'triage' in the emergency department [1]. A more useful approach could actually be aimed at the reduction of the 'pain to reperfusion' time; moreover, owing to the limitations imposed by inadequate resources, the best ED approach should be directed at a safe 'rule in/rule out' protocol. The first chest pain units (CPU) were born with this aim [2–5].

Nevertheless, despite growing scientific interest in the field, the optimal protocol for management in the CPU is still not clear, and despite advances in investigative modalities many scientists agree that a focused history and a subsequent accurate clinical examination including ECG interpretation remain the key tools in the diagnosis. The most powerful features that *increase* the probability of acute myocardial infarction (AMI) and their associated likelihood ratios (LRs) are new ST segment elevation (LR 5.7–53.9), new Q wave (LR 5.3–24.8) and chest pain radiating to both left and right arms simultaneously (LR 7.1).The most powerful features that *decrease* the probability of AMI are a normal EKG result (LR 0.1–0.3), pleuritic chest pain (LR 0.2) and positional chest pain (LR 0.3) [6].

Specificity and sensitivity in diagnosis

A great deal of clinical research has been devoted to looking for the best decision-making aids in the management of acute chest pain or to attempts to determine the optimal level of care for patients admitted with acute chest pain. The main problem, because of the limited beds and resources available, is the possibility of mistakenly discharging patients with AMI: these people have short-term mortality rates of about 25%, i.e. at least twice the rate that would be expected if they were admitted [7, 8]. Attention has therefore been focused on technical resources that could improve the diagnostic strategy [9]:

- ECG secrets
- Bedside evaluation of multimarkers
- Imaging
- Dynamic assessment

ECG secrets. Some electrocardiographic variables are generally accepted as indicating ischaemia or infarction when present in at least two anatomically contiguous leads: (1) pathologic Q waves (≥1 mm in depth and ≥0.3 s in duration); (2) ST segment elevation or depression by 1 mm or more; and (3) elevated or inverted T waves.

The ST segment and T wave abnormalities are not considered diagnostic in the case of left ventricular hypertrophy, left or right bundle branch block (BBB), early repolarisation variant, pre-excitation syndromes or an implanted pacemaker [10]. Further suggestions can be added to allow a more specific insight about the ECG interpretation.

In the case of BBB, it must be borne in mind that the vectorial sum of the QRS axis and T wave axis should normally remain between –20° and + 80°, a sum outside this range suggests acute ischaemia (the so-called ventricular gradient).

A positive R wave in V1 that has not been present before could suggest a true posterior infarction (always look for ultrasound confirmation).

A negative T pattern in V1–3 is normal only if the negativity in V1 is more than in V3; otherwise it strongly suggests anteroseptal ischaemia (the so-called decremental gradient).

The upward ST trend in acute pericarditis is never linked to a mirror image in the opposite leads.

In aortic dissection the ECG could be normal or only minimally abnormal (ischaemia-like pattern) despite a severe clinical presentation

In persons with implanted pacemakers a suspicion of acute coronary events can still arise when the ECG is compared with previous ECG recordings.

Similar criteria can be applied in ischaemia or reinfarction affecting a previously necrosed myocardial zone, and in BBB showing any departure from the usual pattern.

A transient T wave-positive pattern in subjects whose previous ECG recordings showed stable negative T waves (pseudonormalisation) strongly suggests acute ischaemia.

In some dyselectrolytic conditions the interpretation can be particularly difficult; for example an anterior ischaemia should be suspected if a normal or simply flat T wave is recorded against a background of acute hyperkalaemia.

Bedside multimarkers strategy. Cardiac biomarkers play a pivotal part in risk stratification in ACS, so that the results of cardiac biomarker tests can be used to help guide choices between alternative therapies. Some quite newly identified markers of myocardial injury have allowed the use of new strategies for evaluation of patients with acute chest pain. It is interesting to note that the more generally accepted biomarkers have different timing. Levels of creatine kinase MB isoenzyme

(CK-MB) usually rise above the normal range within 4 h after the onset of myocardial infarction, and serial sampling of CK-MB over a period of 12–24 h permits the detection of virtually all AMIs. However, CK-MB elevations can result from causes other than myocardial injury [11, 12].

The cardiac *troponins*, *T* and *I*, are encoded by different genes in cardiac muscle, slow skeletal muscle, and fast skeletal muscle; hence, these markers are more specific for myocardial injury than CK-MB. After myocardial injury, the levels of cardiac troponins rise after approximately the same amount of time as CK-MB levels (6–12 h) but remain elevated for several days [13]. Once elevated, the cardiac troponins are not useful in detecting repeated episodes of myocardial injury owing to the long elimination half-life; nevertheless, they are significantly predictive about the risk of death in the first 42 days (Fig. 1) [14].

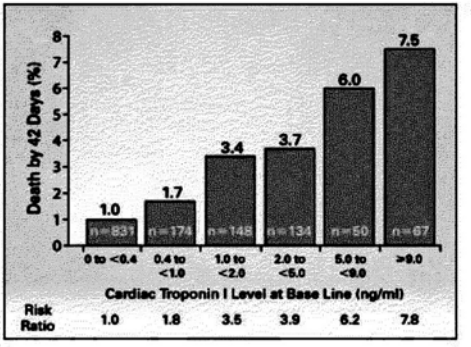

Fig. 1. Quantitative relation between troponin release and risk of death within 42 days. (Adapted from [14])

Recently a few papers have reported spurious troponin elevations, mostly during renal insufficiency [15, 16]. Indeed, studies on small groups of patients with predialytic renal insufficiency without clinical or ECG evidence of acute myocardial ischaemia have included up to 71% of patients with increased TnT [17], while troponin I is increased in only about 7% of patients with renal failure. Moreover, cardiac troponin T predicts long-term outcomes in haemodialysis patients [18]. Unfortunately there are still some pitfalls in the use of troponins (Table 1).

Table 1. Non-ACS causes of troponin elevation

Myocarditis
Cardiac contusion
Cardioversion
Radiofrequency ablation
Congestive heart failure
Chemotherapy (doxorubicin, 5-fluorouracil)
Septic shock
Extreme endurance athletics
Pulmonary embolus

In the first 6 h after myocardial infarction, CK-MB subforms appear to be both more sensitive and more specific than CK-MB mass activity or even than troponins. Myoglobin is a very sensitive, but hardly specific, marker of AMI: its use should therefore be limited to 'ruling out' the diagnosis, and not to 'ruling it in'. Its main real advantage is the very good positive timing (90–120 min) [18], so that it may be helpful in timely detection of even a small extension of an infarction, which is otherwise very difficult to demonstrate during the first few days after an AMI.

Despite some caveats, a recent meta-analysis of the three most widely accepted studies on the predictive value of isolated troponin elevation (PARAGON, GUSTO IIa Troponin Substudy, Checkmate) [19–21] have suggested that baseline troponin elevation, without CK-MB elevation, are significantly associated with elevated risk of early and short-term adverse outcomes [22].

C-Reactive protein is a potent predictor of mortality both independently of and in combination with troponin T in acute coronary syndromes [20].

Many new markers are under investigation (B-type natriuretic peptide [BNP], N-proBNP, high-sensitivity C-reactive protein [hs-CRP], antiplatelet factor 4/heparin antibodies, etc.). While all these are still under evaluation, studies in patients with suspected ACS have consistently shown that BNP and N-proBNP add unique and important prognostic information, even if the two latter are more closely associated with a 'pump failure' secondary to ACS. Interestingly, Sabatine et al. performed analyses in the OPUS-TIMI 16 and TACTICS-TIMI 18 studies, using TnI, CRP end BNP in combination. In multivariate models, each of these biomarkers remained independently linked with adverse cardiac events, demonstrating the unique predictive information that each of these biomarkers provides [23–25].

With a panel of biomarkers that covers the spectrum of pathology of ACS, it is hoped that this heterogeneous syndrome can be treated with a selective rather than a 'shotgun' approach.

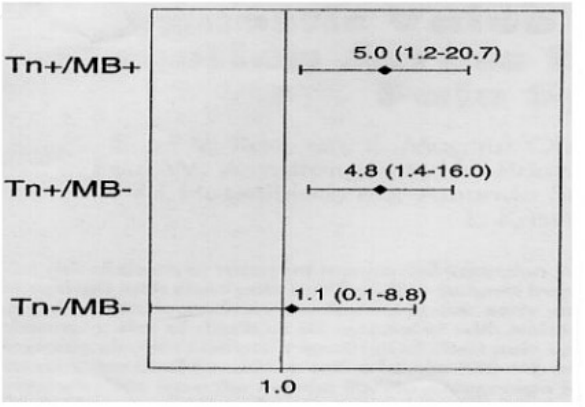

Fig. 2. Adjusted odds ratio and 95% CIs for death in 30 days or MI by marker status. (From [22])

Imaging

Echocardiography. There is a growing body of evidence supporting the pivotal role of ultrasound examination of the heart (echocardiography) in emergency departments [26, 27].

The positive aspects are:

- High sensitivity and efficiency in detection of regional abnormalities of wall motion.
- Timely and direct diagnosis of other cardiovascular diseases as a cause of chest pain: aortic dissection, pulmonary embolism, aortic stenosis, pericarditis; it is also the gold standard for early diagnosis of some *complications* of the AMI (mitral or tricuspid valve acute insufficiency, systolic or diastolic ventricular dysfunction , intracardiac thrombosis).
- Reliable monitoring of the therapeutic strategies (successful or unsuccessful reperfusion, effect of beta blockers).

On the other hand, there is general agreement on some disadvantages:

- Operator dependence in obtaining and/or interpreting the ultrasound images.
- Uncertainty about the age of some kinetic abnormalities (differential diagnosis between previous/recent AMI).
- As this is a form of noncontinuous monitoring, some temporary ischaemic effects (e.g. myocardial stunning) could be misinterpreted as AMI (*false positive*).
- Some *false-negative results* could depend on a very small size of the ischaemic area (so-called noncritical mass).

The best time to perform an echocardiogram in patients complaining of chest pain is still controversial; it seems reasonable to perform this examination:

- In patients whose chest pain is ongoing, has just resolved, or lasted more than 30 min.
- In patients with typical chest pain associated with a nondiagnostic ECG investigation.
- In patients whose history suggests previous AMI with chest pain and inconclusive ECG patterns.
- In patients in whom there is a strong suspicion of aortic dissection or acute pericarditis.

Myocardial scintigraphy. The historical validation of thallium-201 scintigraphy has been largely supported by many studies confirming a near 100% *sensitivity* of the 'cold spot' (the typical thallium imaging in truly ischaemic patients); moreover, it has good *specificity* in patients with acute nontraumatic chest pain and any suspected coronary syndrome.

The two main related problems might be:

- Suboptimal images compared with technetium-99.
- Suboptimal diagnostic reliability when there is any delay in recording the imaging after the tracer injection.

On the other hand, acute positive *rest Tc-99m sestamibi* perfusion imaging accurately identifies patients at high risk of adverse cardiac outcomes, whereas negative perfusion imaging identifies a low-risk patient group [28, 29].

So, depending on the facilities at the institution, myocardial scintigraphy can be a useful, albeit not a first-line, diagnostic tool, which gives better results when performed with technetium-99. Further investigation is necessary to determine whether such a routine approach results in lower costs than are incurred by current standard practice.

Magnetic resonance. Despite its high reliability, magnetic resonance imaging (MRI) still seems too sophisticated a diagnostic aid to be suggested in the emergency department. Nevertheless, there is some room for MRI in the so-called X syndrome subgroup, which usually affects women, whose ECG, echocardiogram and myocardial scintigraphy can be normal or puzzling, even during an acute chest pain crisis [30, 31]. As a matter of fact, in patients with syndrome X there is consistent evidence of an abnormality of myocardial perfusion limited to the subendocardium. This is because transmural resolution is higher with cardiovascular MRI than with other techniques. A possible explanation could be based on the inherent capability for detecting subendocardial ischaemic areas.

Dynamic assessment. The first American guideline on unstable angina (including myocardial infarction without ST segment elevation), published in 1994, emphasised early risk stratification as the pivotal process that drives the initial treatment and decision about triage in the emergency department [32]. Up to then, there had been great concern about the safety of the patient, centring on the possibility of subjecting the patients to exercise testing for detecting ischaemic myocardium. However, studies have shown that patients who have a low *clinical* risk of complications can safely undergo exercise testing within 6–12 h after presentation at the hospital or even immediately [33, 34].

Radionuclide imaging, stress echocardiography, and prompt coronary angiography may all be useful for diagnosing coronary artery disease in some subgroups of patients [35, 36]. Nevertheless it should always be remembered that, for example, studies with stress echocardiography have demonstrated that, despite the chest pain, some patients have had no impairment in contractility. To complicate matters further, it has been shown that the typical chest pain reported by patients with normal coronary angiograms can be evoked by electrical stimulation of the right ventricle, which does not cause myocardial ischaemia: positron emission tomography scanning of the brain has demonstrated an abnormally sensitive perception of cardiac pain in at least some of these patients [37].

Conclusions

Multivariate algorithms have been developed and prospectively validated with the goal of improving the stratification of risk in patients with possible acute ischaemic heart disease [38, 39]. Nevertheless, despite the availability of different diagnostic techniques, such as early monitoring of cardiac enzymes, noninvasive cardiac

imaging, dynamic evaluation and 'chest pain programmes' [40], we still do not know how to reduce the number of missed diagnosis of myocardial infarction or unstable angina. However, some hard facts are remarkable:

- Unstable angina and NSTEMI account for over 1.5 million hospitalisations annually in the United States.
- Coronary artery disease is the leading cause of death in most countries.

In the future, clinicians might use the diagnostic tools available to them to create a specific patient profile that could be used to select personalised therapies aimed at preserving as much muscle as possible, always remembering that "Timing is everything."

References

1. Newby KL, Mark DB (1998) The chest pain unit – ready for prime time? N Engl J Med 339:1930-1932
2. Garber MA, Solomon NA (1999) Cost-effectiveness of alternative test strategies for the diagnosis of coronary artery disease. Ann Intern Med 130:719-728
3. Kuntz MK, Fleischmann KE, Hunink GM et al (1999)Cost-Effectiveness of diagnostic strategies for patients with chest pain. Ann Intern Med 130:709-718
4. Panju AA, Hemmelgarn BR, Giyatt GH et al (1998) The rational clinical examination. Is this patient having a myocardial infarction? JAMA 280:1256-1263
5. Gaspoz JM, Lee TH, Weinstein MC et al (1994) Cost-effectiveness of a new short-stay unit to "rule out" acute myocardial infarction in low risk patients. J Am Coll Cardiology 24:1249-1259
6. Lee TH, Goldman L (2000) Evaluation of the patient with acute chest pain. N Engl J Med 342:1187-1195
7. Pope JH, Ruthazer R, Beshansky JR et al (1998) The clinical presentation of patients with acute cardiac ischemia in the emergency department: a multicenter controlled clinical trial. J Thromb Thrombolysis 6:63-74
8. Zimmerman J, Fromm R, Meyer D et al (1999) Diagnostic Marker Cooperative Study for the Diagnosis of Myocardial Infarction. Circulation 99:1671-1677
9. Roberts R, Fromm RE (1998) Management of acute coronary syndromes based on risk stratification. An idea whose time has come. Circulation 98:1831-1833
10. Theroux P, Fuster V (1998) Acute coronary syndromes: unstable angina and non-Q-wave myocardial infarction. Circulation :1195-1206
11. Adams JE III, Abendschein DR, Jaffe AS (1993) Biochemical markers of myocardial injury: is MB creatine kinase the choice for the 1990s? Circulation 88:750-763
12. Ravkilde J, Nissen H, Horder M et al (1995) Independent prognostic value of serum creatine kinase isoenzyme MB mass, cardiac troponin T and myosin light chain levels in suspected acute myocardial infarction. J Am Coll Cardiol 25:574-581
13. Polanczyk CA, Lee TH, Cook EF et al (1998) Cardiac troponin I as a predictor of major cardiac events in emergency department patients with acute chest pain. J Am Coll Cardiol 32: 8-14
14. Antman EM (2002) Decision making with cardiac troponin tests. N Engl J Med 346: 2079-2082
15. Aviles RJ, Askari AT, Lindahl B et al (2002) Troponin T levels in patients with acute coronary syndromes, with or without renal dysfunction. N Engl J Med 346:2047-2052

16. Freda BJ, Tang WHW, Van Lente F et al (2002) Cardiac troponins in renal insufficiency. J Am Coll Cardiol 40:2065-2071
17. Li D, Jaial J, Corry K et al (1997) Cardiac troponins T and I before and after renal transplantation. Clin Chem 43:411-412
18. Ooi DS, Zimmerman D, Graham J et al (2001) Cardiac troponin T predicts long-term outcomes in haemodialysis patients. Clin Chem 47:412-417
19. Newby LK, Ohman EM, Christensen et al (2001) The PARAGON – B troponin T substudy. Circulation 103:2891-2896
20. The Global Use of Strategies to Open Occluded Coronary Arteries(GUSTO) IIa Investigators (1994). Circulation 90:1631-1637
21. Zalenski RJ, Rydman RY, Mc Careen M et al (1997) Feasibility of a rapid diagnostic protocol for an emergency department chest pain unit. Ann Emerg Med 29:99-108
22. Newby LK, Storrow AB, Gibler WB et al (2001) The CHECKMATE study. Circulation 103:1832-1837
23. Rao SV, Ohman EM, Granger CB et al (2003) Prognostic value of isolated troponin elevation across the spectrum of chest pain syndromes. Am J Cardiol 91:936-940
24. Morrow DA, Rifai N, Antman EM et al (1998) C-Reactive protein is a potent predictor of mortality independently of and in combination with troponin T: a TIMI 11A substudy. J Am Coll Cardiol 31:1460-1465
25. Sonel A, Sasseen MB, Fineberg N et al (2000) Prospective study correlating fibrinopeptide a, troponin i, myoglobin, and myosin light chain levels with early and late ischemic events in consecutive patients presenting to the emergency department with chest pain. Circulation 102:1107
26. Farkouh ME, Smars PA, Reeder GS et al (1998) A clinical trial of a chest-pain observation unit for patients with unstable angina. N Engl J Med 339:1882-1888
27. Braunwald E, Mark DB, Jones RH et al (1994) Unstable angina: diagnosis and management. (Clinical practice guideline no 10) Department of Health and Human Services, Rockville, Md
28. Colon PJ III, Mobarek SK, Milahi RV et al (1998) Prognostic value of stress echocardiography in the evaluation of atypical chest pain in patients without known coronary artery disease. Am J Cardiol 81:545-551
29. Kontos MC, Jesse RL, Schimdt KL et al (1997) Value of acute rest sestamibi perfusion imaging for evaluation of patients admitted to the emergency department with chest pain. J Am Coll Cardiol 30:976-982
30. Hilton TC, Thompson RC, Williams HJ et al (1994) Technetium-99m sestamibi myocardial perfusion imaging in the emergency room evaluation of chest pain. J Am Coll Cardiol 23:1016-1022
31. Cannon RO, Balaban RS (2000) Chest pain in women with normal coronary angiograms N Engl J Med 342:885-887
32. Panting JR, Gatehouse PD, Yang GZ et al (2002) Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. N Engl J Med 346:1948-1953
33. Polanczyk CA, Johnson PA, Hartley LH et al (1998) Clinical correlates and prognostic significance of early negative exercise tolerance test in patients with acute chest pain seen in the hospital emergency department. Am J Cardiol 81:288-292
34. Roberts RR, Zalenski RJ, Mensah EK et al (1997) Cost of an emergency department-based accelerated diagnostic protocol vs. hospitalization in patients with chest pain: a randomized controlled trial. JAMA 278:1670-1676
35. Lewis WR, Amsterdam EA, Turnipseed S et al (1999) Immediate exercise testing of low

risk patients with known coronary artery disease presenting to the emergency department with chest pain. J Am Coll Cardiol 33:1843-1847
36. Nichol G, Walls R, Goldman L et al (1997) A critical pathway for management of patients with acute chest pain who are at low risk for myocardial ischemia: recommendations and potential impact. Ann Intern Med 127:996-1005
37. Kuntz KM, Fleishmann KE, Hunink MG et al (1999) Cost-effectiveness of diagnostic strategies for patients with chest pain. Ann Intern Med 130: 709-718
38. Panza JA (2002) Myocardial ischemia and the pains of the heart. N Engl J Med 346: 1934-1935
39. Salker HP, Griffith JL, Dorey FJ et al (1987) How do physicians adapt when the coronary care unit is full? A prospective multicenter study. JAMA 257:1181-1185
40. Pope JH, Aufderheide TP, Ruthazer R et al (2000) Missed diagnoses of acute cardiac ischemia in the emergency department. N Engl J Med 342:1163-1170
41. Ng SM, Krishnaswamy P, Morissey R et al (2001) Ninety-minute accelerated critical pathway for chest pain evaluation. Am J Cardiol 88:611-617

Chapter 3

The electrocardiogram in the emergency department

F. Schiraldi, F. Paladino, E.G. Ruggiero

In cardiac emergencies, correct diagnosis of the underlying cause is always the first step in the direction of optimal treatment. Nevertheless, a systematic approach to interpretation of the electrocardiogram (ECG) is of paramount importance. In their Advanced Life Support (ALS) Guidelines [1, 2], both the American Heart Association (AHA) and the European Resuscitation Council (ERC) give useful suggestions on how to take quite a simple "first look" at the monitor traces so familiar to any Emergency Department (ED) worker. In this paper, indeed, we first recall the essentials for a practical monitor-based approach, and will later suggest some insider tips on ECGs, which may be useful in daily routine.

The normal ECG

There are many 'normal' ECG patterns, depending on age, gender, race, neurovegetative state etc., but an initial recognition of the different waves of depolarisation/repolarisation allows a quick understanding of many cardiac conditions that are potentially dangerous, so that anybody approaching a patient in the ED should be familiar with these. Moreover, new insights into ECG interpretation are under investigation, as the molecular and biophysical bases of the cardiac action potential have just been discovered [3].

The P wave is the first depolarisation wave to be examined: it usually comes from the sinoatrial (SA) node and spreads throughout the atrial myocardium. An atrial contraction is the mechanical response to this electrical impulse. The intrinsic value of the P wave is linked with its optimal timing as 'responder' to many different stimuli (such as atrial enlargement attributable to hypoxia, diastolic ventricular dysfunction, increase in right or left afterload) [4-6]. Examination of the P wave morphology in the II, III, aVF, aVR and V1 leads is suggested, as these give most information about any P derangements.

In atrial fibrillation and atrial flutter the P wave is replaced by irregular F or f waves, which can notch the isoelectrical line. In junctional rhythm the P wave can be absent or very close to the QRS complex.

The PR interval is related to the relatively slow atrioventricular conduction through the AV node: its normal length is 120–200 ms, with some delay accepted in older patients (Fig. 1).

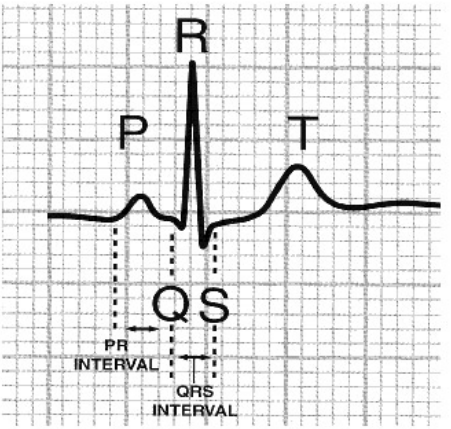

Fig. 1. EKG waves and intervals

The *QRS complex* is due to ventricular depolarisation; it usually lasts 70–120 ms, but whenever one bundle branch is diseased rapid intraventricular conduction through the corresponding ventricle is prevented (RBBB, LBBB), with corresponding QRS enlargement (120 ms). Interestingly, while RBBB can be of negligible importance, the LBBB is always linked to some significant cardiac disease.

The *T wave* is due to an ionic (s.c. repolarising) phenomenon, which is strictly related to the previous depolarising one, so that it should always have the same vectorial expression (positive if the R waves are positive in one of the corresponding leads, and so on); if there is no such vectorial concordance ischaemic problems can be expected.

The ST interval should be on the isoelectrical line; any upward or downward trend should be closely monitored.

The QT interval is of paramount importance in critical care: if it is longer or shorter than its normal length (320–440 ms) the incidence of potentially life-threatening ventricular arrhythmias can increase dramatically. Moreover, there are many electrolyte and acid–base disorders that can interfere with it (Fig. 2).

Finally, the QTc dispersion in the EKG has been newly recognised as an important prognostic factor in many diseases. A study from Taiwan University investigated the significance of QTc dispersion in acute intracerebral haemorrhage (ICH) patients. It was found that patients had less chance of surviving to discharge if they had increased QTc dispersion and a longer maximal QTc interval [7]. A very interesting tool is 'drug-induced' prolongation of the QT interval [8]; the availability of nine structurally unrelated drugs marketed for noncardiovascular conditions was found to be severely restricted because of this form of toxicity (Table 1).

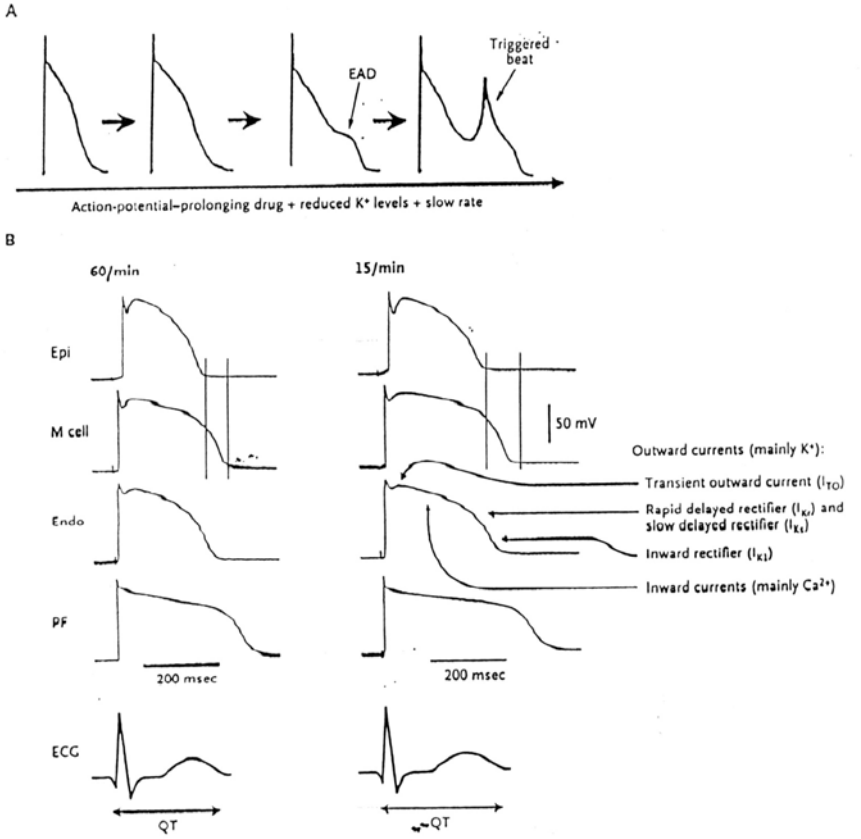

Fig. 2. Drug-induced prolongation of the QT interval. (From [8])

Table 1. Drugs with potential for inducing prolongation of QT interval

Terfenadine
Astemizole
Grepafloxicin
Terodiline
Droperidol
Lidoflazine
Sertindole
Levomethadyl
Cisapride

The TP interval is the real isoelectric line, which should always be referred to in order to appreciate any ST derangement.

How to read a rhythm strip

Anyone analysing a rhythm strip should work systematically through the following checklist:

- Is there any electrical activity?
- What is the QRS rate?
- Is the R–R interval regular?
- Is the QRS width <120 ms?
- Is any atrial activity present?
- Is the atrial activity related to ventricular activity?

Any expert electrophysiologist will find this approach too simple from a scientific point of view, but any intensive care specialist knows how important it is to stabilise the patient as soon as possible, and in the emergency department (ED) setting it therefore seems reasonable to be quite confident in this simple approach, as it can buy time for further diagnostic evaluations.

Wit reference to electrical activity, it is important to note that if the ECG shows only P waves without R waves (s.c. 'P wave asystole'), even if there is no pulse there are still possible ways of performing immediate successful pacing. The other main point is to differentiate the ventricular 'coarse' fibrillation from the ventricular tachycardia, because the former is always responsible for a dynamic arrest while the latter is frequently associated with mechanical activity (pulse present).

The normal ventricular rate is quite an abstract statement, as the heart rate (HR) should always be evaluated in context (think of the 'normal' cardiac response to acute hypovolaemia); in any case careful evaluation is needed in the case of any HR <50 or >120/min, because coronary perfusion and ventricular filling and ejection can be badly affected by such HRs.

The R-R interval is easy to evaluate and allows rapid screening among different arrhythmias, with some caveats:

- A uniform R–R interval does not rule out the presence of some arrhythmias (e.g. many forms of AV block, many re-entrant arrhythmias, some supraventricular arrhythmias with a fixed conduction delay).
- An irregular R–R interval can be of very limited importance in the case of atrial fibrillation, while the presence of a couple or short runs of ventricular extrabeats should be approached very cautiously and sometimes requires early treatment.

The QRS width could suggest any sort of bundle branch block (BBB) or ventricular rhythm. A very different approach is needed when a slow rhythm (<40/min) with large complexes is encountered, which usually requires mandatory pacing (idioventricular rhythm is very likely). On the other hand, a paroxysmal supraventricular tachycardia associated with large QRS complexes could be haemodynamically stable and a medicamentous approach might be reasonable, depending on the specific setting.

The atrial activity has already been discussed, although it is more useful if the physician is familiar with the different PR intervals in the presence of AV blocks (AVBs); indeed, grade I and II AVBs are usually time-limited and responsive to atropine, while type 2 and grade III AVBs require pacing.

A simple suggestion whose adoption can yield deeper insights is to run the EKG at double speed+double voltage, which enables the 'reader' to examine the atrial activity closely, if there is any. The same suggestion could be followed to evaluate the relationship between atrial and ventricular activity in other difficult settings. The admonition to 'Look at the patient' must always be borne in mind, as sometimes the correct policy is to stabilise the patient and seek an arrhythmia expert to devise the best strategy.

Cardiac arrest rhythms

A quick ECG interpretation is even more useful in the setting of cardiac arrest, which is a 'haemodynamic' condition (no pulse, no pressure) that obviously follows a ventricular fibrillation (VF) or asystole, but is sometimes related to ventricular tachycardia (VT) or so-called electromechanical dissociation (EMD). As these require different therapies, it is important to be able to recognise the different presentation rhythms.

The only suggestion we can make about VF is directed at early recognition to allow DC shocking as soon as possible; it must be remembered that the presence of P waves not followed by QRS is a real asystole (not to be discharged). The VT is quite easily recognisable because the rhythm is regular, or almost regular, the rate is between 100 and 300 b/min and the atrial activity often continues independently of ventricular activity. The QRS morphology can be monomorphic or polymorphic.

One important variety of polymorphic VT is called 'torsade de pointes', in which the axis of electrical activity changes in a rotational way. The peculiar importance of this cardiac arrest rhythm is that it can be caused by QT-prolonging drugs or electrolyte disturbances (hypokalaemia, hypomagnesaemia), whose correction could improve the prognosis.

Pulseless electrical activity (PEA) or electromechanical dissociation (EMD) implies the absence of mechanical cardiac activity even if the intrinsic electrical activity is quite normal. It can be caused by a massive myocardial infarction, pulmonary thromboembolism, tension pneumothorax, exsanguination or pericardial tamponade.

Acute coronary syndromes

The generally accepted classification for acute coronary syndromes (ACS) is based on an integrated approach that takes account of history, clinical presentation, bedside diagnostic strategy based on biomarkers and the ECG pattern. It is therefore absolutely unthinkable for any ED doctor not to be aware of the basics of ECG interpretation in suspected ACSs [9–11].

Some electrocardiographic variables are generally accepted as indicating ischaemia or infarction when present in at least two anatomically contiguous leads:

- Pathologic Q waves (≥1 mm in depth and ≥0.3 s in duration).

– ST segment elevation or depression of 1 mm or more.
– Elevated or inverted T waves.

The ST segment and T wave abnormalities are not considered diagnostic in the case of left ventricular hypertrophy, left or right BBB, early repolarisation variant, pre-excitation syndromes or an implanted pacemaker [12]. Further suggestions can be added, which allow a more specific insight into the EKG interpretation:

– In case of BBB, remember that the vectorial sum of the QRS axis and T wave axis should normally stay between –20° and +80°; if it is outside this range it suggests acute ischaemia (the so-called ventricular gradient).
– A positive R wave in V1 that was not present before could suggest true posterior infarction (ultrasound [US] confirmation should always be sought).
– A negative T pattern in V1–3 is normal only if the negativity in V1 is greater than that in V3; otherwise it strongly suggests anteroseptal ischaemia (the so-called decremental gradient).
– The upward ST trend in acute pericarditis is never linked to any mirror image in the opposite leads.
– In aortic dissection the ECG can be normal or only minimally abnormal (ischaemia-like pattern) even with a severe clinical presentation.
– In persons with implanted pacemakers, a suspicion of acute coronary events can be reinforced when previous ECG recordings are examined for comparison.
– Similar criteria can be applied in ischaemia or reinfarction affecting a previously necrosed myocardial zone and in BBB showing any deviation from the usual pattern.
– A transient T-wave-positive pattern in subjects whose previous ECG recordings have shown stable negative T waves (pseudonormalisation) strongly suggests acute ischaemia.
– Particular difficulty can be encountered with interpretation in some disorders of electrolyte metabolism: for example, anterior ischaemia must be suspected if normal or simply flat T wave is registered in the setting of acute hyperkalaemia.
  The last suggestions about suspected myocardial ischaemia are probably obvious, but they are very useful in the clinical field.
– Trust in the 'modifying' pattern: if a doubtful repolarisation is changing while the patient is being monitored, with or without specific therapy; there is very probably an ischaemic substrate.
– If in doubt, trust in hospitals. If the clinical aspect is getting worse, even if the ECG is still normal it is better to admit the patient.

ST segment elevation in conditions other than acute myocardial infarction

In a recent study of normal ECGs from 529 men, the prevalence of ST segment elevation of at least 1 mm in one or more of leads V1–4 was 93% in men aged 17–24 years [13], declining gradually with increasing age; about 20% of women have the same pattern regardless of age. Especially in black men, the ST segment is

elevated by 1–4 mm in the midprecordial leads as a normal variant (so-called early repolarisation). Moreover, in younger men (Fig. 3) the ST segment may be elevated in combination with a T-wave inversion as a normal variant [14].

In acute pericarditis the ST segment elevation is usually diffuse, without any mirror image, if the pericarditis is diffuse, which is a substantial difference from the ST elevation in acute myocardial infarction (AMI). This rule does not apply when the pericarditis is localised.

Since 1956 [15] the ST elevation in hyperkalaemia, which sometimes resembles pericarditis or AMI, has been familiar; interestingly, there are often other features of hyperkalaemia, such as tall T waves, widened QRS complexes and low-amplitude P waves or none at all.

In 1992, Brugada and Brugada described eight patients with a history of cardiac arrest, RBBB and ST elevation in the right precordial leads in the absence of long QT interval and structural heart disease [16, 17]; the disease is probably due to a mutation of the cardiac sodium-channel gene.

Features of pulmonary embolism sometimes seen are: inverted T waves in the right precordial leads, ST elevation in both anteroseptal and inferior leads, S1Q3T3 pattern and complete or incomplete RBBB [18].

The ST segment can be transiently elevated after transthoracic cardioversion [19]. This pattern usually normalises within 3 min.

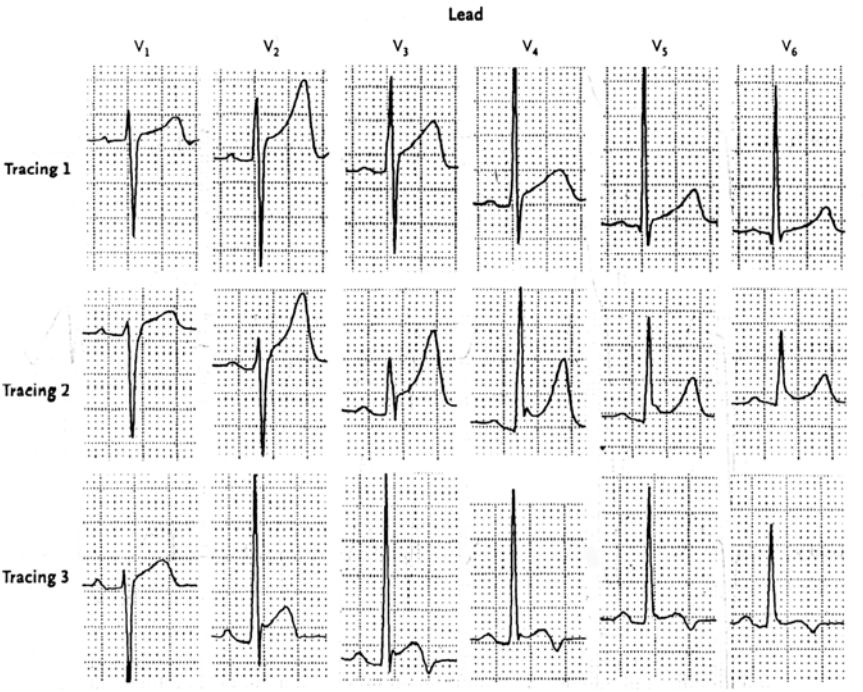

Fig. 3. Three 'normal' repolarisation patterns possible in young people (From [9])

Sometimes an epicardial artery is 'pinched off' as a result of spasm, reflecting transmural ischaemia. There are no specific and reliable ECG features allowing differentiation of this transitory elevation from the more persistent elevation attributable to AMI [20]: thus, this 'Prinzmetal angina' is only distinguishable because it is very quick to resolve spontaneously.

Knowledge of these 'other' causes of ST elevation is mandatory for an ED doctor, as 'time is muscle', but reperfusion therapies could be dangerous if they are not appropriate (Table 2).

Table 2. ST segment elevation in normal circumstances and in various pathologic conditions (from [10])

Condition	Features
Normal (so-called male pattern)	Seen in approximately 90% of healthy young men; therefore, normal Elevation of 1–3 mm, most marked in V2 Concave
Early depolarisation	Most marked in V4, with notching at J point Tall, upright T waves Reciprocal ST depression in aVR, and not in aVL, when limb leads are involved
ST elevation of normal variant	Seen in V3–5 with inverted T waves Short QT, high QRS voltage
Left ventricular hypertrophy	Concave Other features of left ventricular hypertrophy
Left bundle branch block	Concave ST segment deviation discordant from QRS
Acute pericarditis	Diffuse ST segment elevation Reciprocal ST segment depression in aVR, and not in aVL Elevation seldom >5 mm PR segment depression
Hyperkalaemia	Other features of hyperkalaemia present: Widened QRS and tall, peaked, tented T waves Low-amplitude or absent P waves ST segment usually downsloping
Brugada syndrome	rSR' in V1 and V2 ST segment elevation in V1 and V2, downsloping
Pulmonary embolism	Changes simulating MI, seen often in both inferior and anteroseptal leads
Cardioversion	Striking ST segment elevation, often >10 mm, but lasting only 1–2 min immediately after DC shock
Prinzmetal angina	Same ST segment elevation as in AMI, but transient
Acute myocardial infarction	ST segment with a plateau or shoulder or upsloping Reciprocal behaviour between aVL and 3

A look at the 'Cinderella' lead: aVR

Recently some authors have focused their attention on the usually neglected aVR lead [21]. They studied the Holter recording of the 12 standard leads in 30 consecutive patients with symptoms of AMI and ST segment elevation in the inferior ECG leads; what they found was interesting: that it is useful to measure the presence and degree of ST segment elevation or depression 0.06 s after the J point. Moreover, the degree of ST segment depression could help to identify the right coronary artery or the left circumflex coronary artery as the culprit.

Essentials in EKG interpretation in patients with PMK

The two main functions of pacing are 'sensing' and 'capture'. If the PMK spikes seem not to be influenced by the residual spontaneous myocardial activity (e.g., the 'spike-to-spike' interval is always the same, even after any extrasystole), one should first increase the sensitivity and then try to achieve repositioning of the PMK. Sometimes intermittent 'malsensing' can happen owing to partial catheter dislodgement. Sometimes a peak T wave can generate sufficient voltage to be misinterpreted by the sensing system as a QRS complex. Such 'oversensing' will result in suppression of PMK activity.

The failure most commonly not captured is dislodgement of the catheter. Catheter dislodgement may or may not be seen on radiographs, depending on the degree of catheter displacement (a good tip is to observe the magnitude of the PMK deflection (spike): when the magnitude is adequate, failure of capture usually indicates catheter dislodgement; otherwise a voltage increase should be attempted. Obviously, as the PMK tip is usually located near the apex of the right ventricle the expected ECG pattern is that of LBBB with significant left axis deviation.

If any ACS occurs in a 'paced' patient, correct interpretation of the ECG is usually possible only in serial recordings [22].

References

1. American Heart Association (2000) Guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation (Suppl) 102:122-159
2. European Resuscitation Council (2000) Advanced life support manual 2001. Resuscitation Council (UK)–ERC pp 95-105
3. Rosen MR (2002) The electrocardiogram 100 years later: electrical insights into molecular messages. Circulation 106:2173-2179
4. Yue P, Atwood JE, Froelicher V (2003) Watch the P wave. Chest 124:424-426
5. Song J, Kalus J, Caron M et al (2002) P-wave duration and dispersion in patients with decompensated heart failure. Pharmacotherapy 22:564-568
6. Baljepally R, Spoddick DH (1999) Electrocardiographic screening for emphysema: the frontal plane P axis. Clin Cardiol 22:226-228

7. Lasser KE, Allen PD, Woolhandler SJ et al (2002) Timing of new black box warnings and withdrawals for prescription medications. JAMA 287:2215-2220
8. Roden DM (2004) Drug-induced prolongation of the QT interval. N Engl J Med 350:1013-1022
9. Wang K, Asinger RW, Marriott HJL (2003) ST-segment elevation in conditions other than acute myocardial infarction. N Engl J Med 349:2128-2135
10. Hiss RG, Lamb LE, Allen MF (1960) Electrocardiographic findings in 67,375 asymptomatic subjects. Am J Cardiol 6:200-231
11. Madias JE, Sinha A, Agarwal H et al (2001) ST-segment elevation in leads V1-V3 in patients with LBBB. J Electrocardiol 34:87-88
12. Ausubel K, Furman S (1985) The pacemaker syndrome. Ann Intern Med 103:420-429
13. Surawicz B, Parikh SR (2002) Prevalence of male and female patterns of early repolarization. J Am Coll Cardiol 40:1870-1876
14. Goldman MJ (1953) ST segment elevation in the mid and left precordial leads as normal variant. Am Heart J 46:817-820
15. Levine HD, Wanzer SH, Merrill JP (1956) Dialyzable currents of injury in potassium intoxication resembling acute myocardial infarction or pericarditis. Circulation 13:29-36
16. Alings M, Wilde A (1999) "Brugada" syndrome: clinical data and suggested pathophysiological mechanism. Circulation 99:666-673
17. Wilde AA, Antzelevich C, Bjerregaard P et al (1999) The Brugada syndrome: clinical, electrophysiologic and genetic aspects. J Am Coll Cardiol 33:5-15
18. Ferrari E, Imbert A, Chevalier T et al (1997) The ECG in pulmonary embolism: Chest 111:537-543
19. Kok LC, Mitchell MA, Haines DE et al (2000) Transient ST elevation after transthoracic cardioversion in patients with hemodynamically unstable ventricular tachyarrhythmias. Am J Cardiol 85:878-881
20. Prinzmetal M, Kennamer R, Merliss R et al (1959) A variant form of angina pectoris: preliminary report. Am J Med 27:375-388
21. Nair R, Glancy DL (2002) ECG discrimination between right and left circumflex coronary arterial occlusion in patients with acute inferior myocardial infarction. Chest 122:134-139
22. Brady WJ, Perron A, Ullman E (2000) Errors in emergency physician interpretation of ST-segment elevation in emergency department chest pain patients. Acad Emerg Med 7:1256-1260

Chapter 4

The use of imaging to resolve difficult diagnoses

V. Cioffi, L. Calderan, M. Cova

The increasing complexity in treating the intensive care patient combined with recent advances in imaging technology has generated a new perspective on intensive care radiology [1]. This new technology allows a diagnosis in a shorter period of time and with increased accuracy; therefore it can be used to identify particularly difficult conditions. In this article, we focus on the contribution of imaging to the management of the intensive care unit (ICU) patient with lung disease.

It is important to underline that appropriate clinical information is fundamental in the choice of diagnostic imaging modality and technical approach. The capability of diagnostic imaging consists in the direct detection of injuries that are often occult, such as pericardial haemorrhage, major thoracic vascular injuries, small pneumothorax and diaphragm tears, as well as the ability to better define the extent and pattern of other pathological features, such as pulmonary oedema, embolism and parenchyma consolidation.

The clinical evaluation of the intensive care patient relies on imaging, and the portable chest radiograph remains the most commonly requested radiographic examination. Studies have shown that up to 65% of daily radiographs in the ICU reveal significant or unsuspected abnormalities that may lead to a change in the patient's management [1, 2]. However, specific conditions requiring further evaluation with computed tomography (CT) are occasionally highlighted [2–5]. Several studies reported that 70–75% of CT examinations provided clinically important information leading to a change in the management of 20–25% of patients [5].

Pulmonary oedema

In the ICU patient, pulmonary oedema due to heart failure (hydrostatic oedema) or major capillary endothelial or alveolar epithelial injury (permeability oedema) is a frequent diagnostic and therapeutic problem [6].

Under normal conditions, there is a continuous movement of fluids at the alveolocapillary level between the intravascular compartment and the extravascular interstitial space. Fluid moves out of the vessels under the effect of the hydrostatic pressure at the arteriolar level, and back into the vessels at the venular side under the effect of the oncotic pressure. Usually, between the two pressures there is a slight imbalance that favours a net movement of water toward the interstitium.

This water is physiologically removed through the lymphatics, which facilitate its transfer toward the bloodstream. The entire process requires the presence of an intact membrane at the alveolocapillary level [2].

When the pulmonary capillary wedge pressure (PCWP) rises, the extravascular lung water (EVLW) also rises, accumulating in the interstitium and subsequently flooding the alveoli. This condition is called hydrostatic pulmonary oedema. Because the paradigm of this oedema is observed during cardiac failure, hydrostatic pulmonary oedema is also known as cardiogenic pulmonary oedema (CPE). Pulmonary oedema can also occur after injuries acting at the level of the alveolarcapillary barrier, producing a disruption in the membrane. In this condition, the membrane becomes more permeable to the fluids that move from the vascular compartment directly into the alveoli and thus an oedema, called injury oedema, permeability oedema or non-cardiogenic pulmonary oedema (NCPE), is produced. In this circumstance, cardiac function can be normal. It is important to remember that CPE and NCPE can be present at the same time, or one after the other, in the same patient when conditions for their presence occur at the same time. CPE is the oedema of the patients with left ventricular failure of any origin; NCPE is the oedema of ARDS (acute respiratory distress syndrome), a generic term for conditions that result when a lung is damaged by different pathological noxae coming to it either from the bronchi or from the vessels, or because of a direct injury (i.e. trauma) [2, 7].

Air-borne ARDS is induced following the inhalation of toxic fumes and gas, near-drowning, or aspiration of gastric acid. Vessel-borne ARDS follows fat embolism, the dissemination of endogenous toxins or products of necrosis, as in acute pancreatitis, septic conditions or after massive blood transfusions [2].

The chest radiograph is sensitive for the detection of pulmonary oedema but relatively aspecific in differentiating cardiogenic from noncardiogenic oedema. Aberle et al. [8] reported that only 87% of patients with hydrostatic oedema and 60% of patients with permeability oedema could be correctly identified. Both types of oedema manifest as lung opacities that should always be interpreted under clinical guidance, but they also often have very different radiological appearances [2].

The earliest manifestation of CPE on chest radiography is ground-glass opacity, which causes the pulmonary vessels to become indistinct, usually beginning symmetrically in the dependent regions of the lower lobes and the perihilar location. Peribronchial cuffing with septal thickening may be a concurrent finding that is helpful in identifying a hydrostatic component to the oedema [7]. The chest X-ray initially shows thickening of the interlobular septa, the well known Kerley lines (often type B), and subpleural thickening due to accumulation of fluid within the subpleural connective tissue. Eventually, homogeneous confluent gravitational opacities without air bronchogram, which tend to become increasingly homogeneous as the oedema increases, can be seen [2, 9]. All the radiographic signs can change quite rapidly either during worsening of the oedema or, more slowly, when there is regression after therapy.

In ARDS, the radiographic findings follow a predictable course that reflects the

underlying histopathology [5]. The initial radiograph is usually normal; nevertheless, it is useful to exclude the presence of pneumothorax, atelectasis, or pleural effusion as the reasons for respiratory distress. In this phase, which lasts only minutes or hours, there is only diffuse microatelectasis, with some alveoli filled with fluid, while others are simply collapsed. The only visible sign is a diffuse reduction of the lung volumes and this sign, together with the absence of other aspects, is very peculiar for the early phase of ARDS [2, 5, 10, 11]. Within 12-24 h, clinical parameters worsen, with cyanosis, oxygen-resistant hypoxaemia and respiratory failure. The radiological aspect ranges from a slight pulmonary diffuse haziness to multiple, not confluent, bilateral parenchymal patchy opacities spreading from the apex through the lung base, often with air bronchogram. Usually, neither pleural effusion nor heart enlargement nor flow redistribution are identifiable [10, 11].

The progression of the disease is not identical in all patients; some of them recover with "restitutio ad integrum" within a few days. In these subjects, a progressive reduction in the number and density of the parenchymal opacities is observed, whereas in other patients focal areas of interstitial fibrosis and honeycomb aspect can be observed (end-stage lung). Sometimes, during recovery, there are episodes of relapsing disease, that are related, for example, to the new release of toxins. When this happens, chest radiograph shows a worsening of the opacities. From the pathological point of view, cylindrical or cubic pneumocytes coat the alveolar walls, accompanied by variable degrees of interstitial and alveolar inflammation and fibrosis. These manifestations are responsible for a reticular aspect on the radiograph in 20% of patients [12].

The radiological evaluation of the chest during the acute phase of the disease should be made taking into account the parameters of ventilation (particularly PEEP) that can produce alveolar overinflation and thus only an apparent improvement of the radiological opacities [11, 13].

The reason for this different presentation is that hydrostatic oedema consists of water at low viscosity and therefore freely and continuously flowing throughout the interstitium according to the law of gravity (the reason why the opacities predominate in the lower lungs in the half-sitting patient) and to the osmotic gradient, which increases from the periphery to the central lung (which explains the vascular blurring, hilar haze, and bronchial cuffing). For the same reason, the fluid can also fill the bronchi, which are not recognisable within the opacities (absence of air bronchogram).

Injury oedema, by contrast, is a high-viscosity fluid that contains proteins, fibrin, and other material, and thus not flow as easily throughout the interstitium and through the bronchial lumen. This accounts for the presence of an air bronchogram, which appears as a pattern of patchy opacities scattered more or less homogeneously throughout the lungs [2].

The presence of patchy air-space opacification is the most specific sign for differentiating between two patterns of oedema, and occurs in 58% of patients with increased permeability oedema compared with only 13% with hydrostatic oedema. Milne and Pistolesi [14] suggested that hydrostatic pulmonary oedema can be reliably and consistently differentiated from permeability oedema, but knowledge

of the technical factors used in acquiring the portable radiograph is needed for the interpretation. These factors include patient positioning, ventilatory parameters, and film-to-target distance, information that is not commonly available [1].

Although CT is not seldom used to diagnose pulmonary oedema, an awareness of the appearance of this condition on CT is helpful in validating some of the physiologic concepts behind oedema formation and understanding aspects of the radiograph. In patients with hydrostatic oedema, CT findings are similar to those in the radiograph, but the former is more sensitive to early changes [7]. The arteries and veins enlarge and the nondependent vessels enlarge disproportionately ("cephalisation"). Interstitial oedema causes thickening of the interlobular septa (Kerley lines), of the subpleural connective tissue space, and of peribronchovascular connective tissue. The ventral-dorsal density gradient increases with time, probably because of the hydrostatic distribution of oedema and the weight of the ventral lung on the dorsal lung. The distribution of the pulmonary oedema can be altered by patient positioning due to the effects of gravity and by underlying lung disease. Alveolar oedema presents as dense air-space opacification depending on the amount of gas displaced by the oedema and atelectasis. Pleural and pericardial effusion as well as subpleural fluid are more easily diagnosed on CT [1, 6].

Hydrostatic oedema could be absent in the presence of other concomitant lung disease. Chronic obstructive pulmonary disease (COPD), for example, is well known to minimise oedema in underperfused areas and to shift oedema to more normally perfused areas. Zwikler et al. [15], using CT, have shown that pulmonary oedema in experimental animals with pulmonary fibrosis causes less change in lung density in the fibrotic areas than in the apparently normal zones of the lung [6].

Also, in patients with ARDS, CT plays a role in management and provides a better understanding of the disease process. The air-space opacification was originally thought to uniformly involve the lungs. Maunder et al. [16] showed that, despite the extensive abnormality demonstrated on chest radiograph, many areas of the lung appear relatively normal on CT. The CT typically shows patchy areas of air-space opacification of varying density, diffusely but not uniformly distributed throughout the lungs. In the early exudative phase, there is no gravity or central dependence to the air-space opacification; this later becomes more confluent, and gravity-dependent atelectasis develops with a cephalocaudal and dorsal ventral gradient. Cardiac failure, aspiration, and pneumonia can also demonstrate a gravity-dependent distribution to the air-space opacification, but in these conditions, a slow or negligible shift in consolidation occurs with positional change, unlike in ARDS where redistribution is observed in minutes with prone positioning.

Tagliabue et al. [17] reported the CT findings in 74 patients with various stages of ARDS. In the majority of patients, the pulmonary opacities were bilateral, patchy, and associated with bronchograms. Only 25% of the opacities were homogenous in appearance, and 27% were a combination of ground-glass opacification and more dense consolidation. Pleural effusions were common but typically limited. ARDS may be distinguished from cardiac failure by the absence of pulmonary vessel enlargement as well as a redistribution and lack of prominence of interlobular septal thickening [5, 6].

CT plays a role in detecting complication of ARDS, such as bacterial pneumonia, that may otherwise be missed. These pathologies are usually diagnosed post-mortem in up to 70% of patients who die of ARDS. The diffuse air-space consolidation of ARDS frequently obscures the radiographic abnormalities due to pneumonia. On CT, the regions of dense nondependent parenchymal opacification are thought to represent areas of organising pneumonia. In a CT study evaluating ventilator-associated pneumonia in ARDS patients, nondependent opacities were more common in patients with pneumonia than is those without infection. Goodman et al. [10] observed that dense consolidation was more extensive in patients with pulmonary ARDS, while ground-glass opacification predominated in the extra-pulmonary group. Desai et al., however, found that individual CT patterns did not distinguish between the two groups [5].

Other aspects frequently observed on CT in patients with ARDS are bronchiectasis, subpleural cysts and bullae. These latter patterns typically appear after the first week. The development of cysts is highly correlated with prolonged ventilation. The cysts vary in size from few millimetres to several centimetres and are more common at the lung bases and in other areas of dense parenchymal consolidation and may persist for many weeks [5–7].

CT also provides a practical method of evaluating extravascular lung water. Assuming that the density value of 1000 HU corresponds to pure air with no tissue and that 0 HU corresponds to 100% water, CT densitometry and area calculations can be used to determine lung water, weight, density etc., for normal and diseased lungs [6].

Magnetic resonance imaging (MRI) has also been used successfully to evaluate the lung water content both qualitatively and quantitatively. These properties can be used to characterise the microvascular barrier function within the lung. In hydrostatic pulmonary oedema in rats, the T1 relaxation time was significantly longer than in normal controls, whereas the T2 relaxation time was not different. In permeability pulmonary oedema, however, T1 and T2 relaxation times were significantly longer than in normal controls. Using a three-dimensional gradient-echo sequence, which is sensitive to water, the entire lung can be covered with a spatial and temporal resolution sufficient to observe the development of pulmonary oedema in an experimentally induced ARDS. The results indicate that oedema formation can be imaged regionally and quantified globally, estimating the mismatch between transcapillary filtration flow and lymph clearance. Although some MRI diagnostic approaches are already in use, the use of this technique in the diagnosis of pulmonary oedema has not been established in clinical routine [18].

Pneumothorax

Pneumothorax is a potentially life-threatening complication in the ICU, particularly for patients receiving mechanical ventilation. Some studies [19] demonstrated that the mortality rates were significantly different in patients with pneumothoraces of various aetiologies. Complicating tension pneumothorax and concurrent

septic shock were also related to a higher risk of mortality. Most pneumothoraces in the ICU fall into two categories: (1) pneumothorax secondary to barotrauma and (2) traumatic pneumothorax due to thoracic procedures, blunt chest trauma or penetrating chest trauma [5, 19–23]. The majority of pneumothoraces that occur in the ICU are procedure-related, especially thoracentesis and central venus catheter placement [5, 19].

Barotrauma due to mechanical ventilation is considered to be another major cause of pneumothorax in critically ill patients. The incidence of pneumothorax in the ventilated patients varies from 4 to 15% [5]. Often, patients with pneumothorax due to barotrauma have associated lung diseases, such as pneumonia, COPD, lung cancer and ARDS [5, 19]. Alveolar overdistention is likely to be the main factor influencing the escape of alveolar gas. Structural injury, depletion or inactivation of surfactant, and the stress of repetitive expansion are other factors that might play a role in barotrauma, and may explain the correlation between pneumothorax and underlying lung diseases. Tension pneumothorax is another important complication associated with death. Pneumothorax due to barotrauma or tissue necrosis might be associated with delayed healing of the pleural defect because of underlying lung disease. Patients with tension pneumothoraces or pneumothorax due to barotrauma have a higher risk of mortality, and early investigation by physical examination or chest radiography may be necessary to improve their prognosis [19].

The radiological signs of massive pleural air collection, flattening of the cardiac border, contralateral shift in the mediastinum, and depression of the diaphragm can suggest a tension pneumothorax also in the presence of a pleural drainage tube. However, the size of the pneumothorax can correlate poorly with its clinical significance, and the radiologist should better recognise the initial, more subtle signs of baro-and volotrauma before the occurrence of their more harmful consequence. This awareness is of utmost importance in ventilated patients, in trauma subjects with pulmonary lacerations, and in patients with emphysema and bullae. The radiological diagnosis of a small pneumothorax may not be easy because air tends to collect at the base of the thorax within the anterior costophrenic sulcus (which is the highest portion of the thorax in supine patients) and in the subpulmonary recess more than at the apex, where it would be more easily recognised. The alerting signs are the presence of unexplained basilar lucencies at low chest level with diaphragmatic and heart profiles too clearly recognisable, the visibility of the anterior costophrenic sulcus projected with inferior convexity over the right or left upper quadrant, and, often, the lateral costophrenic sulcus deeper and more lucent than normal. Other classic signs include an increased sharpness of the mediastinal lines, more recognisable distribution of pleural air occurring in the presence of lower atelectasis because air is forced to also collect posteromedially, and a sharper visualisation of the azygos vein, the supradiaphragmatic inferior vena cava, and the mediastinal posterior recesses. When in doubt, it is relatively easy, even in uncooperative subjects, to perform a cross-table lateral chest X-ray or an AP view with the patient lying on the contralateral side. This manoeuvre allows the detection of very tiny collections of air within the pleural space [2, 3, 5, 21, 22, 24].

In the presence of a densely consolidated lung or severe chronic lung disease, the radiographic appearance and distribution of a pneumothorax will be altered. In these patients, the lung will often collapse in a nonuniform manner, and areas of aerated lung may cause the appearance of lung markings lateral to the pleural margin. A posteromedial pneumothorax is associated with lower lobe pathology, with air preferentially surrounding the medial aspect of the collapsed lobe. This appearance may resemble pneumomediastinum as pleural air contours the posterior mediastinal structures. Differentiation relies on identification of mediastinal air tracking into the abdomen. In patients with pleural adhesions, the pneumothorax may be located in an unusual site [5].

Lung collapse and mediastinal displacement are seen both in a simple pneumothorax and in a tension pneumothorax. Flattening of the cardiac border and of the superior vena cava is the most specific radiographic sign of a tension pneumothorax and reflects the impaired venous return to the heart. Inversion of the diaphragm, unilateral increase in the rib interspace, and displacement of the azygo-oesophageal line are supportive features. In patients with severe lung disease, particularly in ARDS, the radiological signs of a tension pneumothorax may not be obvious. Any new hyperlucency seen in the chest radiograph of a rapidly deteriorating ventilated ARDS patient should be considered a pneumothorax until proven otherwise by CT [5].

Unfortunately, the supine chest radiograph misses 20–40% of pneumothoraces. A delayed pneumothorax (>24 h post-injury), particularly in blunt chest trauma, develops in approximately 3% of patients [25].

In the acutely injured patient, supine chest X ray is often obtained because the patient cannot be placed in an upright position. In the supine patient, free air in the pleural space accumulates in the anteromedial and subpulmonary recesses which are the least dependent portions of the pleural cavity [26, 27]. Tocino [28] found that up to 30% of pneumothoraces are not detected on supine films because of difficulty in visualising these areas. CT is more accurate in the detection of pneumothoraces than supine or erect chest radiography and will show smaller amounts of air. Pneumothoraces seen only on CT have been called "occult" [26, 29]. It is important to remember that subcutaneus emphysema on chest X-ray can obscure underlying pneumothorax, and sometimes even relatively large pneumothoraces are not detected [29]. Moreover, the size of the pneumothorax and the position of a chest tube are poorly determined from a chest X-ray. Engdahl et al. [30] studied both a patient group and an artificial lung model and found that chest X-ray examination of the size of a pneumothorax correlates neither with the size measured on CT nor with the amount of air aspirated at the time of chest tube insertion. This is easily explained by the fact that the lung does not collapse uniformly and therefore must be viewed in three dimensions. Kerns and Gay [31] illustrated that chest X-ray identifies only 5% of malpositioned chest tubes and therefore recommended CT as a more accurate modality.

Wolfman et al. [29] devised a classification that divides pneumothoraces seen on CT into three subgroups: (1) minuscule (<1 cm in greatest thickness), (2) anterior (>1 cm in greatest thickness, but not extending beyond the midcoronal

line) and anterolateral (extending beyond the midcoronal line). The authors suggested the use of this classification system in determining whether a pneumothorax seen on CT should be initially treated with percutaneus tube thoracostomy or whether the patient should only be observed without definitive treatment. Patients with a small pneumothorax, as shown by CT, were managed without percutaneous tube thoracostomy; none developed complications. Management of anterior pneumothorax not extending beyond the midcoronal line depends on the clinical situation, while anterolateral pneumothoraces, extending beyond the midcoronal line, are always treated with a percutaneous thoracostomy tube [29].

References

1. Trotman-Dickenson B (2003) Radiology in the intensive care unit (part I). Intensive Care Med 18:198-210
2. Maffessanti M, Berlot G, Bortolotto P (1998) Chest roentgen logy in the intensive care unit: an overview. Eur Rad 8:69-78
3. Mirvis SE (2004) Diagnostic imaging of acute thoracic injury. seminars in ultrasound, CT, and MRI 25:156-179
4. Omert L, Yeaney WW, Protetch J (2001) Efficacy of thoracic computerized tomography in blunt chest trauma. Am Surg 67:660-664
5. Trotman-Dickenson B (2003) Radiology in the intensive care unit (part 2). Intensive Care Med 18:239-252
6. Goodman LR (1996) Congestive heart failure and adult respiratory distress syndrome. New insights using computed tomography. Intensive Care Radiolgy 34:33-46
7. Nowers K, Rasband JD, Berges G, Gosselin M (2002) Approach to ground-glass opacification of the lung. Seminars in Ultrasound, CT, and MRI 23:302-323
8. Aberle DR, Wiener-Kronish JP, Webb WR et al (1988) Hydrostatic versus increased permeability pulmonary oedema: diagnosis based on radiographics criteria in critically ill patients. Radiology 168:73-79
9. Fraser RG, Muller NL, Colman, Parè PD (1999) Pulmonary hypertension and oedema. In: Diagnosis of diseases of the chest. Saunders, Philadelphia
10. Goodman LR, Putman C (1983) Intensive care radiology: imaging of the critically ill. Saunders, Philadelphia
11. Maffessanti M, Bortolotto P, Berlot G (1991) L'esame radiologico del torace nella terapia intensiva. Radiol Med 82:107-117
12. Maffessanti M, Pirronti T, Pistolesi M (1988) Diagnosi radiologica dell'oedema polmonare. In:aggiornamento professionale continuativo SIRM (ed) Radiologia Toracica quattro. Apollonio, Brescia, pp 47-62
13. Zimmermann JE, Goodman LR, Shahvari MBG (1979) effect of mechanical ventilation and positive end-expiratory pressure PEEP on chest radiograph. AJR 133:811-815
14. Milne ENC, Pistolesi M (1999) Reading the chest radiograph. A physiologic approach. CV Mosby, St. Louis
15. Zwikler MP, Peters TM, Michel RP (1994) Effects of pulmonary fibrosis on the distribution of oedema: computed tomographic scanning and morphology. Am J Respir Crit Care Med 149:1266
16. Maunder RJ, Shuman WP, McHugh JW et al (1986) Preservation of normal lung regions

in the adult respiratory distress syndrome: analysis by computed tomography. JAMA 255:2463-2465
17. Tagliabue M, Casella TC, Zincone GE et al (1994) CT and chest radiography in the evaluation of adult respiratory distress syndrome. Acta Radiologica 35:230
18. Kauczor HU, Kreitner KF (1999) MRI of the pulmonary parenchyma. Eur Radiol 9:1755-1764
19. Kuan-Yu C, Jih-Shuin J, Wei-Yu L et al (2002) Pneumothorax in the ICU patient outcomes and prognostic factors. Chest 122:678–683
20. Gavelli G, Canini R, Bertaccini P et al (2002) Traumatic injuries: imaging of thoracic injuries. Eur Radiol 12:1773-1294
21. Wicky S, Wintermark M, Schnyder P et al (2000) Imaging of blunt chest trauma. Eur Radiol 10:1524-1538
22. Reuter M (1996) Trauma of the chest. Eur Radiol 6:707-716
23. Wolfman NT, Gilpin JW, Bechtold RE et al (1993) Occult Pneumothorax in patients with abdominal trauma:CT studies. J Comput Assist Tomogr 17:56-59
24. Zinck SE, Primack SL (2000) Radiographic and CT findings in blunt chest trauma. J Thoracic Imaging 15:87-96
25. Mayberry JC (2000) Imaging in thoracic trauma: the trauma surgeon's perspective. J Thoracic Imaging 15:76-86
26. Marts B, Durham R, Shapiro M et al (1994) Computed tomography in the diagnosis of blunt thoracic injury. Amer J Surg 168:688-692
27. Hill SL, Edmisten T, Holtzman G et al (1999) The occult pneumothorax: an increasing diagnostic entity in trauma. Amer Surgeon 65:254-258
28. Tocino IM, Miller MH, Fairfax WR (1985) Distribution of pneumothorax in the supine and semirecumbent critically ill adult. AJR 144:901-905
29. Wolfman NT, Gilpin JW, Bechtold RE et al (1993) Occult pneumothorax in patients with Abdominal Trauma: CT Studies. J Comput Assist Tomogr 17:56-59
30. Engdahl O, Toft T, Boe J (1993) Chest radiograph: a poor method for determining the size of a pneumothorax. Chest 103:26-29
31. Kerns SR, Gay SB (1990) CT of blunt chest trauma. Am J Radiol 154:55-60

Chapter 5

Assessment of pain

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Effective pain relief is very important not only for humanitarian and ethical reasons, but also in order to avoid postoperative complications and to obtain a faster recovery from surgery and an earlier discharge from hospital. Good pain management in the peri- and postoperative period helps to ensure the best outcome for the patient [1].

Pain relief per se does not significantly improve postoperative outcome, with the exception of patient satisfaction and pulmonary complications. Thus, postoperative morbidity and hospital stays are dependent on multiple factors, including preoperative information, quality of analgesia and existing programs for postoperative care and rehabilitation, including orders for mobilisation, oral nutrition and discharge criteria [2].

Surveys in the 1980s showed that as high as 30-70% of patents received inadequate pain treatment [3, 4]. Most patients, physicians, surgeon and nurses still consider moderate to severe pain to be an acceptable consequence of surgical interventions.

The key points for improving acute pain management are: (1) safe and simple analgesic methods, in order to accommodate increasing demands of quality assurance in pain and patient satisfaction; (2) regular pain assessment and documentation; (3) evidence-based decision making; (4) appropriate choice of drugs and their route, mode of delivery and (5) an interdisciplinary approach to the post-surgical patient.

Acute pain service

The recognition that unrelieved pain contributes to preoperative morbidity and mortality has led many institutions to develop an Acute Pain Service (APS) in an attempt to provide effective postoperative relief. Immediate and sustained formal support for APSs and the recommendations of various medical and health care organisations, has promoted their widespread introduction [5-15]. The introduction of APSs has led to the successful and safe implementation of multi-modal pain management strategies [16] and an increase in the use of specialised pain relief methods, such as patient-controlled analgesia (PCA) and epidural infusions of local anaesthetics/opiod mixtures, in surgical wards. These methods represent real advances in improving patient well-being and reducing postoperative morbidity

[1, 17]. Furthermore, provision of an APS is presently a prerequisite for accreditation for training by the Royal College of Anaesthetists and the Australian and New Zealand College of Anaesthetists. In-service education and training is another important aspect of the APS. The introduction of an APS into a hospital leads to improved knowledge and understanding of pain assessment and control by both staff and patients. Education of the patients and their families at the time of the pre-anaesthetic evaluation is pivotal in facilitating the optimal care of patients, who should be fully informed preoperatively about the range of treatments available and their adverse effects [18]. Patient ignorance and fear of what to expect with regard to postoperative pain and its control can increase both patient dissatisfaction and the degree of pain experienced in the postoperative period. A proportion of patients may not wish to be faced with options but would instead welcome guidance on the best form of pain control available. For those patients who wish to receive information, the discussion should include what pain to expect, what treatment is available for pain and nausea or vomiting, and its risks and side effects. Patient awareness of pain and the ability to control pain are important components of pain assessment.

The Association of Anaesthetists guidance on risk management [19] recommends the provision of information leaflets or videos describing the process of anaesthesia, and it may be added that this should include advice on postoperative pain and emetic control.

The role of pain assessment

Pain is invisible on most hospital wards. Severity of pain is not assessed and consequently cannot be effectively treated. The intensity of postoperative pain after surgery is often under-estimated and therefore under-treated by healthcare providers.

One of the key points in improving postoperative pain is to introduce pain assessment as the fifth vital sign (after temperature, pulse, blood pressure and respiratory rate). Monitoring the management of postoperative pain is important to ensure its safety and effectiveness. There is solid consensus [20] that acute pain and the effects of its management (the patient's verbal ratings of pain, the nurses' rating of sedation, and the breathing rate) should be recorded routinely along with the other postoperative vital signs. An educational programme specifically for nurses strongly increases the use of regular pain assessment and may contribute to an improvement in postoperative analgesia [21].

Anaesthesiologists in collaboration with others should use pain assessment instruments to facilitate the regular evaluation and documentation of pain, the effects of pain therapy and side effects caused by the therapy. Pain score at rest and on movement, sedation level, blood pressure, breathing rate and urine output are all essential.

Pain should be assessed and documented: (1) preoperatively; (2) routinely at regular intervals postoperatively, as determined by the surgery and subsequent

severity of the pain; (3) with each new report of pain. Most important, the team should evaluate immediately each instance of unexpected intense pain, particularly if sudden or associated with oliguria or altered vital signs – such as hypotension, tachycardia, or fever – and consider new diagnoses including wound dehiscence, infection, or deep venous thrombosis. Not all observations need to be undertaken at the same frequency and no consensus exists regarding the optimal frequency of observations, which will be higher at first and then decrease over time.

Hospital guidelines describing the type and the frequency of observation to be performed and documented are necessary. The target for best practice should be that less than 7% of postoperative patients should experience a failure of analgesia in the first 24 h. In the absence of a nationally agreed upon pain scoring system, a score above 50% of the pain scale at two or more four-hourly recordings in the first 24 h constitutes a failure of analgesia [22].

Assessment of pain severity in adults

Postoperative pain is usually characterized by abrupt onset, variable intensity and duration of less than 7 days. It varies in different patients and even in the same patient over time. This variability depends not only on the pre-existing diseases, its location, and the type of surgery, but also and sometimes mainly on the factors resulting from the pain/tissue injury ratio, which is associated with cultural, religious, socio-economic and racial aspects and depends on the patient's history and his or her previous experience of pain.

Pain measurement is mandatory in the postoperative period to assess pain intensity, to control the efficacy of analgesic treatment and to ensure a confident relationship between the patient and the medical team [23]. Preoperative preparation of patients (and families, when appropriate) assists patients in understanding their responsibility in pain management.

A comprehensive approach to postoperative pain assessment requires evaluation of: patient perceptions, physiological responses, behavioural responses and cognitive attempts by the patient to manage pain. Physiological responses, such as heart rate, blood pressure, and respiratory rate, provide critical information in the immediate postoperative period. Once the patient has recovered from anaesthesia, the mainstay of pain assessment should be the patient's self-report to assess pain perceptions (including description, location, intensity-severity, and aggravating and relieving factors) and cognitive response. Patient self-report is the single most reliable indicator of the existence and intensity of acute pain and any concomitant affective discomfort or distress [5]. Neither behaviour nor vital signs can substitute for a self-report.

Self-assessment using unidimensional methods, which measure only the sensory component of the painful experience, has been validated in acute pain management; it reduces the risk of under- or over-assessment of pain by nurses.

Pain severity is usually assessed by using rating scales. These methods, either words or numbers, are simple and can be readily understood.

The visual analogue scale (VAS) is considered the gold standard method for postoperative pain assessment. It consists of a line, most often 100-mm long, with two descriptors representing extremes of pain intensity (e.g. no pain and the worst imaginable pain) at each end. Patients rate their pain intensity by making a mark somewhere on the line, and the VAS is scored by measuring the distance from the "no pain" end of the line. It has been shown to be reliable and valid and it is useful in assessing the degree of improvement following intervention. Nevertheless, in some clinical situations, this method may not be reliable [24]. The VAS is not easy to use in the immediate postoperative period because of residual anaesthesia, blurred vision, or nausea, and some patients may require additional instructions to complete the assessment. In using the VAS for treatment decision, or for the measurement of the effects of pharmacological interventions, it should be noted that this it has an imprecision of about +20 mm. The numerical rating scale (NRS) consists of a series of numbers ranging from 0 "no pain" and 10 (or 100) "the worst imaginable pain"; the patient chooses the number that best corresponds to the intensity of his or her pain. Another often-used measurement of postoperative pain is the five-point verbal rating scale (VRS). The patient reads a list of verbal pain descriptors and chooses one word (Table 1); a score is assigned to each descriptor (no pain=0, mild pain=1, moderate pain=2, severe pain=3, and unbearable pain=4).

Table 1. Verbal Rating Scale (VRS)

No pain	0
Mild pain	1
Moderate pain	2
Severe pain	3
Unbearable pain	4

For each of these scales, the clinician should request the patient's self-report, not only with the patient at rest but also during routine activity, such as coughing, deep breathing, or moving (e.g. turning in bed). Pain on movement may be recorded separately from pain at rest, being amenable to different types of treatment. Furthermore, the patient should be observed for behaviours that often indicate pain, such as splinting the operative site, distorted posture, impaired mobility, insomnia, anxiety, attention seeking, and depression. Questions like "where does it hurt?" and "what does it feel like?" may allow a qualitative evaluation of pain.

The use of a unidimensional quantitative scale is questionable in view of the belief, overwhelmingly supported by clinical experience as well as by empirical evidence from multidimensional scaling and other sources, that pain has at least two dimensions: sensory qualities and affect [25]. The patient's score on an unidimensional pain intensity scales reflects the emotional qualities of pain much more than its sensory intensity or other qualities. Accordingly, such scales may be poor indicators of analgesic requirement and patient's postoperative anxiety and depression may thus be inadequately treated.

Another issue concerns the clinical significance of a change in the VAS score. How much of a decrease is necessary before it is noticed by patients? How much is

necessary for such a change to be deemed significant and meaningful by the patient? Unfortunately, relatively little research has examined the question of clinical meaningfulness of changes in pain ratings. Some surveys suggest that a 33% decrease in pain represents a reasonable standard for determining that a change in pain is meaningful from the patient's perspective [26]. Occasionally, apparent discrepancies between behaviours and the patient's self-report of pain may occur. For example, patients may describe pain as having a score of 8 of 10 on a pain scale while smiling and walking freely, or as 2 out of 10, while tachycardic, splinting, and sweating. Discrepancies between behaviour and a patient's self-report may result from excellent coping skills. The patient who uses distraction and relaxation techniques may engage in diversionary activities while still experiencing severe pain. Patients may deny severe pain for a variety of reasons including fear of inadequate pain control or a perception that stoicism is expected or rewarded.

When discussing pain assessment and control with patients, members of the pain care team should emphasise the importance of a factual report, thereby avoiding both stoicism and exaggeration.

The multidimensional qualitative scales, such as McGill Pain Questionnaire (MPQ), Brief Pain Inventory (BPI) and Memorial Pain Assessment Card, evaluate pain more widely but require more time and are often difficult for the patient. The MPQ is a checklist of 82 items divided into 20 subclasses, describing the patient's symptoms, and it provides a quantitative profile of three mayor psychological dimensions of pain: sensory-discriminative, motivational-affective and cognitive-evaluative. It has been successfully employed to evaluate chronic post-surgical pain [27] but it is not routinely recommended for assessing acute postoperative pain, because it requires about 20 min to complete. In patients with acute pain, frequent and fast evaluations are mandatory to obtain a good quality of analgesia.

A psychologist's behavioural assessment of the patient, including the character and frequency of verbal complaints and an awareness of nonverbal complaints (moaning, grimacing, posturing), may be a helpful addition to psychological testing. A psychological interview helps evaluate the degree of psychological distress associated with the patient's pain.

Behavioural scales are helpful when a patient with cognitive defect or a residual anaesthesia cannot answer to or understand self-reporting scales but they are influenced by the patient's personality. Furthermore, they provide an indirect (objective) measurement of pain intensity, an under-estimation of pain intensity and have a poor correlation with direct (subjective) evaluation scales.

Patients unable to communicate effectively with staff require special considerations for pain assessment, e.g. neonates and children, developmentally delayed persons, psychotic patients, patients with dementia, and foreign patients. Children and cognitively impaired patients require simpler or modified pain measurements scales and assessment approaches (see section on pain in children). The staff should work with both the patient and parent or guardian pre- and postoperatively. Staff should endeavour to find a translator for the foreign patient, at least one, to determine a convenient way to assess pain.

Assessment of pain in children

It has been reported that the management of pain in children tends to be inadequate. It is now well established that failure to manage pain may have immediate deleterious physiological, biochemical and behavioural effects and longer-term consequences.

As with adults, pain assessment presents a mayor challenge. Several attempts have been made to develop observational scales that could be useful to assess pain in children. The Facial Pain Scale (Smiley Analogue Scale) is a self-evaluation unidimensional test available for children more than 5-years-old (Fig. 1). It consists of a series of faces with various expressions ranging from sad to happy. The child is asked to select the face that depicts how he or she feels. A colour Scale is also valid in younger children.

Behavioural scales are necessary in children less than 5 years of age because a self-evaluation test is usually impossible to perform. The Children's Hospital of Eastern Ontario Postoperative Scale (CHEOPS) is the most popular (Table 2) It is based on six items (crying, facial expressions, verbalisation, body posture, attempts to touch surgical wounds, legs' posture), with three or four points for every item. The total score ranges from 3 to 14 and is correlated with the intensity of pain.

Table 2. Children's Hospital of Eastern Ontario Pain Scale (CHEOPS)

Crying	None, moaning, crying, screaming
Facial	Composed, grimace, smiling
Verbal	None, other, pain, both, positive
Torso	Neutral, shifting, tense, shivering upright, restrained
Touch	None, reach, touch, grab, restrained
Legs	Neutral, squirming, drawn-up, standing, restrained

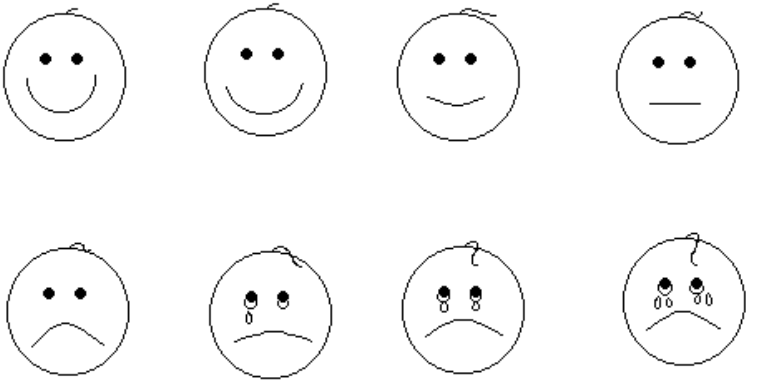

Fig. 1. Facial Pain Scale

The Comfort Behaviour Scale consists of six items (alertness, calmness, muscle tone, physical movements, facial tension and respiratory behaviour or crying) on a five-point scale ranging from 1 to 5 (total score ranging from 6 to 30). Physiological scales help to assess pain intensity and the effect of rescue therapy in releasing pain by monitoring vital signs (respiratory rate, heart rate, blood pressure).

Of all the nonverbal acute pain indicators, facial expression appears to be the most prominent. Not only do facial expressions differentiate pain from anger and sadness, for caregivers and nurses they are also more consistent and salient than crying, body movements or heart rate.

The importance of the face has been acknowledged in all multidimensional pain instruments. Neonatal Facial Coding System (NFCS) is an anatomically based measure in which the occurrence of ten different facial actions is individually coded [28, 29]. It has been validated for use in premature neonates, term-born neonates and infants up 18 months of age. It differentiates between noxious (e.g. heel stick) and non-noxious (e.g. heel swab) stimuli. Although the NCFS consists of ten facial actions, some investigators have suggested that the three most commonly observed facial actions (brow bulge, eye squeeze and nasolabial furrow) suffice for pain assessment. The other facial actions are: open lips, horizontal mouth stretch, vertical mouth stretch, taut tongue, pursed lips, chin quiver and tongue protrusion. Tongue protrusion is associated with acute pain in pre-term neonates less than 32 weeks old but not in term-born infants.

The Objective Pain Scale (OPS) is a four-item example of an integrated scale and is particularly useful in children from one month to 3 years (Table 3). In children from 7- to 16-years-old, either CHEOPS or VAS scales may be used. Options are summarized in Table 4.

Table 3. Objective Pain Scale (OPS)

Blood pressure (increment)	<10%, 10-20%, >10%	Score 0 ,1, 2
Crying	None, consolable cry, inconsolable cry	
Movement	None, restlessness, convulsed	
Agitation	Asleep, mild, severe and continuous	

Table 4. Pain assessment in infants

Children 3 years	OPS, CHEOPS, parent's report, nurse's report, physiologic measurements, NFCS
Children 3-6 years	Faces Pain Scale, Oucher Scale, Poker Hip Tool, VAS, observation tools, parent's report, nurse's report
Children 6-7 years	Self-report (VAS, NRS), observation scales, parent's report, nurse's report

Assessment of side effects

Pain severity measurement is not the only assessment in postoperative analgesic care. Studies consistently report the overall incidence of postoperative nausea and vomiting (PONV) to be 36%. These problems can lead to aspiration, electrolyte imbalance, wound dehiscence, impairment of oral absorption of drugs and nutrition and delayed recovery. Furthermore, it has been shown that the patient's memory of PONV is greater than that of the pain experienced after surgery [30]. Research evidence suggests that guidelines should be developed for anti-emetic prescriptions, risk factors should be identified, anti-emetic drugs should be prescribed for every patient, the PONV score should be included on the regular observation chart and ward nurses educated to treat PONV actively.

Close attention should be paid to the fluid balance and urine output of patients on NSAIDs. With intravenous or epidural opioids, the breathing rate should be frequently monitored.

Postoperative sedation should be assessed using a sedation scale, for example a five-point modified scale (0=alert and orientated, 1=awake but drowsy, 2=sleeping but arousable by verbal commands, 3=sleeping but arousable by tactile stimuli, and 4=comatose).

With epidural analgesia, evaluation of motor blockade (Bromage scale) is necessary.

Our clinical experience

Without an organized process by which pain can be recognized, documented, assessed and reassessed on a regular basis, staff efforts to treat pain may become sporadic and ineffectual. For this reason, since 1998, our APS at Cattinara Hospital in Trieste (Italy) has provided 24-h coverage of postoperative pain management. The program consists of a nurse- and resident-anaesthesiologist-based, anaesthesiologist on duty-supervised model, and it is a variation of the nurse-based low-cost model of Rawal [31].

The APS provides postoperative pain management for general, orthopaedic, vascular, urological, thoracic, ear-nose-throat, plastic and neurosurgical patients after elective and acute interventions. The section anaesthetist selects the modality of analgesia among standard protocols, taking into account the type of surgery, the severity of postoperative pain and patients' co-morbidities. Pain intensity measurements at rest and on movement (by VAS or NRS and VRS) heart rate, blood pressure, respiratory rate, sedation level, nausea and vomiting and other side effects are assessed and recorded on a postoperative chart by a specially trained acute-pain nurse every hour during the first 3 h and three to four times daily for 3-4 days postoperatively. If VAS (or NRS) values are higher than 3 or if a side effect due to the analgesic technique occurs, the anaesthesiologist is called to give a rescue-dose or to change the analgesic treatment, respectively

Periodic evaluation studies should be conducted to monitor the effectiveness

of pain assessment and management procedures. In 2003, our APS followed up 1186 surgical patients. The expected postoperative pain was mild (12.6 %), moderate-severe (55.88%) and severe (31.31%). Patients received intravenous (84.75 %), epidural (12.55 %) and intrathecal (2.70 %) analgesia. The pain assessments of the acute-pain nurse and the anaesthetist were 11892 and 2309, respectively. A rescue dose of analgesic drug was necessary in 25.8 % of patients. Side effects were present in 8.6 %, most often hypotension (4.89%), nausea or vomiting (3.54%), followed by confusion, hallucinations and itching. The overall trend of VAS both at rest and on movement was always below 3 (Fig. 2).

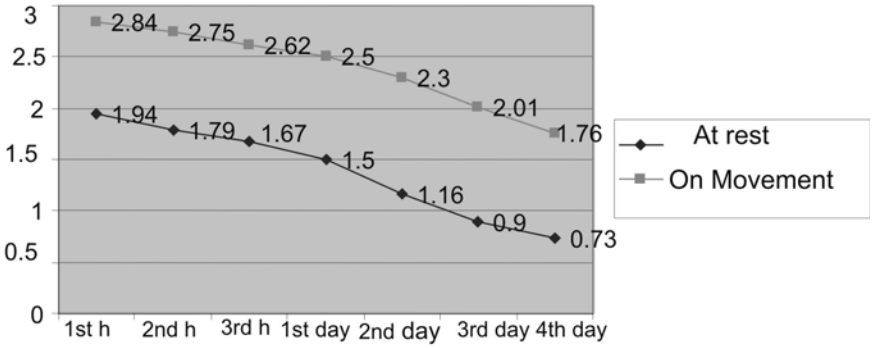

Fig. 2. The overall trend of VAS in 2003 at Cattinara Universtity Hospital of Trieste

The studies of Jamison et al. [32] indicated that low pain-intensity ratings are a good predictor of satisfaction with pain management and the helpfulness of treatment.

Audits are very important to assess the quality of pain management. Thus, a four-point pain satisfaction questionnaire (1=very dissatisfied, 2=somewhat dissatisfied, 3=somewhat satisfied, 4=very satisfied) was utilised to investigate patient satisfaction before discharge from hospital. Most patients (71.2%) expected pain of moderate to severe intensity and 49.5% reported to have experienced such pain levels. In spite of this, the satisfaction level was high: 86% of patients were very satisfied, 4% were somewhat satisfied and only 10% were somewhat dissatisfied. The majority of patients, if they would have needed surgery again, would like to have been treated in the same way (93%). Furthermore, patients were asked what they would change in their pain management: 10.8% requested more information about their analgesic treatment, 5.8% a better analgesia and 83.4% would not change anything. Since most patients claimed to have experienced moderate to severe pain in the postoperative period, it is surprising to note that the majority of patients were nonetheless satisfied with the pain management provided. Interestingly, Ready [33], in a retrospective report, stated that there did not seem to be any relation between the experienced severity of incident pain and the satisfaction score. Nevertheless, a number of organizations have suggested that measures of patient satisfaction should be included in quality or outcome assessment of pain

management, although the relevance has been a matter of debate. The observed discrepancy between actually experienced pain and patient satisfaction indicates that clinical pain management from the patient's point of view may not be as poor as pain intensity measurements suggest. It could be [34] that the pattern of pain relief, rather than pain severity as such, is be a critical determinant of satisfaction. Most probably, satisfaction depends more on the quality of communication between physician and patient than on the analgesic efficacy. Thus, patient ratings of satisfaction, as a measure of APS' efficacy, have to be evaluated cautiously [35].

Conclusions

One of the key points in improving postoperative pain management is the regular assessment and documentation of pain. The "golden rule" of pain assessment is: "Do not forget to ask the patient!" Self-assessment, in fact, is the single most reliable indicator of the existence and the intensity of pain and the efficacy of treatment.

Acute Pain Services have an important role in improving knowledge and understanding of pain assessment in staff and patients. Low pain intensity may be a good predictor of patient satisfaction. However, communication between APS staff and patients appears to be just as important as analgesic efficacy in determining patient satisfaction. Patients rate their satisfaction according to the care received, their pain control and their overall hospital experience.

References

1. Cousins MJ, Power J, Smith G (2000) 1996 Labat lecture: pain-a persistent problem. Reg Anesth Pain Med 25:6-21
2. Kehlet H (1997) Multimodal approach to control postoperative pathophysiology and rehabilitation. Br J Anaesth 78:606-67
3. Smith G (1991) Pain after surgery (editorial). Br J Anaesth 67:232-233
4. Donovan M, Dillon P, Mc Guire L (1983) Incidence and characteristics of pain in a sample of medical-surgical patients. Pain 30:69-78
5. National Health & Medical Research Council of Australia (1999) Acute pain management scientific evidence. Canberra, Australia: Ausinfo
6. American Pain Society (1991) Quality assurance standards for relief of acute pain and cancer pain. In: Bond MR, Charlton JE, Woolf CJ (eds) Proceeding of the VIth World Congress on Pain. Elsevier, Amsterdam, pp 185-189
7. Ready LB, Edwards WTY (1992) Management of acute pain: a practical guide. IASP Publications, Seattle
8. US Department of Health and Human Services, Agency for Health Care Policy and Research (1992) Acute pain management: operative or medical procedures and trauma. Publication no. 92-0032. AHCP Publications, Rockville, Maryland
9. (1995) Practice guidelines for acute pain management in the perioperative setting: a report by the American Society of Anesthesiologists Task Force on Pain Management, Acute Pain Section. Anesthesiology 82:1071-1081

10. Wulf H, Neugebauer E, Maier C (1997) Die Behandlung akuter perioperative und posttraumatischer Schmerzen: Empfehlungen einer interdisziplinaeren Expertenkommission. G Thieme, New York
11. Joint Commission on Accreditation of Healthcare Organizations (2001) 2001 Hospital accreditation standards. JCAHO, Oakbrook Terrace, Illinois
12. Zimmerman DL, Stewart J (1993) Postoperative pain management and acute pain service activity in Canada. Can J Anaesth 40:568-75
13. Gouche CR, Owen H (1995) Acute pain management in Australia and New Zeeland. Anaesth Intensive Care 23:715-717
14. Rawal N, Allvin R (1998) Acute pain services in Europe: a 17-nation survey of 105 hospitals. The EuroPain Acute Pain Working Party. Eur J Anaesthesiol 15: 354-363
15. Rawal N (1994) Organization of Acute Pain Services. Pain 57:117-123
16. Gould TH, Crosby DL, Harmer M (1992) Policy for controlling pain after surgery: effect of sequential changes in management. Br Med J 305:1187-1193
17. Werner Mu, Soholm L, Rotholl-Nielsen P (2002) Does acute pain service improve postoperative outcome? Anesth Analg 95:1361-1372
18. Sioling M, Nordahl G, Olofsson N (2003) The impact of preoperative information on state anxiety, postoperative pain and satisfaction with pain management. Patient Educ Couns 51(2):169-176
19. Association of Anaesthetists of Great Britain and Ireland (1998) Risk Management. AAGBI, London
20. Royal College of Surgeons of England and the College of Anaesthetists. Commission on the provision of surgical services. Report of the working party on pain after surgery. Royal College of Surgeons, London
21. Ravaud P, Keita H, Porcher R (2004) Randomized clinical trial to assess the effect of an educational programme designed to improve nurse' assessment and recording of postoperative pain. Br J Surg 91(6):692-698
22. (2000) The Royal College of Anaesthetist. Raising the Standard
23. Feeley TW (1990) The postanesthesia care unit. In: Miller RD (ed) Anesthesia, 3rd edn. Churchill Livingstone, London 3:2113-2133
24. Aubrun F, Paqueron X, Largeron O (2003) What pain scales do nurse use in postanaesthesia care unit? Eur J Anaesthesiol 20(9):745-749
25. Clark WC, Yang J, Tsui SL (2002) Unidimensional pain rating scales: a multidimensional affect and pain survey (MAPS) analysis of what they really measure. Pain 98(3):241-247
26. Jensen MP, Chen C, Brugger AM (2003) Interpretation of visual analogue scale ratings and change scores: a reanalysis of two clinical trials of postoperative pain. J Pain 4(7):407-414
27. Bruce J, Poobala AS, Smith WC (2004) Quantitative assessment of chronic postsurgical pain using the McGill Pain Questionnaire. Clin J Pain 20(2):70-75
28. Peters JW, Koot HM, Grunau RE (2003) Neonatal Facial Coding System for assessing postoperative pain in infants: item reduction is valid and feasible. Clin J Pain 19(6):353-363
29. Merkel SI, Voepl-Lewis T, Shayevitz JR (1997) The FLACC; a behavioural scale for scoring postoperative pain in young children. Pediatr Nurs 23:293-297
30. Orkin FF (1992) What do patients want-preferences for immediate postoperative recovery. Anesth Analg 74:5225
31. Rawal N (1997) Organization of acute pain services: a low-cost model. Acta Anaesthesiol Scand Suppl 11:188-190

32. Jamison RN, Mitchell JR, HHopman P et al (1997) Assessment of postoperative pain management: patient satisfaction and perceived helpfulness. Clin J Pain 13:229-236
33. Ready LB (1999) Lesson learned from 25000 patients. Reg Anesth Pain Med 24:499-505
34. Svensson I, Sjostrom B, Hallljamae H (2001) Influence of expectation and actual pain experience on satisfaction with postoperative pain management. Eur J Pain 5:125-133
35. Afilalo M, Tselios C (1996) Pain relief versus pain satisfaction. Ann Emerg Med 27:436-438

Chapter 6

Titration of opioids for acute pain management

Y. Leykin

The International Association for the Study of Pain describes pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" [1]. The relief of pain has always been central to medicine, and opioids have played an important part in this.

Opioids are drugs derived from opium and include morphine, codeine and a wide variety of related alkaloids, and synthetic peptides that bind to opioid receptors. Ancient writings and archaeological data indicate that the Sumerians cultivated poppies and isolated opium from their seed capsules at the end of the Third Millennium BC [2].

Opioid receptors and opioid peptides are located not only in the CNS but also in the peripheral nervous system, which includes dorsal root ganglia, spinal cord and brain stem [3]. The term 'opioid' describes all substances binding to these receptors, while the term 'opiate' is confined to the natural derivatives of morphine.

Opioids are the most broadly effective analgesics available, possibly a reflection of their supraspinal, spinal and peripheral sites of action. These drugs produce a dose- and concentration-dependent reduction in the intensity of acute pain as well as other short-term effects such as:

1. Respiratory depression
2. Sedation
3. Euphoria
4. Vasodilatation
5. Bradycardia
6. Cough suppression
7. Mitosis
8. Nausea and vomiting
9. Skeletal muscle hypertonia
10. Constipation
11. Urinary retention
12. Biliary spasm

Interindividual variability in opioid requirement

Numerous factors contribute to interindividual variability in opioid requirement for analgesia:

1. The location and intensity of the pain stimulus
2. Psychological factors
3. Therapeutic drug interactions
4. Age
5. Certain pathophysiological conditions
6. Hepatic and renal dysfunction
7. Sex
8. Genetic differences

Psychological factors. Previous positive or negative experiences with analgesics can influence subsequent responses.

Therapeutic drug interactions. Treatments with other analgesics or sedative/hypnotic drugs and alcohol ingestion can reliably potentiate opioid analgesia and increase the risk of toxicity.

Age. Because of pharmacokinetic changes, elderly patients are more sensitive to opioids, although some older patients may require high doses for adequate analgesia [5].

Pathophysiologic conditions. Hypothyroidism or pre-existing CNS disease can increase opioid sensitivity. In asthmatic patients decreased cough reflex or deep breathing caused by opioids can lead to inspissation of secretions and bronchospasm.

Hepatic and renal dysfunction. Dysfunction of the liver or kidney can lead to accumulation of parent drug or active metabolites, but CNS sensitivity does not appear to be greatly altered [6, 7].

Sex differences. There are sex-related differences in the ventilatory responses to a given concentration of morphine [8].

Genetic differences. Colombian Indians are more sensitive to the respiratory depressant effects of morphine and have a lower capability to form morphine glucuronides than white or Latino patients [9]. About 10% of whites and most Chinese have less CYP2D6 enzyme and are poor metabolisers of codeine with an inadequate analgesic effect [10].

Acute pain

1. Postoperative pain
2. Acute trauma
3. Myocardial infarction
4. Biliary colic
5. Renal colic

Postoperative pain

Postoperative pain is the most common form of acute pain; 50–70% of patients experience severe, and 20–40% moderate pain after surgery [11]. The ideal drug for postoperative analgesia should have a wide therapeutic range with minimal cardiovascular and respiratory depression and the lowest possible incidence of unpleasant side effects such as nausea, emesis, sedation and dysphoria. It should be possible to antagonise the agent in an emergency [11]. The available opioids offer different compromises, all of which are less than ideal. The greater the analgesic effect of the agent, the greater is the risk of side effects.

Postoperative pain is caused by a tissue lesion and by neuronal activation in the surrounding area [12]. These sensitive areas come about as a result of changes both to the neurons positioned at the back of the spinal cord and to the tissue surrounding the nervous system, regardless of the area damaged [13]. Sensitive and hyperaesthetic reactions are associated with the cortical sensitisation that determines stress-related responses [14–16].

The damage done to the tissue during surgery creates two different types of pain: the first is a direct consequence of the damage done during the operation, while the second is a result of an inflammatory reaction to the tissue damage that persists throughout the healing process [17]. The best form of analgesic treatment must therefore be able to eliminate both the first and the second phases of the hyperexciting stimulant.

Therapeutic success

Success depends on:
1. Appreciation of the unpredictability of postoperative pain
2. Rational choice of opioids
3. Appropriate route of administration
4. Interindividual variability

Unpredictability of postoperative pain

The correlation between intensity of postoperative pain and type of operation is poor, contrary to common belief [11]. The reason for this situation is based on the fact that the final pain results from the combination of: the interindividual variability in sensitivity among patients, the type of premedication, the anaesthetic technique and the surgery. Therefore, the first step in supplying adequate postoperative pain relief to patients is the appropriate appraisal of their analgesic requirements, which is obtained by observation of pain behaviour in the immediate postoperative period [11].

Routes and methods of administration

The routes and methods of administering the opioids have a relevant role in the overall outcome of the treatment given. The administration routes include:

1. Intramuscular
2. Intermittent subcutaneous
3. Oral
4. Intermittent intravenous
5. Continuous intravenous
6. Rectal
7. Transdermal
8. Transmucosal
9. Regional

The methods of administration are:

1. Intermittent boluses
2. Titration
3. Continuous infusion
4. Patient-controlled analgesia (PCA)

Intramuscular. The intramuscular route has become the most common route of administration. Traditionally i.m. opioids have been prescribed 4-hourly, but its half-life is about 3 hours!! After absorption from the injection, therefore, the first dose may result in a blood level that only just enters the 'analgesic corridor' for the patient, leading to very little pain relief if any at all.

The second two doses may result in higher blood levels and better pain relief for longer periods. Fourth and subsequent doses may increase blood concentrations to a level that starts to produce side effects as well as giving pain relief.

It is better to avoid this route for postoperative analgesia treatment. Furthermore, the minimum effective analgesic concentration (MEAC) varies by between four-fold and five-fold for some patients, and therefore the best way to achieve good pain relief is to titrate the dose to the individual needs of each patient. This requires the prescription of an appropriate initial dose and dose interval, followed by monitoring of the effectiveness of analgesia and the signs of an excessive dose [18, 19].

Intermittent subcutaneous. Opioids are often given by intermittent subcutaneous administration in the treatment of cancer pain, and this route has become increasingly popular in the management of acute pain. A small intravenous cannula is inserted into the subcutaneous tissue, often just below the clavicle in the upper anterior aspect of the arm and covered with a transparent dressing. The injection can be administered through a cap or one-way valve on the indwelling needle. The advantages of this route over the i.m. route include improved patient comfort, as the number of skin punctures is decreased, and a reduced risk of needlestick injury.

If injection through the indwelling needle is painful it may be that the rate of injection is too rapid or that the needle has been inserted too superficially. The

insertion site should be changed if pain on injection persists or if any redness or swelling develops at the site. Normally the indwelling needle will only need to be replaced every 3-4 days. Morphine is the drug most commonly given by intermittent subcutaneous injection. Subcutaneous opioids should be given in a solution that is sufficiently concentrated to avoid the need for large volumes, as these can be another source of tissue irritation [20].

Oral. Delays in gastric emptying are common after surgery and injury. Because of this and the possibility of postoperative nausea and vomiting, the use of oral opioids for the treatment of moderate to severe acute pain has not been common practice. If gastric emptying is delayed the opioids will not pass through to the small intestine when they are absorbed. The doses required when opioids are given orally are larger than the doses required for parenteral administration because of the first-pass effect.

Oral opioids are titrated in a very similar to i.m. and s.c. opioids. Doses for oral opioids should be based on the age of the patient. If a dose appears to have no effect, a delay in gastric emptying should be suspected and a return to parenteral opioids should be considered. The onset of action is a little slower with oral opioids than with intermittent i.m./s.c. injections, and the dose interval is 4 hours. Pain scores, sedation scores and respiratory rate should be monitored.

Intermittent intravenous. This regimen can result in wide variations in the blood concentration of the drug and is not a particularly effective way of administering opioids. If sustained pain relief is to be obtained without side effects, much smaller doses have to be given much more often. Pain medication is managed by nursing staff, usually in postanaesthetic recovery areas or other specialised areas. There is no limit to the total amount of opioid that can be given. The smaller the dose the more often it can be administered, the less variation there will be in the blood levels of the drug and the easier it will be to titrate the drug to suit each patient and different pain stimuli. This is the rationale behind patient-controlled analgesia (PCA) and one of the reasons why PCA has been so effective. This method of analgesia is not recommended for routine maintenance of pain relief in general wards, because it would cause major logistical and staffing problems. This technique is, however, the best way to obtain rapid analgesia and should be used to:

1. Obtain initial pain relief (immediately after an operation), and load the patient so that blood levels rapidly reach the MEAC for the patient;
2. Provide analgesia for patients who are hypovolaemic or hypotensive, when uptake of drug from muscle or subcutaneous tissue is poor;
3. Cover episodes of incident pain or inadequate analgesia.

Dose ranges should be based on the age of the patient. The dose interval is 15 min, but it is too long if analgesia is to be obtained rapidly. A reasonable balance between absolute safety and efficacy is to use a dose interval of 3–5 min.

Continuous intravenous. In an attempt to avoid the 'peaks and troughs' in blood concentration associated with intermittent administration, continuous i.v. infu-

sions of opioids are sometimes used in the management of acute pain. While it may be possible to maintain a reasonably constant blood level with this technique, it is difficult to predict what the level will need to be for a particular patient or what dose is needed to achieve it. It must also be borne in mind that acute pain is not constant and the amount of drugs required by a patient will vary with differing pain stimuli.

During continuous infusion of an opioid with a half-life of 3 h (e.g. morphine and meperidine), analgesia is obtained within 3 h of the start of an infusion. If this infusion continues at the same rate, the blood concentration will continue to rise for some hours and side effects may result. Equipment used for continuous infusion of opioids will continue to deliver the drug regardless of whether the patient is sedated or not. For this reason, continuous i.v. opioid infusions are probably the least safe way to administer opioids in a general ward.

Rectal. The submucosal venous plexus of the rectum drains into the superior middle and inferior rectal veins. Drug absorbed from the lower half of the rectum will pass into these veins and into the inferior vena cava, thus bypassing the portal vein and the first-pass metabolism in the liver. This is one of the advantages of this route of administration.

Rectal absorption is often variable owing to differences in the site of placement of the drug, the contents of the rectum and the blood supply to the rectum. In addition, patient – and indeed staff – acceptance of this route of administration there is not always widespread.

Transdermal. Opioids that are very highly lipid soluble (e.g. fentanyl) can be absorbed through the skin. However, skin permeability can be affected by a number of factors, such as age, skin temperature, body area and ethnic group: these factors can lead to unpredictable rates of drug transfer across the skin. To minimise the influence of variable skin transfers, the transdermal fentanyl delivery system currently available incorporates a membrane that is much less permeable than skin, which ensures a more predictable rate of drug transfer. The deeper layers of the skin act as a reservoir for fentanyl before it is absorbed into the bloodstream. Once the patch is placed on the patient there is a rapid absorption of the drug from the patch into the skin reservoir because of the large concentration gradient between the two. The drug is then released from the skin more slowly, and it may be 14–28 h before the peak blood concentration is reached. Fentanyl patches are usually replaced every 72 h. They are not suitable for routine acute pain management. The slow onset of action does not allow easy titration of analgesic effect, and the incidence of significant side effects is reported to be high, besides which these side effects may persist for some time even after the patch is removed. A newer method of transdermal delivery, called iontophoresis, effects a more rapid transfer of drug through the skin by application of an external electric field. It is not yet in common clinical use [21].

Transmucosal. Transmucosal drug administration refers to drug delivery through nasal, oral or pulmonary mucosal membranes. It is particularly suited to

the more highly lipid-soluble opioids, such as fentanyl, sufentanyl, alfentanyl, diamorphine and meperidine. It has the advantage of avoiding first-pass metabolism. Mean times for achieving maximum serum concentration vary from 5 to 50 min, while the mean bioavailability vary from 46% to 71%. Mean onset times vary from 12 to 22 min and times to peak effect, from 24 to 60 min. There is a considerable interindividual variation of pharmacokineties and clinical outcome. Patient-controlled nasal analgesia is an effective alternative to i.v. PCA. Adverse effects are mainly those related to opioids themselves, rather than to nasal administration. This kind of opioid administration has promising features, but it is still in its infancy [22].

Patient-controlled analgesia. PCA is not restricted to a single route or method of analgesic administration or a single class of analgesic drug, but means that patients can determine when and how much analgesic they receive. PCA has generally been associated with better pain relief and greater patient satisfaction than intermittent opioid injections. The reasons for this include:

1. Small and frequent intravenous bolus doses of opioid can be given whenever the patient becomes uncomfortable, enabling individual titration of pain relief and maintenance of blood concentration of opioid within their therapeutic range;
2. This flexibility helps to overcome the wide interpatient variation in opioids requirements in each age group;
3. The intensity of acute pain is rarely constant and PCA means that the amount of opioid delivery can be rapidly titrated if pain increases and higher blood levels of drug are required;
4. Patients are able to titrate the amount of opioid delivered against dose related side effects.

The patients who benefit most from PCA are those who have had major surgery and are not permitted oral fluid, those with marked incident pain and those who cannot be given i.m. injections even for a short time (e.g. haemophilic patients or patients taking anticoagulants) [23].

Contraindications. The contraindications are:

1. Untrained nursing and medical staff: in fact inadequate understanding of the PCA mechanism, drugs and doses used, monitoring requirements and management of common problems can increase the risk of complications. Nursing education and accreditation programmes that have to be completed by each nurse before he or she can take responsibility for a patient with PCA are recommended.
2. Patient rejection: the majority of patients appreciate the control that PCA gives them and the ability to titrate their own analgesia rapidly and to balance pain relief against the severity of any side effects that may occur. On the other hand some patients may not want this technique, preferring the nursing and medical staff to manage their pain relief.
3. Inability to comprehend the technique: for PCA to be used both safely and

effectively the patient must be able to understand the technique, and have no mental impairment or language barrier. If staff feel that patient does not understand PCA, an alternative method of pain relief will be needed. Patients who are confused are often not offered PCA, and when any become confused PCA may have to be discontinued.

4. Patient age: the technique has been successfully used in patient of almost all ages. It is enough if they understand the explanation given and are willing to be active participants in their own care. In the case of paediatric patients the PCA can be used when they are over 6 years of age.

Loading dose. PCA is a maintenance therapy. It is a good way to maintain patient comfort, but is an ineffective way of achieving that comfort in the first place. This means that to make the patient comfortable before PCA is started a loading dose of opioid is needed. It may be better to individualise this dose for each patient, because of the possible individual variation.

Incremental dose. The bolus dose is the amount of opioid that the PCA machine will deliver when the demand button is pressed. Opioids with a very short or a very long duration of action are not usually recommended. Partial agonist or agonist–antagonist opioids are used less commonly than pure opioid agonists.

The size of the incremental dose, along with the lock-out interval, can determinate the effectiveness of PCA. The optimal incremental dose for each patient is one that results in appreciable analgesia without side effects. The dose of opioid prescribed should be reduced as the age of the patient increases. As patients with PCA can vary the total daily dose according to the number of demands they make, a progressive decrease in dose with increasing age is not necessary. Therefore it is reasonable to start with a smaller PCA incremental dose in patients over 70 years.

Lock-out interval. The lock-out interval is designed to increase the safety of PCA by allowing the patient to feel the effect of one dose before receiving the next. In practice, lock-out intervals of 5–8 min are commonly prescribed. A longer lock-out reduces the patient's capacity for rapid titration of the amount of opioid required, decreasing the effectiveness of PCA. Lock-out intervals of 5–8 min mean that a patient could demand and receive up to ten doses of opioid each hour. If analgesia is inadequate it may be preferable to increase the size of the bolus dose rather than shorten the lock-out interval or instruct the patient to press the button more often.

Continuous infusion. Most PCA machines can deliver a continuous infusion when used at a low rate in addition to the PCA mode; it was hoped that in this way a constant but subanalgesic blood concentration could be maintained. Therefore, it was thought, when a bolus dose of opioid was delivered the blood level would reach the analgesic corridor more rapidly. It was also hoped that a continuous infusion would enable patients to make fewer demands, sleep for longer periods and wake in less pain.

Unfortunately, experience has shown that a continuous infusion:

1. Does not always reduce the number of demands made by the patient.
2. May increase the total amount of opioid delivered.
3. Has been shown to increase the risk of side effects.
4. Does not always result in better analgesia.
5. Does not always result in improved sleep patterns.

Continuous infusion reduced the inherent safety of the PCA technique, and routine use of a background infusion is not therefore recommended.

Concentration. For consistency and safety the volume delivered following each demand should be no less than 0.5 ml.

Hourly limits. Large interpatient variations in opioid requirements make it impossible to predict the safe limit for each patient. The setting of a limit could give staff a false sense of security and cannot compensate for any shortcomings in monitoring.

Complications. Complications of PCA may be related to the equipment (malfunction, operator error, inappropriate patient or nonpatient use, tempering), the side effects of the opioids (nausea and vomiting, which make an appropriate antiemetic drug necessary, itching that can be treated with antihistamines, which may add to the risk of sedation and respiratory depression), sedation and respiratory depression (if a patient has a sedation score of 2 a reduction in the size of the PCA bolus dose is indicated; if a patient has a sedation score of 2 and a respiratory rate below 8 breaths per minute the administration of a small dose of naloxone can also be considered, in addition to a reduction in the size of bolus dose), urinary retention (PCA need be discontinued), inhibition of bowel motility (patients should be encouraged to mobilise).

Inadequate analgesia. The analgesia achieved may be inadequate for a number of reasons, including inadequate dose, inappropriate patient use, presence of side effects and ineffective PCA prescription.

1. Inadequate loading dose: 'reloading' may be needed.
2. Inappropriate patient use: patients are unaware that they can press the button as often as required.
3. Presence of side effects: an antiemetic therapy is necessary.
4. Ineffective PCA prescription: if the number of doses is fewer than three per hour, further instruction is needed and the patient should be encouraged to use PCA more often. On the other hand, if the patient receives four or more doses per hour the size of bolus may need to be increased by 50–100%.

Morphine titration in PACU

In the postanaesthesia care unit (PACU) the use of titrated doses of morphine is often the first step in postoperative pain treatment [24]. Morphine by titration requires initial assessment of pain but provides rapid analgesia and the ability to adapt the dose to individual requirements [25]. Intravenous administration of

Table 1. Pharmacokinetic characteristics of opioids in current use

Drug	Time to onset	Plasma half-time	Equivalent doses (morphine)	Duration	Suggested daily max. dose	Starting dose	Maintenance
Morphine	p.o. < 60 min	1–4	1	1–4 h	100 mg–(age)	0.1 mg/kg	Effective dose every 4–6 h
	i.m. 5 min						
	i.v. <1min						
	Epidural 15–60 min	6–24 h			<6mg/day	0.05 mg/kg	0.1–0.15 mg/kg per h
Tramadol	Every 5 min	5–7	1/10	6 ore	400–600 mg	1 mg/kg	15 mg/h
	i.m. 10–20 min				1–2 mg/kg per hour		
	p.o. 20 min / 1 h						
Fentanyl	Ev <30 s	3	75–125	30–60 min	500 mg	1µg/kg	0.5–1 µg/kg per h
	Epidural 4–10 min		4–6 h	1 µg/kg	10–30µ/h		
Pethidine	Ev <1 min	3–4	1/10	2–4 h	600 mg	0.5-1 mg/kg	0.3–0.6 mg/kg per h
Sufentanil	Ev 1–3 min	15 min	10/1 fentanyl	20–45 min		2–10 µ	2–20 µ/h
	Epidural 4–10 min	5/1 fentanyl	2/4 h			0.2 m/kg	2-6 µ/h

boluses of morphine requires regular assessment of pain and sedation. Dahmani et al. concluded that ethnicity (Caucasians), emergency surgery, major surgery, duration of surgery (in excess of 100 min) and pain score on arrival in PACU are predictive factors in morphine requirements in the early postoperative period [24].

Peroperative titration of morphine. The transition between anaesthesia and adequate analgesia in awake patients is sometimes difficult to manage. One possibility is to start administering analgesia before the end of surgery. Pico et al. studied the influence of preoperative administration of titrated morphine on quality of postoperative pain control when morphine doses were adjusted according to the respiratory rate reduction in patients emerging from anaesthesia. Morphine was titrated at the end of surgery (3 mg i.v. every 5–10 min) in spontaneously breathing intubated patients until the respiratory rate decreased. There respiratory rate decrease was correlated with a lesser need for morphine in the PACU and with a less pronounced respiratory depression [26].

Postoperative titration of intravenous morphine in the elderly patients. Elderly patients have been noted to be more susceptible to the effects of opioid analgesic than younger patients [27]. Some phases of pharmacokinetics are affected in ageing, including distribution, metabolism and elimination [28]. In elderly patients, the morphine volume of distribution is approximately half that of young patients. The smaller central compartment distribution is thought to be attributable, at least in part, to decreased cardiac output.

However, because of the extraordinary variation in dose requirements for pain managements in the PACU and because titration adapts the dose strictly to pain, there is no evidence that a titration protocol also needs to take account of the age of patients. Aubrun et al. have demonstrated that i.v. morphine titration can be safely administered to elderly patients. Because titration is adapted to individual pain, the same protocol can be applied to both young and elderly patients [29]. The authors used i.v. morphine titration as a bolus of 2 (body weight < 60 kg) or 3 (body weight > 60 kg) mg. There was no limitation on the number of boluses given until pain relief was achieved or a severe adverse effect occurred. The total dose of morphine administered per kilogram of body weight did not differ significantly between young and elderly groups [29].

Acute pain of other origin

The principles discussed for postoperative pain with reference to unpredictability, route of administration and advantage of individual titration apply to all types of acute pain [11]. Ideally, the analgesic management of acute trauma involves titrating i.v.-administered pure agonists against the patient's pain. Pain from myocardial infarction needs immediate treatment, because the sympathetic stimulation caused by pain results in unfavourable haemodynamic responses, which may increase myocardial ischaemia. The intravenous titration of morphine seems to be a very

reasonable approach. Treatment of the pain of renal or biliary colic presents a special problem. In these cases pain might even be increased by the use of opioids, which cause contraction of smooth muscles. Pethidine, with its specific spasmolytic effect, seems to be the only useful opioid [11].

Conclusions

The most outstanding feature of the clinical use of opioids is the extraordinary variation in dose requirements for pain management [4]. The wide interindividual variation in opioid requirement makes it clear why opioids need to be titrated to give the optimal analgesic effects and to reduce the possible side effects.

References

1. Merskey H (1986) Classification of chronic pain. Pain (Suppl 3):1
2. Brownstein MJ (1993) A brief history of opiates, opioid peptides, and opioid receptors. Proc Natl Acad Sci USA 90:5391
3. Stein C (1995) The control of pain in peripheral tissue by opioids. N Engl J Med 332: 1685
4. Upton RN, Semple TJ, Macintyre PE (1997) Pharmacokinetics optimization of opioid treatment in acute pain therapy. Clin Pharmacokinet 33:225
5. Rooke GA, Reves JG, Rosow CE (2002) Anesthesiology and geriatric medicine: mutual needs and opportunities. Anesthesiology 96:2
6. Dershwitz M, Hoke JF, Rosow CE et al (1996) Pharmacokinetics and pharmacodynamics of remifentanil in volunteer subjects with sever liver disease. Anesthesiology 84:812
7. Hoke JF, Shlugman D, Dershwitz M et al (1997) Pharmacokinetics and pharmacodynamics of remifentanil in persons with renal failure compared with healthy volunteers. Anesthesiology 87:533
8. Dahan A, Sarton E, Teppema L et al (1998) Sex-related differences in the influence of morphine on ventilatory control in humans. Anesthesiology 88:903
9. Cepeda MS, Farrar JT, Roa JH et al (2001) Ethnicity influences morphine pharmacokinetics and pharmacodynamics. Clin Pharmacol Ther 70:351
10. Caraco Y, Sheller J, Wood AJ (1999) Impact of ethnic origin and quinidine coadministration on codeine's deposition and pharmacokinetic effects. J Pharmacol Exp Ther 290:413
11. Schug SA, Merry AF, Acland RH (1991) Treatment principles for use of opioids in pain of non-malignant origin. Drugs 42:228
12. Basbaum AI (1998) Spinal mechanism of acute and persistent pain. Reg Anesth Pain Med 24:59
13. Siddel PJ, Cousins MJ (1998) Introduction to pain mechanism. In: Cousins MJ, Bridenbaugh PO (eds) Neural blockade in clinical anesthesia and management of pain. Lippincott-Raven, Philadelphia
14. Raja SN, Dougherty PM (2000) reversing tissue injury-induced plastic changes in the spinal cord. The search for magic bullet. Reg Anesth Pain Med 25:441
15. Weissman C (1990) The metabolic response to stress: an overview and update. Anesthesiology 73:308

16. Kehlet H (1989) Surgical stress: the role of pain and analgesia. Br J Anaesth 63:189
17. Berti M (1999) Il dolore postoperatorio: la teoria e la pratica. CE.DI.S, Rome
18. Cooper I.M (1996) Morphine for postoperative analgesia: a comparison of intramuscular and subcutaneous routes of administration. Anesth Intensive Care 24:574
19. Alexander Williams JM, Rowbotham DJ (1998) Novel routes of opioid administration. Br J Anesth 81:3
20. Semple TJ, Upton RN et al (1997) Morphine blood concentration in elderly postoperative patients following administration via on indwelling subcutaneous catheter. Anaesthesia 52:318
21. Peng WH, Sandler AN (1999) A review in the use of fentanyl analgesia in the management of acute pain in adults. Anesthesiology 90:576
22. Dale O, Hjortkjer R et al (2002) Nasal administration of opioids for pain management in adults. Acta Anaesthesiol Scand 46:759
23. Lehamann KA (1999) Patient-controlled analgesia: an efficient therapeutic tool in the postoperative setting. Eur Surg Res 31:112
24. Dahmani S, Dupont H, Mantz J et al (2001) Predictive factors of early morphine requirements in the post-anaesthesia care unit (PACU). Br J Anaesth 87:385
25. Perry F, Parker RK, White PF et al (1994) Role of psychological factors in postoperative pain control and recovery with patient controlled analgesia. Clin J Pain 10:57
26. Pico L, Hernot S, Nègre I et al (2000) Peroperative titration of morphine improves immediate postoperative analgesia after total hip arthroplasty. Can J Anaesth 47:309
27. Wall RT (1990) Use of analgesics in the elderly. Clin Geriatr Med 6:345
28. Kaiko RF (1980) Age and morphine analgesia in cancer patients with postoperative pain. Clin Pharmacol Ther 28:823
29. Aubrub F, Monsel S, Langeron O et al (2002) Postoperative titration of intravenous morphine in the elderly patients. Anesthesiology 96:17

Chapter 7

Neonatal Mechanical Ventilation

A. Bougatef

The application of mechanical ventilation to neonates with respiratory disorders is one of the many breakthroughs in the history of neonatal care.

For more than 40 years, neonates with respiratory failure have been treated by assisted mechanical ventilation. In 1962, researchers and pioneer physicians began to intubate pronounced-dead babies using a Cole rubber tube and a Bird Mark VIII ventilator with the infant J circuit system (to extend his function in neonatal application) at the Toronto Hospital for Sick Children. The acquired experience and the incorporation of cardiopulmonary resuscitation with intubation and ventilation, are crowned with success in 1963 when the first newborn survived without air leak or cerebral abnormalities, albeit with chronic lung disease. The introduction in 1969 of the "Babybird" respirator, time cycled, pressure limited, IMV device, has allowed the survival of innumerable neonates with respiratory distress syndromes, stimulating the development of a new era in neonatology. However, this increase in survival and the widespread availability of mechanical ventilation were associated with an advent of short- and long-term pulmonary morbidity.

During the most of this time, intermittent mandatory ventilation (IMV) has been the mainstay of neonatal ventilatory support, using time cycled pressure-limited devices.

With the IMV system, the baby breaths spontaneously, between breaths from continuous flow in the respirator circuit, and receives support by positive end expiratory pressure (PEEP). This form of ventilation is easy to use and leaves all parameters to the clinician's discretion. However, IMV has been associated with asynchronous breathing between patient and respiratory device, leading to complications as the air-leak syndrome, instable cerebral blood flow (which results in intraventricular haemorrhage and periventricular leukomalacia), and chronic lung disease.

Thanks to advanced technology, respiratory devices became more sophisticated, and new modes and forms of mechanical ventilation were introduced for the treatment of the newborn with respiratory disorders [1]. While efforts are devoted to find and develop the optimal ventilation strategy, the goals of mechanical ventilation in neonates should be to achieve adequate pulmonary gas exchange, to minimise the risk of lung injury, and to reduce the infant's work of breathing [2].

Physiologic concepts

Neonates increase their ventilation in response to increased $PaCO_2$ or hypoxia. Preterm infants have a blunted $PaCO_2$ response and a depression of respiration during hypoxia. This decline in respiratory drive is an important cause of hypoventilation or apnoea in the newborn period. It is also important to consider, in neonates undergoing conventional mechanical ventilation (CMV), the Hering-Breuer reflex, which is defined as a brief period of decreased or absent respiratory effort immediately following inflation. Due to the Hering-Breuer reflex, lung inflation during inspiration shortens the duration of inspiration, whereas lung inflation during expiration prolongs the duration of expiration itself. Therefore, synchronisation of IMV with spontaneous breathing is difficult, because lung inflation during inspiration tends to reduce spontaneous inspiratory time, and inflation during expiration tends to prolong the expiratory time.

Newborns have a higher vulnerability to impaired gas exchange owing to their high metabolic rate, decreased functional residual capacity, and decreased compliance. They also may develop right-to-left shunting through the ductus arteriosus or foramen ovale. Hypercapnia or hypoxaemia occur during respiratory failure. Hypercapnia is usually caused by hypoventilation or ventilation-perfusion mismatching. Carbon dioxide elimination is directly proportional to minute ventilation. Usually hypoxaemia is a result of ventilation-perfusion mismatching or shunting, of diffusion abnormalities and hypoventilation. Oxygenation is determined by FiO_2 levels, and by mean airway pressure. However, a high mean airway pressure may cause overdistension leading to intrapulmonary shunt, while an increase in intrathoracic pressure results in a decrease in cardiac output.

Continuous positive airway pressure (CPAP)

CPAP was applied in the mid-1930s to treat pulmonary oedema and asthma in adult patients. In 1970, Gregory et al reported the use of endotracheal-tube CPAP in the treatment of respiratory distress in the newborn. Originally, CPAP was administered via head box or endotracheal tube. However, in 1973 Agostino et al. reported of a low birth-weight newborn with respiratory distress syndrome (RDS), who was successfully treated with nasal CPAP. Over the years, a variety of different non-nasal CPAP devices were developed, including a pressurised plastic bag fitted over the patient's head, face chambers, face masks. More recently, CPAP is usually applied by nasal prongs. It is used in spontaneously breathing newborns to prevent alveolar collapse and to decrease the work of breathing.

Among its physiological effects, CPAP is believed to result in progressive alveolar recruitment and stability, to inflate collapsed alveoli, and to reduce intrapulmonary shunt. Some of the effects of CPAP have been measured. First of all, CPAP increases lung volume. When functional residual capacity increases, gas exchanges improves, PaO_2 increases and $PaCO_2$ decreases, resulting in a decrease in pulmonary vascular resistance, an increase in pulmonary blood flow, and a

decrease in intrapulmonary shunts. However, an excessive CPAP can lead to the air-leak syndrome, to an increase in intrathoracic pressure, which may decrease venous return to the heart, and to cardiac output.

Clinical investigations in neonates using nasal CPAP shortly after birth, demonstrated a reduction in the need of mechanical ventilation, and part of them noted a reduction in the incidence of chronic lung disease. Other data suggest that nasal CPAP following mechanical ventilation, reduces the incidence of extubation failure.

An ideal CPAP delivery system should include a patient-system capable of producing stable pressures at the desired levels, with minimal dead space and low resistance to breathing, easily applicable, non-traumatic to the patient. It appears that all CPAP devices are not equivalent, and further studies need to focus on the most-effective nasal CPAP interface and the best mode of pressure generation for the delivery of nasal CPAP.

Conventional mechanical ventilation (CMV)

Based on better knowledge of pulmonary mechanics and principles of gas exchange, strategies for optimizing CMV have been developed. Also, a new generation of microprocessor-based ventilators with sophisticated, sensitive transducers were developed. Currently, new ventilators offer a continuous graphic display of pressure, flow, and volume, as well as numerical values of pressure tidal volume and flow. The objective is a better assessment of neonates to improve their management and to offer recommendations in general neonatal care. However, because of the great variability of the results obtained from the same patient and between patients, these technological developments in the assessment and treatment of newborn patients bring poor contributions.

Intermittent mandatory ventilation (IMV)

IMV was virtually the only mode used with newborns for more than two decades. The clinician sets a rate at which the ventilator will deliver mechanical breaths, which cycle at regular intervals. The patient may breathe between mechanical breaths but, unfortunately, infants often breathe asynchronously with the ventilator. Asynchrony results in inefficient gas exchange, but is associated with irregularities in arterial blood pressure, cerebral blood flow, and risks of intraventricular haemorrhage in premature babies.

Synchronised intermittent mandatory ventilation (SIMV)

SIMV represents an improvement over IMV. This mechanical ventilation technique attempts to link the onset of the delivered breath to the onset of spontaneous patient breath. The clinician selects the ventilator rate, but the mandatory breaths

are held within a timing window until initiation of a patient breath, to which it is then synchronised. If the infant breaths within this timing window, a mechanical breath will be matched to the onset of spontaneous breathing Although the onset of inspiration is synchronised, expiratory asynchrony may occur if the infant's own inspiratory time is shorter than that chosen by clinician, as the baby will begin to exhale while positive pressure is still being applied by the ventilator. If the infant fails to breath, the ventilator will cycle on schedule. The patient is free to breath spontaneously between mechanical breaths and is supported by positive end-expiratory pressure (PEEP).

Assist/control ventilation (A/C)

As a time-cycled, pressure-limited ventilation, A/C is characterised by continuous flow and adjustable inspiratory time, which result in a constant inspiratory pressure. With A/C, the synchronised breaths are delivered with each spontaneous breath meeting preset threshold criteria. In the event of apnoea or insufficient effort, mechanical breaths are provided at a rate set by the clinician. Moreover, every spontaneous breath is assisted; therefore ventilator peak inspiratory pressure and inspiratory time should be minimised. To reduce the risk of barotraumas, the weaning is accomplished by reducing the peak inspiratory pressure first. Most clinicians prefer SIMV to ventilate neonates because the ventilation rate is adjustable and the infant does not receive ventilator breaths with every spontaneous breath.

Pressure support ventilation (PSV)

Usually applied in conjunction with SIMV, PSV provides an inspiratory pressure assist to the patient's spontaneous breaths. PSV is primarily a weaning mode, in which spontaneous breaths receive an inspiratory boost to reduce the work of breathing and unload the respiratory musculature. Also, PSV has a variable inspiratory flow, which is proportional to patient effort and helpful in overcoming increased resistance. In PSV, the patient initiates an inspiratory effort that results in a deflection of pressure below a baseline. Spontaneous breaths can be fully supported, partially supported, or minimally supported. The clinician sets trigger sensitivity at maximum; once the breath is triggered, flow is delivered to the patient's airway, and pressure rises to the preselected pressure support setting.

Patient-triggered ventilation (PTV)

SIMV, A/C, and PSV are all forms of patient-triggered ventilation, in which a mechanical breath is provided in response to measured or presumed respiratory efforts by the patient. There are various form of trigger signals used with infants,

including a change in airway pressure or flow, abdominal motion, and thoracic impedance. The important feature of PTV is the response time, also referred to as trigger delay.

Most clinical trials comparing any form of PTV to IMV have demonstrated superiority of patient-triggered ventilation [3, 4].

Pressure control ventilation (PCV)

PCV is a pressure-limited form of ventilation. With PCV, during inspiration pressure is constant and the flow rate is variable depending upon patient effort. Initially, flow delivery is rapid, and it is followed by a deceleration, while peak inspiratory pressure remains stable. Some ventilators offer an adjustable rise time, which enables the clinician to alter the slope of the pressure waveform as the patient's status changes. The flow variability during PCV reduces the patient's inspiratory muscle workload, disables lower peak inspiratory pressure, and improves gas distribution, ventilation-perfusion matching, and oxygenation.

Proportional assisted ventilation (PAV)

PAV is a ventilation technique in which the amount of ventilatory support is continuously proportional to the patient's respiratory effort throughout the respiratory cycle. The PAV system measures the respiratory system compliance and resistance, and calculates the amount of ventilatory assistance needed to improve the patient's work of breathing. The patient has complete control of all aspects of the breathing pattern (inspiratory and expiratory duration, tidal volume, and flow rate). Pressure delivered at the airway increases in proportion to the patient's instantaneous effort, and the proportionality applies from breath to breath, as well as continuously throughout each inspiration. This means that the principal disadvantages of PAV are a dependence on the patient's spontaneous effort, a possible change in the patient's breathing pattern, or an increase in the potential for ventilatory instability. Clinical trials on PAV resulted in increased comfort, lower mean airway pressure and fraction of inspired oxygen, improvement in minute ventilation, and decreased work of breathing. Further trial is needed to confirm these preliminary results.

Volume-controlled ventilation (VCV)

In this form of ventilation, the clinician chooses a specific tidal volume to be delivered to the patient while allowing the pressure required to deliver that volume to be variable, although the pressure may be limited for safety [5]. Because there is always air leak around the endotracheal tube (cuffed endotracheal tubes are not used in newborns), true volume cycling dos not occur. VCV involves a constant

flow rate. It is important to measure the delivered volume as close to the airway as possible, and to know the compliance of the ventilator circuit itself. During VCV, there is a slow rise in peak pressure, and therefore the distribution of ventilation may not be optimised, particularly if lung disease is heterogeneous. The set flow rate may not match the patient's demand, resulting in small tidal volumes and a condition referred to as "flow starvation". There can also be an increased muscle workload, which can compromise patient comfort and gas exchange. The advantage of this technique is that it automatically weans the peak inspiratory pressure as compliance improves, thus decreasing the risk of hyperinflation. When patient compliance is low, pressure will be high, but as compliance improves, the ventilator will automatically wean peak inspiratory pressure to deliver the same tidal volume, and thus it may be more effective in conditions characterised by rapid changes in compliance, such as after surfactant administration.

Pressure regulated volume control (PRVC)

This ventilation technique produces a variable decelerating flow pattern, resulting in time-cycled breaths. The inspiratory pressure is regulated based on the pressure-volume calculation of the previous breath and compared to a target tidal volume. The ventilator continuously adapts the inspiratory pressure in response to changing compliance and resistance in order to maintain the target tidal volume. However, tidal volume is measured distally and not at the patient airway; thus there may be differences between the actual and measured delivered tidal volumes.

Volume assured pressure support (VAPS)

This is a hybrid ventilation technique, which combines the best features of pressure-limited and volume control ventilation. The ventilator delivers a breath to a set pressure limit. If the target volume has not been delivered to the patient at this pressure, the breath will be prolonged to guarantee delivery of tidal volume. Inspiratory time and peak inspiratory pressure are increased, and the guaranteed volume is provided on the current breath without the need for previous breath averaging. VAPS looks like a variable flow-volume ventilation. It measures the flow and pressure continuously, and calculates the delivered volume. During the VAPS breath, the decision-point is made when flow decelerates to the lowest level set. If the targeted tidal volume has been delivered, inspiration is terminated and the breath is flow-cycled. If the preset tidal volume has not been achieved, the set flow will persist until the desired volume has been reached. Thus, the breath changes from being flow-cycled to being volume-targeted. VAPS may be useful for patients requiring a substantial level of ventilatory support, despite having a vigorous ventilatory drive to improve gas distribution and synchrony. Also, it may be beneficial for patients with unstable ventilatory drive but who have been weaned from the ventilator. Potential benefits of VAPS are decreased work of breathing,

lower peak airway pressure, better gas distribution, enhanced patient comfort, and less need for sedation.

High Frequency Ventilation (HFV)

High frequency ventilation was conceived to improve patient outcome using tidal volumes lower than the patient's anatomical dead-space, with high intrapulmonary delivery rates to affect pulmonary gas exchange, at lower alveolar pressures than traditional CMV. Introduced into neonatal practice in the early 1980s, there are few categories of HFV: High Frequency Oscillatory Ventilation (HFOV), High Frequency Jet Ventilation (HFJV), and High Frequency Percussive Ventilation (HFPV), a hybrid form. There are no rigorous scientifically comparisons among the different devices [6].

Through experimentation on lung models and adjustments of empiric equations, it is apparent that adequate ventilation and carbon dioxide elimination can be achieved when tidal volume is less than anatomical dead space volume. It is difficult to measure the tidal volume during HFV, and changes in tidal volume are ventilator specific. The tidal volume delivered is dependent on the frequency and impedance (resistance to air flow) of the respiratory system. As frequency and impedance decrease, tidal volume delivery increases. The distribution of gas transport is different during HFV. It is more uniform but affected by tidal volume, frequency, and lung pathologies.

High Frequency Oscillatory Ventilation (HFOV)

HFOV uses rates of 10 to 15 Hz/ min. Also called continuous distending pressure (CDP), mean airway pressure is used to inflate the lung to a static volume, the oscillation affects gas exchange. Animal studies have shown that HFOV is most effective in reducing lung injury when used immediately after birth rather than after several hours of CMV [7]. Early human trial comparing HFOV with CMV for RDS therapy produced disappointing results, but recent studies using HFOV have been more encouraging [8-12].

High Frequency Jet Ventilation (HFJV)

HFJV uses rates of 5 to 10 Hz/min. It is used in combination with conventional ventilators, which provide PEEP and optional sigh breaths. High velocity pulses of gas are injected into the proximal airway using a special connector or a multiple lumen endotracheal tube. Ventilator settings are the same as CMV: peak pressure and PEEP control the amplitude. The first prospective randomised multicenter clinical trial demonstrated the superiority of HFJV to conventional mechanical ventilation in resolving pulmonary interstitial emphysema in premature infants

[13]. However, management of infants on HFJV is complicated and requires experience.

High Frequency Percussive Ventilation (HFPV)

HFPV is a hybrid form of high frequency ventilation. It is a pneumatically powered and controlled, time cycled, pressure limited ventilator. High frequency pulses of gas are delivered to the patient through a nongated sliding Venturi connected to the endotracheal tube. The sliding Venturi operates as inspiratory, expiratory, and PEEP valves all in one. There are two gas flows originating from the ventilator. The first is the pressurised pulse flow delivered into the sliding Venturi. The second is a continuous flow of gas to power the nebuliser, which in turn provides humidification. Gas from the nebuliser travels to the Venturi where, due to the Bernoulli and Venturi effects, it can be entrained or vented to the atmosphere. The typical proximal airway pressure tracing is characterised by a progressive accumulation of subtidal volume breaths that build to a set of pressure during inspiration, followed by passive exhalation.

Conclusions

It is quite impossible to force a diseased lung to comply to a constant high flow-rate of gas, and expect optimal alveolar distribution. Ideally, the medical respirator must have a flow-variable function, served by the back pressure as pulmonary structures are dilated by the inspiratory pressure producing the proximal-distal flow gradient into the lung.

Therefore, the development of ventilation and oxygen-exposure strategies to minimise lung injury is a priority for improving patient outcome. Moreover, good knowledge in basic pathophysiology remains the cornerstone to enable clinicians to design strategies with the aim of improving the management of patient-ventilator interaction.

References

1. Donn SM, Sinha SK (2002) Newer techniques of mechanical ventilation: an overview. Seminars in neonatology. 401-407
2. Jobe AH, Bancalari E (2001) Bronchopulmonary dysplasia. Am J Resp Crit Care Med 163:1723-1729
3. Bernstein G, Mannino F, Heldt GP et al (1996) Randomized multicenter trial comparing synchronized and conventional intermittent mandatory ventilation in neonates. J Pediatr 128(4):453-463
4. Greenough A (2001) Update on patient-triggered ventilation. Clin Perinatol 28(3):533-546

5. Bandy KP, Nick JJ, Donn SM (1992) Volume-controlled ventilation for severe neonatal respiratory failure. Neonatal intensive care 5(3):70-73
6. Clark RH, Gerstmann DR (1998) Controversies in high-frequency ventilation. In: Clinics in perinatology. Saunders, Philadelphia 25:113-121
7. Meredith KS, deLemos RA, Coalson JJ (1989) Role of lung injury in the pathogenesis of hyaline membrane disease in premature baboons. J Appl Physiol 66:2150-2158
8. Courtney SE, Durand DJ, Asselin JM et al (2002) High-frequency oscillatory ventilation versus conventional mechanical ventilation for very-low-birth-weight infants. N Engl J Med 347:643-652
9. Gerstmann DR, Minton SD, Stoddard RA et al (1996) The Provo multicenter early high-frequency oscillatory ventilation trial. Improved pulmonary and clinical outcome in respiratory distress syndrome. Pediatrics 98:1044-1057
10. HIFI Study Group (1989) High frequency oscillatory ventilation compared with conventional mechanical ventilation in the treatment of respiratory failure in preterm infants. N Engl J Med 320:88-93
11. HIFO Study Group (1993) Randomized study of high-frequency oscillatory ventilation in infants with severe respiratory distress syndrome. J Pediatr 122:609-619
12. Johnson AH, Peacock JL, Greenough A et al (2002) High-frequency oscillatory ventilation for the prevention of chronic lung disease of prematurity. N Engl J Med 347:633-642
13. Keszler M, Houchang DM, Brudno DS et al (1997) Multicenter controlled clinical trial of high-frequency jet ventilation in preterm infants with uncomplicated respiratory distress syndrome. Pediatrics 100:593-599

Chapter 8

Extracorporeal circulation in the intensive care unit

V. Gašparović, M. Merkler

Extracorporeal circulation is now an important supportive procedure in critically ill patients. Usually, one of the dialysis or haemofiltration procedures, plasmapheresis and haemoperfusion, is selected. In haemodialysis water-soluble solutes are eliminated according to concentration gradients, whilst in the case of haemofiltration solutes are swept across the membrane. In plasmapheresis we eliminate protein structures, and in haemoperfusion liposoluble substances, from the blood. Haemodialysis and haemofiltration are safe procedures that can be applied in patients in acute renal failure and in multiple organ failure. In renal failure supportive procedures are used both to control electrolyte and water disturbances and to control azotaemia. In applying the most recent haemofiltration procedures we try to interfere with septic process, which is the most common factor in the aetiology of acute renal failure (ARF). Multiple organ failure (MOF) is a clinical syndrome characterised by failure of two or more organs and a high mortality rate. Numerous attempts have been made to improve survival in this condition, such as various ventilation strategies, some drug treatments, vasoactive substances, biocompatible membranes and high flux. Nevertheless, the death rate remains high [1]. ARF, on the other hand, is mostly one part of MOF and it is rare for it to occur in isolation as an independent clinical situation. As is already known, with increasing number of organs in failure the mortality rate will also be higher [2]. Plasmapheresis, other important extracorporeal procedure, is a very useful procedure in critically ill patients with hyperviscosity. Clearance of protein structures will normalise the viscosity of the blood and improve the clinical picture of critically ill patients. Other indications for plasmapheresis in critically ill patients are various immunology disorders (Goodpasture syndrome, Wegener granulomatosis, Guillain-Barré polyradiculoneuritis, LE glomerulonephritis, etc.). Haemoperfusion is indicated in some cases of severe poisoning and in vital indications when liposoluble substances can be eliminated by this procedure.

Discussion

In this article we will try to explain the role of different extracorporeal procedures in critically ill patients in the settings in which they are most commonly applied. Extracorporeal circulation is a supportive therapy usually used to correct disturbances of body electrolytes, fluid overload, acidosis and azotaemia in organ failure.

MOF is a clinical syndrome that has a high mortality rate. It is well known that the death rate rises with an increasing number of organs in failure. Failure of one organ results in a death rate of 25–30%, of two organs, 50–60%, of three organs 80% or more, and of four organs, 100%. As pointed out in the Introduction, evaluation of the role of a supportive procedure is hampered by the fact that the principal indicator of outcome is the underlying disease itself. Since sepsis is the most frequent cause of MOF in both surgical and medical intensive care, only control of sepsis allows evaluation of the procedure of extracorporeal circulation [3–5]. In the current literature there is no prospective randomised study showing better patient survival with continuous than with intermittent procedures. Nonetheless, the majority of intensive care specialists advocate this technique of renal function replacement, because it is generally accepted that it has less effect on the circulation of patients who are already haemodynamically unstable [6–8]. In oral communications it is not uncommon to hear that it is "probably better". To determine the procedure of choice in critically ill patients, it is necessary to eliminate certain forms of intermittent haemodialysis, which are themselves beset with frequent problems during extracorporeal circulation. Since the machines with controlled ultrafiltration and bicarbonate dialysate imply a lower incidence of complications, only these devices can be considered comparable with continuous haemofiltration. A meta-analysis of a number of studies that compared biocompatible and bioincompatible membranes indicates that a biocompatible membrane is better: we used machines with controlled ultrafiltration, bicarbonate dialysate solution and a biocompatible polysulfone membrane in our study. There is no doubt that haemodialysis can take effect on hypercalcaemia and volume excess faster, and it disperses the acute threat of electrolyte and water imbalances more rapidly. The weekly dose of haemodialysis in CRF is defined mainly by the quotient $Kt/V>1.2$. The required dose of extracorporeal elimination in ARF is not sufficiently well defined, but it does not differ in essence from the said quotient. The duration of the intermittent procedure sessions is also not well defined. They mostly last 3–4 hours, but some specialists have used prolonged intermittent dialysis lasting 9 hours without obtaining different survival rates than obtained with continuous procedures. It has been well established that cytokines affect the severity of the septic process. According to some recent publications, continuous renal replacement therapy (CRRT) might play a significant role in the elimination of proinflammatory cytokines, in addition to clearing nitrogen products and other large and medium-sized molecules. The possible removal of proinflammatory mediators may permit a blockade of systemic inflammation and a modulation of the altered immune response in these patients, and it may lead to partial or total restoration of the lost homeostasis [9–13]. A statistically significant reduction in heart rate and an increase in systemic vascular resistance and systolic blood pressure were documented in the group of patients who underwent CRRT [14, 15]. On the other hand, according to the meta-analysis of published and unpublished trials in any language, CRRT does not improve survival or renal recovery over those achieved with IHD in unselected critically ill patients with ARF [16]. On the other hand, continuous haemofiltration has less effect on the stability of circulation. Comparison of the values achieved with

intermittent haemodialysis and with continuous haemofiltration should therefore be considered in the light of this. In our prospective randomised study with 104 patients, we also did not observe any difference between the two treatment modalities in 28-day survival or total survival rate or in the frequency of circulatory instability. Even in a subgroup of 80 patients with sepsis and septic shock there was no difference in survival. Sepsis was the underlying disorder in 52 and septic shock in 28 patients out of 104 analysed in this study. The statistical evaluation of the data obtained revealed no significant difference in patient outcome between the two methods of renal replacement therapy under scrutiny [17, 18]. These data are corroborated by the data available in the literature. The number of hypotensive attacks defined by declines in blood pressure by over 10 mmHg was not significantly smaller in our group of patients undergoing continuous procedures. However, in one randomised prospective study survival was better with high-volume haemofiltration (35 ml $kg^{-1} h^{-1}$) than with low-volume ultrafiltration in which a volume of 25 l is replaced in 24 hours [19]. We were not able to validate this difference. When choosing the method of extracorporeal circulation, even though prospective randomised studies have not documented better survival with any of them, intensive care specialists are advised to use the method with fewer side effects and the greater benefit in any given case. Our prospective randomised study did not show a statistically significant difference between the two methods of renal replacement therapy. Survival rates were not affected and neither was the incidence of haemodynamic instability. We therefore believe that management of the underlying condition outweighs the choice of the procedure of renal replacement. Currently, the use of these methods in different parts of the world. Almost all intensive care units in England use continuous methods. In USA intermittent procedures are used more commonly than continuous ones, which is similar to the situation currently found in Croatia. We believe that the two methods are complementary: IHD being beneficial in terms of faster elimination of electrolytes and elimination of waste products and CRRT in terms of regulation of higher calorie requirements and for haemodynamically unstable patients. The expectation that one method would prove superior in terms of better survival have not been corroborated by the data currently available in the literature. The choice of method should be individualised, because both methods have advantages and disadvantages. ARF, which is an integral part of MOF, is a problem frequently encountered in critically ill patients treated in the ICU, but the outcome of these patients depends heavily on control of basic event. Evaluation of each of the supportive procedures is therefore hampered by the fact that it is the underlying disease that has the crucial effect on survival and not so much the type of supportive procedure applied. It is our opinion that these patients are more likely to be treated by continuous methods by appropriately trained ICU personnel.

Plasmapheresis is extracorporeal procedure in which the plasma eliminated is substituted with isotonic 5% human albumin solution. The indications for this are hyperviscosity syndrome and different immunology disorders in which elimination of toxic factors from the plasma can improve the clinical picture in critically ill patients. The elimination of specific antibodies such as those present in Goodpasture syndrome, Wegener granulomatosis, systemic lupus and ascending polyra-

diculoneuritis is important for clinical improvement. The only indication for plasma, as a substitution, in plasmapheresis is thrombotic thrombocytopenic purpura (TTP). TTP is a disease affecting small blood vessels and characterised by thrombotic occlusive lesions, haemolysis, fragmented erythrocytes, thrombocytopenia, dysfunction of the CNS and kidneys, and fever. In TTP patients the deficiency of von Willebrand factor (vWF)-cleaving protease results in low clearance of large multimers of vWF from plasma. The presence of unusually large multimers of vWF in plasma leads to platelet clumping in the microcirculation, with the development of microangiopathic disorders in TTP patients. The acquired deficiency of vWF-cleaving protease is mediated by an antibody to vWF-cleaving protease, while in patients with familial TTP there is complete deficiency of vWF-cleaving protease with the absence of an inhibitor.

Different extracorporeal procedures such as haemodialysis, haemofiltration, haemoperfusion and plasmapheresis are very helpful in some severely ill patients, depending on the basic illness. In most cases these procedures are forms of supportive therapy, but in some new indications and conception these procedures are used to influence the basic disease by means of immunoregulation. In the next few years extracorporeal procedures may help significantly not only in the regulation of electrolyte and water disturbances and the correction of acidosis but also in immunomodulation in severely ill septic patients.

References

1. Bihari D (2001) Preventing renal failure in the critically ill. BMJ 322:1437-1439
2. Brady HR, Singer GG (1995) Acute renal failure. Lancet 346:1533-1540
3. Knaus WA, Draper EA, Wagner DP et al (1985) APACHE II: a severity of disease classification system. Crit Care Med 13:818-829
4. Marschall JC (1994) A scoring system for multiple organ dysfunction syndrome. In: Reinhart K, Eyrich K, Sprung C (eds) Sepsis—Current perspectives in pathophysiology and therapy. (Update in intensive care and emergency medicine) Springer, Berlin Heidelberg New York, pp 38-39
5. Vincent JL, Mendoca A, Cantraine F (1996) The SOFA (Sepsis Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med 22:707-710
6. Oudemans-van Straaten HM, Bosman RJ, Van der Spoel JI et al (1999) Outcome of critically ill patients treated with intermittent high-volume haemofiltration: a prospective cohort analysis. Intensive Care Med 25:814-821
7. Swartz RD, Messana JM, Orzol S (1999) Comparing continuous hemofiltration with hemodialysis in patients with severe acute renal failure. Am J Kidney Dis 34:424-432
8. Bellomo R, Mansfield D, Rumble S et al (1993) A comparison of conventional dialytic therapy and acute continuous hemodiafiltration in the management of acute renal failure in the critically ill. Ren Fail 15:595-602
9. Kutsogiannis DJ (2000) Continuous venovenous hemodiafiltration for renal failure and sepsis. CMAJ 162:537-538
10. Kellum JA, Johnson JP, Kramer D (1998) Diffusive vs. convective therapy: effects on mediators of inflammation in patient with severe systemic inflammatory response syndrome. Crit Care Med 26:1995-2000

11. Bauer M, Marzi I, Ziegenfuß T et al (2001) Prophylactic hemofiltration in severely traumatized patients: effects on post-traumatic organ dysfunction syndrome. Intensive Care Med 27: 376-383
12. Ronco C, Belomo R, Ricci B (2001) Continuous renal replacement therapy in critically ill patients, Nephrol Dial Transplant 16S5:67-72
13. Gopal I, Bhonagiri S, Ronco C et al (1997) Out of hospital outcome and quality of life in survivors of combined acute multiple organ and renal failure treated with continuous venovenous hemofiltration/hemodiafiltration. Intensive Care Med 23:766-772
14. John S, Griesbach D, Baumgartel M et al (2001) Effects of continuous haemofiltration vs intermittent haemodialysis on systemic haemodynamics and splanchnic regional perfusion in septic shock patients: a prospective, randomised clinical trial. Nephrol Dial Transplant 16:320-327
15. Honore PM, Jamez J, Wauthier M et al (2000) Prospective evaluation of short-term, high-volume isovolemic hemofiltration on the hemodynamic course and outcome in patients with intractable circulatory failure resulting from septic shock. Crit Care Med 28:3581-3587
16. Cole L, Bellomo R, Journois D et al (2001) High-volume haemofiltration in human septic shock. Intensive Care Med 27:978-986
17. Gasparovic V, Djakovic K, Merkler M et al (2001) Place and role of new membranes in multiple organ failure: an advance or rumors. Ren Fail 23:175-181
18. Tonelli M, Manns R, Feler-Kopman D (2002) Acute renal failure in the intensive care unit: a systematic review of the impact of dialytic modality on mortality and renal recovery. Am J Kidney Dis 40:875-885
19. Ronco C, Bellomo R, Homel P et al (2000) Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. Lancet 356:26-30

Chapter 9

Clinical decision-making in the management of sepsis and septic shock

F. Baratto

Background

The incidence of sepsis remains high despite the increasing array of powerful antibiotics. Septic shock is the most common type of shock encountered by internists, and it is still a growing cause of death in the United States and Europe, affecting 18 million people worldwide every year, with each case costing an average of more than € 22, 000 to treat [1]. In the United States, there is a valued annual incidence of more than 750, 000 cases: the most important cause of death in intensive care units (ICUs) that is not related to cardiac pathologies [2-3]. In an Italian study [4], mortality rates were 36% in patients with sepsis, 52% in those with severe sepsis and 81.8% in those with septic shock. Despite progress in this field of medicine, severe sepsis is still related to a death rate difficult to tolerate, especially if we consider that mortality due to sepsis has an infective start point and is not due to incurable disease (like advanced cancer). The incidence of sepsis is increasing, not just in the ageing of population but also because of the development of antibiotics resistance. Even with successful treatment, the effects of sepsis can be long-lasting, with a significantly lower quality of life for survivors. Considered from the pathophysiologal viewpoint, sepsis can be seen as the pro-inflammatory and pro-coagulative response to an external agent, leading to the destabilisation of both functions. Sepsis can be defined as the sum of clinical conditions originating from the immune response to an infective process or trauma. The inflammation and coagulation systems interact in a chaotic way that leads to systemic derangement of coagulation and fibrinolysis. The result is an important pro-coagulative impulse and disseminated microthrombosis causing severe alteration of the microcirculation and organ failure.

In 1992, a consensus conference by the American College of Chest Physicians and the Society of Critical Care Medicine recognised three steps in the hierarchy of the inflammatory response to infections, with a progressive increase in the risk of organ-insufficiency and death: (1) sepsis, (2) severe sepsis and (3) septic shock. Patients who have infections and two or more SIRS elements meet the "sepsis" standards; those who also have organ dysfunction or hypoperfusion are considered to have a "severe sepsis"; and those with hypotension not responsive to fluid resuscitation belong to the "septic shock" group [5, 6].

An increasing amount of information to aid in clinical decision-making has become available due to the increased sophistication of diagnostic technology; paradoxically, however, this has not always been to the advantage of the clinician. This is also the case when monitoring septic syndrome. While more is known about sepsis, its origin and development, the complexity of the immune response, the importance of genetic factors, etc., if this abundance of information is poorly organised many clinical errors can be made [7].

There is a strong need to improve the quality of health care through increased awareness of proper management techniques for septic patients. One of the most common problems faced by physicians is deciding which therapeutic intervention is the most appropriate for their patients. Clinical decision-making for the management of patients with sepsis and septic shock is very challenging, beginning with the diagnosis, which is often not clear-cut. ICU physicians often miss the diagnosis of sepsis and too much time is lost when sepsis is misdiagnosed. Early and accurate treatment are essential for increasing a person's chances of recovery. Other aspects faced by clinicians are the choice of diagnostic procedure as well as the type of therapy, which frequently requires a multidisciplinary approach.

The situation of a life-threatening illness not being properly treated because clinicians could not identify it or did not identify it until it reached an advanced stage is often the case when it comes to sepsis. In 2002, The Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) conducted an international survey among physicians to discover their views on sepsis and, in particular, their satisfaction with the current definition. Telephone interviews were conducted with 1,050 physicians from France, Germany, Italy, Spain, United Kingdom and United States. The results showed that 67% of doctors were worried by a lack of a common definition for sepsis; 83% were concerned that the lack of common definition is, at least in part, responsible for misdiagnosis; 81% agreed that a common definition for the global medical community would be a significant step toward better treatment; 87% agreed that the pathogenesis of sepsis is not completely understood; and 82% agreed that the symptoms of sepsis can easily be attributed to other conditions [8]. In this setting, it is clear that a correct medical decision-making procedure would not only increase recognition of the septic condition but also reduce the incidence of errors and decrease the interval between diagnosis and therapy.

The tools that can be used in the decision–making procedure are, synthetically, the following.

Evidence-based medicine

There is no doubt that the "best available evidence" is an important component of medical decision-making, and evidence-based medicine should be seen as a powerful method to identify this evidence [9]. Evidence-based medicine (EBM) is an approach to caring for patients that involves use of the clinical research literature combined with an understanding of pathophysiology and a recognition of clinical

experience. Enthusiasm for EBM has grown at a time of increasingly overt economic constraints in healthcare.

The EBM approach may improve clinical decision-making by:

1. Incorporating the best available scientific literature.
2. Reducing the bias that occurs when medical decisions are based on most recent patients.
3. Explicity balancing the risks and benefits of a clinical decision.

EBM is an important strategy for assessing the vast amounts of published data and applying the conclusions drawn from them to patients. However, in intensive care medicine, there is often a shortage of "gold standard" randomised controlled trial evidence to support specific therapeutic or diagnostic decisions [10].

EBM is widely used in internal medicine, but there is a great need to apply it to critical care medicine as well. Clinical decision-making may be improved by encouraging physicians to explain their medical decision-making, including citation of the literature on which their decisions were based.

A large number of important clinical trials focusing on critically ill patients have been concluded in the last few years [11]. Positive strides have been made in clinical trials, where it was shown that an increased number of interventions results in better outcomes. Most of these studies have focused on patients with severe sepsis, because this population has been the source of frequent mortality and augmented hospital costs. These trials have been among the first critical-care clinical trials to demonstrate reduced mortality in the critically ill. As in any adaptation of EBM, it is essential to strongly examine the trials and to verify whether the benefits can be translated to the individual patient. Some of the interventions, such as small tidal volume mechanical ventilation in patients with acute lung injury or the administration of low-dose corticosteroids to patients with septic shock, are cost-effective and relatively simple to put into practice. Others, such as use of activated protein C in patients with severe sepsis or "tight" glycaemic control in patients with hyperglycaemia, require either significant pharmaceutical expenditure or, possibly, additional health care staff. Nevertheless, the trials represent substantial advances in the field of critical care medicine and should at least be considered for implementation in all ICUs.

EBM-oriented intensive-care physicians face four tasks:

1. To use evidence summaries in clinical practice.
2. To update selected systematic reviews or evidence-based guidelines in their field.
3. To enrol patients in studies of treatment, diagnosis and prognosis on which medical practice is based.
4. Not to consider EBM as a tool to avoid health-care changes that may benefit the patient but which are uncomfortable or challenge the established order.

Guidelines

Clinical guidelines describe how a medical practitioner should respond under certain circumstances for certain patients. Application of such guidelines requires a specialist to collect and interpret the clinical data, apply standard therapeutic or diagnostic programmes and revise them if necessary.

For the management of sepsis and septic shock, a priceless instrument is available: the "Surviving Sepsis Campaign" (SCC) guidelines, which are a product of the collaboration of three major intensive-care organisations: the European Society of Intensive Care Medicine (ESICM), the Society of Critical Care Medicine (SCCM), and the International Sepsis Forum (ISF) [12]. The initial funding for the campaign was provided by the Eli Lilly Company, with subsequent contributions from both Baxter and Edwards Lifesciences. The evidence-based guidelines are aimed at treating sepsis and are of practical utility at the bedside. They are listed by category and not by importance or hierarchy and originate from a systematic examination of scientific literature of the last 10 years. Using a modified Delphi method (expert agreement), the consensus conference made five recommendations, from A to E, with A being derived from studies of more scientific relevance (Table 1).

Table 1. Grading system for SCC guidelines

Grading of recommendation		
	I.	Supported by at least two level I investigation
	II.	Supported by one level I investigation
	III.	Supported by level II investigation only
	IV.	Supported by at least one level III investigation
	V.	Supported by level IV or V evidence
Grading of evidence		
	I.	Large, randomised trials with clear-cut results
	II.	Small, randomised trial with uncertain results
	III.	Nonrandomised, contemporaneous controls
	IV.	Nonrandomised, historical controls and expert opinion
	V.	Case series, uncontrolled studies and expert opinion

Thanks to the SCC, a very useful tool to aid in the therapy of sepsis has been provided. These recommendations regard each aspect of the acute management of severe sepsis and septic shock [13]: initial resuscitation with the correct use of fluids, vasopressors and inotropes; an aetiologic diagnosis; a definitive therapy, such as source control and antimicrobials; adjunctive therapy, including steroids and the use of recombinant human activated protein C; nutritional strategies; the correct use of haemoderivatives; metabolic control; respiratory strategies; sedation-analgaesia protocols; and deep-vein thrombosis and stress-ulcer prophylaxis (Table 2).

Table 2. Arguments of SCC guidelines

A.	Initial resuscitation
B.	Diagnosis
C.	Antibiotic therapy
D.	Source control
E.	Fluid therapy
F.	Vasopressors
G.	Inotropic therapy
H.	Steroids
I.	Recombinant human activated protein C
J.	Blood-products administration
K.	Mechanical ventilation of sepsis-induced ALI/ARDS
L.	Sedation, analgesia and neuromuscular blockade in sepsis
M.	Glucose control
N.	Renal replacement
O.	Bicarbonate therapy
P.	Deep-vein thrombosis prophylaxis
Q.	Stress-ulcer prophylaxis
R.	Consideration for limitation of support

The SCC action plan is based on six points:

1. Increase the awareness of health-care professionals, governments, health and funding agencies and the public of the high frequency and mortality associated with sepsis.
2. Improve early and accurate diagnosis by providing a clear definition of sepsis.
3. Increase the use of appropriate treatment, urging its timely use.
4. Encourage the education of all health-care professional who manage septic patients.
5. Provide a framework for improving and accelerating access to post-ICU care and counselling for sepsis patients.
6. Recognise the need for clear referral guidelines that are accepted and adopted at a local level in all countries by initiating the development of global guidelines.

The hope is to increase awareness and improve outcome for the critically ill patient. The SCC guidelines are not a formally static document: their impact will be tested and the recommendations will be updated almost annually as important new knowledge becomes available.

Although the SCC campaign aims to provide guidance for the clinical care of a patient with severe sepsis or septic shock, the recommendations are not applicable to all patients and should not be implemented indiscriminately. They cannot replace the clinician's common sense and decision-making capability when he or she is confronted with a patient's unique set of clinical variables.

Local protocols

The role of medical protocols is becoming increasingly important in intensive care medicine as a mean to support both diagnosis and treatment. Their importance is due to the potential to promote high-quality medical practice and reduce variations in care while improving cost-effectiveness. For this aim, protocols need to be optimised, that is, without ambiguity and incompleteness. It is necessary to keep in mind that the need for a rapid clinical decision may complicate application of EBM in the ICU setting. In fact, in the ICU, decisions must be much more rapid than in the normal care setting of hospitalised patients. In such cases, pre-scripted information may be extremely effective.

It is becoming generally accepted that implementation of the latest evidence-based research in clinical practice, in the form of protocols, can improve the quality, consistency and cost-effectiveness of health care. It should be noted that medical protocols presume its users to have a certain background knowledge, and that it is unnecessary to explain in complete detail.

New telematic technologies offer great potential in streamlining guideline development and updating activities by supporting remote collaborations in reviews of the literature and the setting of guidelines and by enabling hypermedia versions of literature reviews [14].

The referral guidelines must be accepted and adopted at a local level, and transformed into local protocols, which are instruments of more practical application than generalised guidelines. Local protocols provide a patient approach that is well-known to the entire intensive-care staff, which thereby forms a single instrument to care for the patient. They also act as a reusable skeletal plan that can be refined when applied to a particular patient. Local protocols must be obtained by adapting and eventually adjusting the generalised guidelines to the local reality, (which can be very different from country to country or from region to region), with its organisational problems, its personal practices and limits. The resulting protocols, usually written in text combined with some additional formats, e.g. tables, flow-charts and graphs, can greatly improve patient outcome based on improvements in the quality of care and in methodology [15].

The most advantageous characteristics of a local protocol are: it is defined by the physician and under appropriate medical direction; it is easily modifiable (not being a static document, it has to be reviewed periodically); it is clearly stated, easily intelligible and easily accessed by all components of the health-care staff .

Mortality risk prediction in sepsis

Clinical judgment remains a major part of medical decision-making. The prognosis of the septic patient can actually influence the strategies that can be applied, the correct evaluation of risk/benefits assessment of treating patients with particular devices or drugs, and lastly (but not applicable to all countries) withholding or withdrawing life support from critically ill patients.

Mortality risk prediction in sepsis has evolved from identification of risk factors and a simple count of organ failure to sophisticated techniques that mathematically transform a raw score into a predicted risk of death that is made depending on the expression of specific biomarkers that reflect the septic course of action and its severity [16].

Illness scoring systems

Although early scoring systems were designed only for comparing observed and expected outcomes, some second and third generation scoring systems have been promoted as methods to guide clinical care and treatment, for example, when to withdraw treatment or when to discharge a patient. While the subject of considerable debate, these scoring systems have been shown to be as good as clinical experience in predicting survival. However, current scoring systems only provide probabilities and do not accurately predict whether an individual will survive. Therefore, they should not be used alone to influence clinical decisions about the septic patient and do not replace common sense, which must remain a key aspect of decision-making.

The use of severity-of-illness scoring systems in treating patients with sepsis or septic shock has mainly been aimed at stratifying the numbers in clinical trials or evaluating the performance of the ICU. Few studies have determined whether a scoring system can be used at the onset of sepsis to predict the mortality of a patient who fulfils the sepsis criteria [17].

The first generic physiological scoring system developed to quantify severity of illness according to patient characteristics was the Acute Physiology and Chronic Health Evaluation (APACHE) method. Since the original system was too complex and time-consuming to be used routinely, two derivations were developed: the Simplified Acute Physiology Score (SAPS) and the APACHE II system. These were both subsequently updated to APACHE III and SAPS II [18-19]. At almost the same time, several intensive care scores were developed for the evaluation and quantification of organ failure: Multiple Organ Dysfunction Score (MODS) and the Sequential Organ Failure Assessment (SOFA) [20]. These scoring systems are aimed more at patient description than at outcome prediction. Based on a review of the literature comparing various severity-of-illness scoring systems (APACHE II & III, MPM II0 & MPM II24, SAPS II, SOFA), it can be assumed that APACHE II is the most widely used and perhaps the most appropriate [21]. It is probably therefore also important to calculate SAPS II and SOFA in order to be assured of the validity of the results and their reliability in assisting in clinical decision-making.

Biomarkers

A biomarker is a specific biochemical in the human body with molecular feature useful for measuring the progress of disease or the effects of treatment. Since sepsis

involves complex molecular changes, the identification of specific and sensitive molecular markers is of utmost importance. Modern sepsis research focuses on the inflammatory/immunologic host response to the infection, although the best biomarker of sepsis remains to be determined.

Calcitonin precursors, especially procalcitonin (PCT), is a reliable markers for diagnosing sepsis in critically ill patients. In fact, it may be even more accurate than established markers such as C-reactive protein, lactate, and leukocyte count [22-23]. Elevated PCT concentration appears to be a promising indicator of prognosis, although its low specificity prevents it from being 100% reliable. This is because there are many causes of increased procalcitonin, and only one of these is sepsis; however, a low procalcitonin level makes the diagnosis of sepsis much less likely [24].

Interleukin (IL)-6 levels correlate well with prognosis: patients who die earlier have higher IL-6 levels at baseline than those who die later or who eventually survive. Nonetheless, the pattern is not uniform, since biosynthesis is triggered in both infectious and non-infectious processes [25].

Septic shock and multiple organ failure are associated with coagulation activation, disseminated fibrin formation, and consumption of coagulation inhibitors, such as antithrombin III and protein C. Antithrombin III activity decreases from normal baseline levels and is significantly lower in the group of patients who progress to septic shock than in those who develop severe sepsis. In this sense, it can be a sensitive (but not specific) marker of an unfavourable outcome [26].

Protein C (PrC) is the zymogene of activated protein C (APC), an enzyme that plays an important role in the regulation of haemostasis. This property derives from its ability to inactivate factors Va and VIIIa, with consequent inhibition of thrombin formation. The activation of PC to APC occurs locally and through the thrombin/thrombomodulin complex at the level of receptors (EPCR) located on the endothelial surface [27]. The activated form (APC) becomes linked to protein S on the surface of activated cells, where it can induce anticoagulant and fibrinolytic functions (by directly blocking the inhibitor of fibrinolysis, PAI-1) as well as anti-inflammatory functions (through reduced production of thrombin and direct inhibition of NF-kB, an important nuclear transcriptor of inflammatory cytokines) leading to the inhibition of cytokine responses to endotoxin. The reduction in PC concentration may play a central role in the development of disseminated microthrombosis and organ failure in sepsis. The plasma PC level has been shown to be a valid index of severity in sepsis [28]. Furthermore, PC levels at the start of sepsis seem to be highly predictive of outcome within that phase, with an inversely proportional correlation between plasma levels and mortality. Severe PC deficiency (<40% of the level of PC in pooled normal human plasma) and continued PC deficiency are associated with mortality resulting predominantly from refractory shock and multiple organ dysfunction [29].

Age, underlying co-morbidities, and level of disability are predictive of overall outcome but do not differentiate between early and late death, the latter being primarily the result of non-sepsis-related events. The findings suggest that hospital survival may be dependent on the interplay between the extent of the host response to infection and the patient's physiologic reserve. The latter is the basis on which

abnormalities in biomarkers of inflammation and coagulation are related to disease severity and mortality outcome in patients with severe sepsis.

Personal clinical experience

Human factors are essential in the process of decision-making. There is little use in knowing that an intervention is supported by high-grade evidence if the clinical expertise to treat the individual patient is lacking. In this sense, the importance of good teamwork (doctors, nurses, and physiotherapists) emerges. It must be remembered that not every patient is the same, that randomised controlled studies do not give the answer for individual patients and that the clinical profile of each patient is important [30].

Clinical decision-making capability based on personal experiences embraces a three-phase hierarchy (Fig. 1]):

1. Hypothetical/deductive synthetic thought (originate a solution, diagnosis or treatment for patients for whom no obvious pattern or rules fit the case).
2. Use of rules (rules, algorithms, clinical pathways, heuristics).
3. Pattern recognition (recognise patterns of symptoms, signs and diagnostic tests to reach a diagnosis or treatment strategy).

It is important to remark that medical decision-making cannot be based on most recent or most significant patients; this can lead to a hazardous bias and erroneous conclusions. In addition, during the management of a septic patient

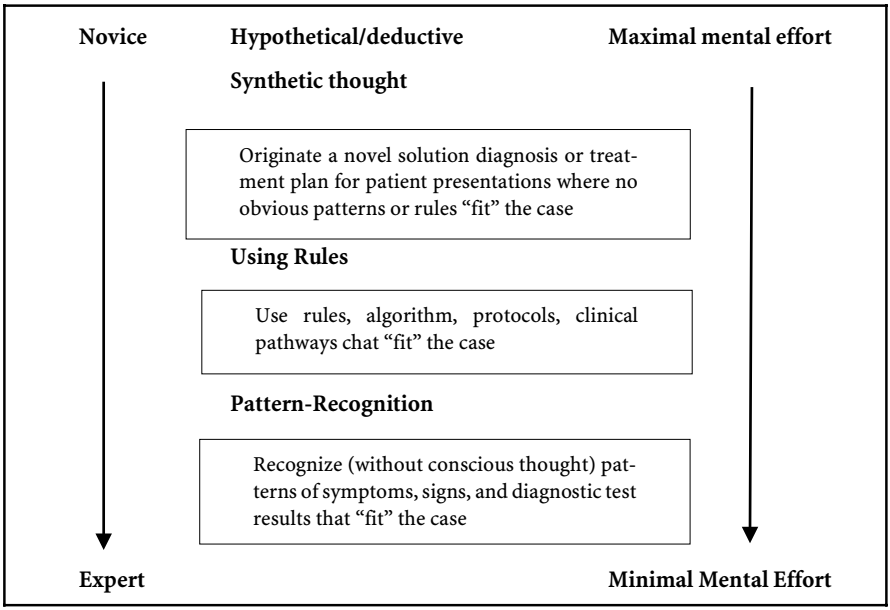

Fig. 1. Clinical decision-making hierarchy

relevant decisions often have to be made without the aid of pre-written protocols and guidelines and without clear indications from the literature. These decisions are made on the base of competence and common sense, by understanding the nature and the consequences of different options, with the aim of making an accurate choice among options using a best risk/benefit assessment. Examples of such situations include the decision to transfer the patient from the emergency room or normal care rooms to the ICU, and vice-versa; which broad-spectrum antibiotic therapy is indicated, based on our hypothesis regarding the source of the infection; or when a surgical intervention is indicated for the source control of infection. Other points to consider are the indication for a continuous or intermittent renal replacement, the need for haemodynamic invasive monitoring, and when to perform a tracheostomy to protect airways from prolonged intubation.

Some studies have indicated that the presence of a properly skilled critical-care physician can have a significant impact on outcome [31]. Rounds at the bedside may also result in better outcomes. To increase the value of bedside rounds, a sequence of questions should be raised systematically in front of each patient, for example, whether the patient is mechanically ventilated, can he/she be weaned from mechanical ventilation? Is nutrition adequate? Is the head of the bed elevated?

Conclusions

Many residents prefer to work in the ICU. The units are almost continuously active, require rapid decision-making and have the aura of life and death. Nevertheless working in ICU is extremely stressful, and there is not always time enough for each patient. In addition, potential tension with the patient's family may lead to their lack of trust in health-care providers, anger, hostility, and litigation. In this landscape, clinical decision-making requires particular attention as well as strategies for reducing errors to a minimum or even zero. It is not possible (and perhaps it is not the "gold standard") to remain a coolly dispassionate, hyper-rational physician systematically considering well defined options on the basis of careful weighing of the evidence [32].

The optimal decision-making strategy in the management of a critically ill patient with severe sepsis or septic shock can be summarised as follows:

1. Sit at the patient's bedside to collect a thorough history and perform an uninterrupted physical exam.
2. Collect data to exclude or confirm the diagnosis of sepsis, keeping in mind widely accepted definitions.
3. Assess, if possible, the gravity of sepsis and its prognosis.
4. Use guidelines and protocols.
5. Allow 2-3 min of uninterrupted time to mentally process each patient.
6. Avoid decision-making when overly stressed or angry.
7. Call for help if the decision is exceptionally difficult.

The use of guidelines and protocols for specific diagnostic or therapeutic decision conserves mental energies while on duty. The clinician should use EBM

techniques to substantiate decisions with facts – while understanding the limits of the evidence – and to consider specific issues, such as the utility of diagnostic tests, the risk/benefit of a therapy, the proper management plan and disease prognosis.

References

1. Kochanek KD, Smith BL, Anderson RN (2001) Deaths: preliminary data for 1999. National Vital Statistic Rep 49:1-48
2. Murphy SL. Deaths: final data for 1998. National Vital Statistics Report Web site. In: http://www.cdc.gov/nochs/data/nvs48_11.pdf
3. Angus DC, Linde-Zwirble WT, Lidicher J et al (2001) Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 29:1303-1310
4. Salvo I, de Cian W, Musicco M (1995) The Italian SEPSIS study: preliminary results on the incidence and evolution of SIRS, sepsis, severe sepsis and septic shock. Int Care Med 21(2):S244-S249
5. Bone RC, Balk RA, Cerra FB et al (1992) American College of Chest Physicians\Society of Critical Care Medicine Consensus Conference. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest 101(6):1644-1655
6. Levy MM, Fink MP, Marshall JC et al (2003) 2001 SCCM/ESICM/ACCP/ATS/SIS International sepsis Definitions Conference. Crit Care Med 31:1250-1256
7. Chapman DM, Char DM, Aubin CD et al (2002) Clinical decision making. In: Marx, Hockemberger & Walls (eds) Rosen's emergency medicine: concepts and clinical practice, pp 107-115
8. SCCM press room - press releases (2002) in: http//www. sccm.org/press_room/press_releases/2002/sepsis_definition.asp
9. Sackett, DL, Rosenberg, WMC, Gray, JAM et al (1996) Evidence-based medicine: what it is and what it isn't. BMJ 312:71-72
10. Vincent JL (2004) Evidence-based medicine in the ICU: important advances and limitations. Chest 126:592-600
11. Craig JC, Irwig LM and Stockler MR (2001) Evidence-based medicine: useful tools for decision making. MJA 174:248-253
12. Dellinger RP, Carlet JM, Masur H et al (2004) Surviving Sepsis Campaign Guidelines for management of severe sepsis and septic shock. Crit Care Med 32(3):858-873
13. Slade E, Tamber PS, Vincent JL (2003) The Surviving Sepsis Campaign: raising awareness to reduce mortality. Crit Care Med 7(1):1-2
14. Kovacs G, Croskerry P (1999) Clinical decision making: an emergency medicine perspective. Acad Emerg Med 6(69):947-952
15. Clayton P, Hripsak G (1995) Decision support in healthcare. Int J Biomed Comp 39:59-66
16. Barriere S, Lowry S (1995) An overview of mortality risk prediction in sepsis. Crit Care Med 23(32):376-393
17. Moreno R, Matos R (2001) Outcome prediction in intensive care. Solving the paradox. Intensive Care Med 27:962-964
18. Knaus WA, Draper EA, Wagner DP et al (1985) APACHE II: A severity of disease classification. Crit Care Med 13:818-829
19. Le Gall JR, Lameshow S, Saulner F (1993) A new simplified acute physiology score

(SAPSII) based o a European/North American multi-center study. JAMA 270:2957-2966
20. Herbert PC, Drummond AJ, Singer J et al (1993) A simple multiple system organ failure system predicts mortality of patients who have sepsis syndrome. Chest 104:230-235
21. Ferreira FL, Bota DB, Bross A et al (2002) Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA 286:1754-1758
22. Wanner GA, Keel M, Steckholzer U et al (2000) Relationship between procalcitonin plasma levels and severity of injury, sepsis, organ failure, and mortality in injured patients. Crit Care Med 28:950-957
23. Vincent J-L (2000) Procalcitonin: The marker of sepsis? Crit Care Med. 28:1226-1227
24. Harbath S, Holeckova K, Froidevaux C (2001) Diagnostic value of procalcitonin, interleukin-6, and interleukin-8 in critically ill patients admitted with suspected sepsis. Am J Respir Crit Care Med 1:164(3):396-402
25. Kinasewitz GT, Yan SB, Basson B (2004) Universal Changes in biomarkers of coagulation and inflammation occur in patient with severe sepsis, regardless of causative micro-organism. Crit Care 8(2):R82-R90
26. Mesters RM, Mannucci PM, Coppola R (1996) Factor VIIa and antithrombin III activity during severe sepsis and septic shock in neutropenic patients. Blood 88:881-886
27. Esmon CT (2003) The PC patway. Chest 124(Suppl):268-328
28. Heuer JG, Sharma GR, Gerlitz B et al (2004) Evaluation of protein C and other biomarkers as predictor of mortality in a rat cecal ligation and puncture model of sepsis. Crit Care Med 32(Suppl):S223-S228
29. Fisher CJ, Yan SB (2000) Protein C levels as a prognostic indicator of outcome in sepsis and related diseases. Crit Care Med 28(Suppl):S49-S56
30. Elstein AS, Shulman LS, Spratka SA (1978) Medical problem solving: analysis of clinical reasoning. Harvard University Press, Cambridge
31. Pronovost PJ, Jenckes MW, Dorman T et al (1999) Organizational characteristics of intensive care units related to outcomes of abdominal aortic surgery. JAMA 281:1310-1317
32. Leape LL (1994) Error in medicine. JAMA 272(23):1851-1857

Chapter 10

Intracranial haemorrhage: the solution offered by recombinant factor VIIa

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Intracranial haemorrhage (ICH) occurs as a result of bleeding into the brain parenchyma with formation of a focal haematoma. It accounts for approximately 10–15% of all strokes and is associated with the highest mortality rate of any type of stroke, a 1-year survival rate lower than 50% and a higher degree of disability among the survivors than is calculated for all strokes. ICH is twice as common as subarachnoid haemorrhage, and primary ICH, accounting for more than 75% of cases, originates from spontaneous rupture of small vessels damaged by chronic hypertension or amyloid angiopathy. Secondary ICH occurs in a minority of patients in association with vascular abnormalities, tumours, or impaired coagulation. Anatomical, aetiological and clinical features make it possible to distinguish between deep, typical ICH (30–50%) and superficial, atypical ICH (30%), but transitional forms are also possible [1]. Computed tomography of the brain allows accurate definition of the site and size of haematoma, surrounding oedema, midline shift and ventricular invasion. Possible sites of bleeding are the basal ganglia (35–44%), the thalamus (10–15%), the cerebellum (5–10%), cerebral lobes (19-25%), the pons (5–9%) and the medulla (rare).

In contrast to large amount of evidence derived from randomised clinical trials of treatment in acute ischaemic stroke, the data available from randomised surgical vs medical trials in intracerebral haemorrhage are sparse. In the latter, neither surgical nor medical treatment has been definitely shown to be effective in patients with ICH. Increasing attention is being devoted to the development of new treatment that will hopefully make it possible to prevent the deterioration of neurological function after an ICH.

Several agents (fresh-frozen plasma, human and recombinant factors VII and IX, cryoprecipitate, aminocaproic acid, tranexamic acid, aprotinin and activated recombinant factor VII) could theoretically be used. Activated recombinant factor VII seems to be the best candidate for limitation of early haemorrhage growth, since it acts primarily on the endothelial disruption and vascular injury site and has a relatively short half-life, contributing to reduction of the high risk from continued bleeding in acute ICH patients [2].

Epidemiology and risk factors

ICH shows an incidence of 37–52 per 100,000, increasing with age (in people over 80 years of age the risk is 25 times that in the general population), although it occurs earlier and with a higher risk of fatality than cerebral infarction. The incidence of ICH varies with ethnicity as well as with age, being higher in Japan than in Europe, although Japanese men who emigrate to live in America subsequently have lower ICH rates than those who remain living in Japan [3]. African Americans have a significantly higher risk of ICH then whites, while Hispanic persons living in New Mexico and New York City seem to have higher rates of ICH than do whites living in the same areas [4, 5]. One recent cohort study found that the increased relative risk for stroke in blacks was reduced after data adjustment hypertension and educational level, while there is indirect evidence that the higher rate of ICH in Hispanic people living in New Mexico might be due to an increased prevalence of cavernous haemangiomas in that population [6]. The 30-day case-fatality rate in the L'Aquila register in Italy was 47.6% and the 1-year case-fatality rate, 56.8%. In subjects under 45 years of age primary ICH accounted for 20% of the first-ever stroke cases, with a crude annual incidence rate of 2 per 100,000 [7].

The types and causes of intracerebral haematomas are reported in Tables 1 and 2.

Table 1. Types of intracerebral haematomas (From [8])

Spontaneous		Traumatic
Hypertensive		Head injury
Nonhypertensive	Amyloid angiopathy	Postoperative
	Haemorrhage into cerebral infarction ('red infarct')	
	Coagulopathy (including iatrogenic)	
	Vascular disease (aneurysm, arteriovenous malformation, vasculitis, etc.)	
	Haemorrhage into brain tumour	
	Drug abuse (cocaine, amphetamines, alcohol)	

Table 2. Common causes of intracerebral haematomas by age (From [8])

Young adulthood	Middle age	Old age
Vascular malformation	Vascular malformation	Amyloid angiopathy
Ruptured aneurysm	Haemorrhage into brain tumour	Hypertensive
Drug abuse	Ruptured aneurysm	Haemorrhage into brain tumour or infarct

The presence of risk factors also greatly increases the incidence of intracerebral haematoma, as do male sex and alcoholism [9].

Degeneration with subsequent rupture of small perforating arteries or arterioles (diameter 50–200 μm) caused by sustained hypertension is the most common

cause (more then 60% of cases) of ICH [2]. ICH attributable to hypertension typically occurs in the basal ganglia, thalamus, pons and cerebellum; these deep regions of the brain are frequently affected by lacunar infarctions, and in some cases both hypertensive ICH and lacunar disease are present in the same patient simultaneously [10].

Many cohort studies started before CT was commonly available in Japan [11, 12] demonstrated elevated risk and mortality of ICH in people with low (<160 mg/dl) serum cholesterol levels. The reason for this association, which is also confirmed by an American cohort study [13], is as yet unknown. The Multiple Risk Factor Intervention Trial [14] reported an interaction between hypertension and low cholesterol level, with an increased risk of death due to ICH in the presence of baseline diastolic blood pressure higher than 90 mmHg; no such interaction has been demonstrated by the Honolulu Heart Study [15] or the Kaiser Program cohort [13], but a link is supported by a recent case-control study [16]. At least theoretically, a deliberate reduction in serum cholesterol to prevent myocardial infarction or cerebral ischaemia might increase the risk of ICH, because of the possible role of cholesterol in vessel wall integrity. In the absence of a definite answer derived from actual data, the association observed between low cholesterol level and ICH needs further confirmation in larger prospective studies.

A relationship between alcohol consumption and ICH has been emphasised by case-control and cohort studies [17, 18]. Larger case-control studies have also yielded a possible J–shaped or U–shaped dose–response relationship between hypertension, alcohol consumption and risk of ICH [19]. A cut-off for the 'protective' level should fall below 60 g/day of alcohol consumption in each study.

Cerebral amyloid angiopathy (CAA) is characterised by deposition of congophilic amyloid-B protein in cerebral cortical and leptomeningeal vessels and has long been recognised as a common pathological substrate for haemorrhage in the elderly in the absence of hypertension or coagulopathy. Typically, ICH associated with CAA is lobar, occurring in the cerebral cortex or subcortical white matter. CAA is now increasingly recognised as a cause of lobar ICH in the elderly, accounting for approximately 10% of cases [2]. ICH is also a complication of thrombolytic therapy for acute myocardial infarction, pulmonary embolism, and ischaemic stroke. There is increasing evidence to suggest that CAA, which itself can cause haemorrhage, may be a risk factor for thrombolysis-related ICH. CAA and thrombolysis-related ICH have some clinical features in common, such as a predilection for lobar or superficial regions of the brain, multiple haemorrhages, increasing frequency with age, and an association with dementia [20].

Many studies have demonstrated a significant association between apolipoprotein-ε4 and haemorrhage with CAA (CAAH); this association is not linked with the presence of Alzheimer disease. Apoliprotein-ε4 seems to increase the likelihood of vascular amyloid-B protein deposition, whereas apolipoprotein-ε2 may elevate the risk of haemorrhage in patients with CAA through vessel wall degradation [21].

ICH recurs more frequently in the lobar form than in deep haemorrhage, and the concept of recurrent haemorrhage characterises the definition of CAA. Lobar ICH exhibits a recurrence rate of 2.4% per year for all cases of ICH, while for

cerebral infarct the corresponding rate is 3.0% per year [22]. The only predictor of recurrent ICH is a lobar location, whereas there is a relationship between the apoliprotein-ε allele and recurrent ICH.

Medical and surgical therapy

Management of ICH should be initially directed towards stabilising respiration and circulation. Early intubation might be necessary, mainly in the case of major ICH, decreased level of consciousness or impairment of the reflexes that protect the airways. Because of the localised nature of the mass effect, marked elevation of the intracranial pressure (IP) may be present in patients with massive ICH. Elevated IP is defined as a pressure over 20 mmHg for more than 5 min. Patients with a decreasing level of consciousness due to increased IP causing cerebral herniation, brain stem compression or severe mass effect should be treated medically with osmotic agents (mannitol or glycerol), steroids, hypovolaemia, controlled hyperventilation, and barbiturate coma in anticipation of surgery (if any) at the most appropriate time. A search of the medical literature failed to find evidence supporting the use of mannitol in acute ICH [23], while glycerol did not prove to be superior to placebo in improving survival and functional outcome in patients with acute ICH [24]. Only three randomised controlled trials on the use of steroids in acute ICH have been reported. One of them was terminated prematurely because of lack of benefit in the presence of more frequent infections, gastrointestinal haemorrhage and diabetogenic effects than in the placebo group [25]. None of the remaining medical options had shown definite benefit in acute ICH.

The management of hypertension in acute ICH also remains controversial. Theoretically, an aggressive reduction of blood pressure could lead to worsening owing to impairment of perfusion pressure, although two recent studies have been unable to detect any clear evidence of a 'penumbra' of ischaemic tissue close to the haematoma. This is actually recommended to keep the mean blood pressure below 130 mmHg [26], but therapeutic trials are needed.

As to the surgical approach to treating acute ICH, two recent pilot studies of craniotomy or stereotactic clot evaluation have emphasised early intervention [27, 28]: the results in terms of for the evacuation of intraventricular haemorrhage were promising when urokinase was used to facilitate drainage via a catheter [29]. Standardisation of surgical techniques and early intervention may be the key to effective management in view of the paucity of the evidence (based on case series and nonrandomised cohort studies) and the low grade of relevant recommendations (mainly C) that are also evidenced in the guidelines for ICH management written by a panel of experts for the America Heart Association [26].

Ultra-early haemostatic therapy and recombinant factor VIIa

Recently, early haematoma growth has been considered a cause of early neurological deterioration after ICH. Bleeding in ICH was classically considered as complete in few minutes, while neurological deterioration occurring during the 1st day was attributed to cerebral oedema and a mass effect around the haemorrhage. It is well recognised that early haematoma growth occurs in 18–38% of ICH cases studied with CT within the first 3 h of onset, and a correlation between this growth and early clinical deterioration has been established [30, 31].

Only one study has been conducted prospectively in order to evaluate this phenomenon [30]. A CT scan performed within 3 h of onset in consecutive cases of ICH demonstrated a significant increase in the volume of intraparenchymal haemorrhage (>33%) in 26% of patients when rescanned 1 h later. In a further 12% of cases haematoma growth occurred between the 1-h and the 20-h CT scan. The 38% of ICH patients in whom the haematoma growth phenomenon was observed also had a higher mortality (44% versus 34%) and worse disability scores 30 days after onset, although these differences were not statistically significant.

ICH growth has been shown to occur very commonly within 6 h of onset in retrospective studies. The same studies have also linked early haematoma growth to early neurological deterioration and increased mortality. This phenomenon has been attributed to persistent bleeding or rebleeding from a single site of arterial or arteriolar rupture. However, it can also derive from secondary bleeding into perilesional tissue in the periphery of the clot (where multiple microscopic and macroscopic haemorrhages have been revealed), so that ICH growth results from the confluence of multiple haemorrhages to the periphery of an existing clot in the perilesional low-flow zone.

Pressure in the local tissue rises and cerebral blood flow (CBF) to the region decreases, causing subsequent ischaemia. Some researchers have speculated that reperfusion injury in the first few hours immediately after ICH onset is a major factor in the development of perilesional ischaemia. However, the alteration in perilesional blood flow is still only poorly understood. In any case, the secondary brain injury that develops in the hours immediately after the insult is most often far more severe than that caused by the haemorrhage itself.

The relevance of early growth haematoma derives from the notion that haematoma volume represents the single most powerful predictor of 30-day mortality after ICH, and therefore that the arrest of haematoma growth might reduce the neurological deterioration related to either early (haematoma growth) or late (oedema around the haematoma and mass effect) worsening. When effective, ultra-early haemostatic therapy might also make early evacuation of the haematoma safe. It is important to observe that (according to extrapolations from the data from Brott et al.) in view of the fact that early rebleeding could occurs at something midway between a linear and an exponential rate, even if haemostatic intervention is completely effective enlargement of the haematoma might occur nonetheless in 10%, 17%, or 22% of ICH cases 15, 30, or 45 min after the baseline CT scan.

Besides the well known haemostatic agents (fresh-frozen plasma, factor IX concentrate, prothrombin complex concentrate, human and recombinant factors VIII and IX, cryoprecipitate, DDAVP) that are useful in pathologic conditions (coagulopathy, platelet disorders, etc.) in the normal coagulation process the most feasible haemostatic therapies include aminocaproic acid, tranexamic acid, aprotinin, and activated recombinant factor VII (rFVIIa).

Aminocaproic acid and tranexamic acid are synthetic derivatives of the aminoacid lysine. Their primary effect is to inhibit fibrinolysis, and they are more suitable for clot stabilisation than for the promotion of clot formation. They reduce the frequency of rebleeding after aneurysmal subarachnoid haemorrhage, but increase the frequency of delayed cerebral ischaemia and other thrombotic complications, so that the net result is no benefit in outcome. Aprotinin is a polypeptide that primarily inhibits the initiation of both coagulation and fibrinolysis and for which the main indication is the need to reduce perioperative bleeding (cardiac surgery, orthotopic liver transplantation).

Activate recombinant factor VII (rFVIIa), a powerful initiator of haemostasis approved for the treatment of bleeding in patients with haemophilia, may also promote haemostasis in patients with normal coagulation [2]. This drug exerts its primary effects locally in regions of endothelial disruption and vascular injury [32, 33]. In most physiological conditions, triggering of haemostasis is initiated by an interaction between circulating activated coagulation factor VII (FVIIa) and tissue factor (TF) following exposure of TF at the site of injury. FVIIa is only proteolytically active when it forms a complex with TF. TF is normally expressed in the deep layers of the vessel wall, and is only expressed following injury. This fact ensures highly localised, and not disseminated, activation of coagulation. TF may also be exposed after widespread tissue damage, extensive atherosclerotic lesions or sepsis and is expressed on monocytes; this may predispose the patients thus affected to adverse events following administration of FVIIa.

The FVIIa–TF complex initiates the conversion of factor X to Xa, which in turn converts prothrombin to thrombin. Pharmacological doses of rFVIIa amplify this process and catalyse the conversion of factor X to Xa on the surface of activated platelets in the absence of TF.

In many years (since 1996) of clinical use for the treatment of haemophilic patients with inhibitors, rFVIIa has shown a low risk of systemic coagulation or thromboembolic complications and has a good record in the treatment of ICH. Preliminary clinical trials indicate that rFVIIa also promotes haemostasis in patients with normal coagulation systems. Its action is very rapid, and its half-life of 2.5 h corresponds well to the duration of continued bleeding in the acute stage of ICH. Its safety in ICH patients has been tested in two earlier trials. In the phase IIb trial recently presented at the Vancouver 5th World Stroke Congress (23–26 June 2004), 400 ICH patients have been recruited worldwide (73 centres) and randomised to receive rFVIIa (Novoseven, Novonordisk) at one of the three doses (40 mg/kg, 80 mg/kg, 160 mg/kg) or placebo, with 100 patients in each group. ICH was confirmed by CT scan within 3 h of symptom onset, and treatment consisted in a single bolus of rFVIIa i.v. within 1 h of the CT scan. To quantify the effect of

the treatment, the volume of the haematoma was measured on the initial and on the second CT scan obtained 24 h after treatment. The number of patients dead or disabled after 90 days was also recorded. In patients who received rFVIIa the percentage increase in size of the haematoma was smaller at all doses tested than in those who received placebo. A 35% reduction in mortality was also found, as was an improved outcome in terms of disability [4]. A total of 17 adverse thromboembolic events, such as myocardial infarction and ischaemic stroke, were recorded among the subjects treated with the active treatment (as might have been expected with a drug promoting clotting). Of course, this study, whose final results are to be published, needs further confirmation, and the real impact of adverse events should be studied in order to identify ICH patients who are at risk of side-effects and determine which can and cannot be treated with rFVIIa [34].

If the results of this study are confirmed, ICH patients may have a real chance of receiving adequate and effective treatment. As happens with thrombolytic therapy in ischaemic stroke, this fact might expand the perspective of stroke neurologists, internists and emergency physicians in treating haemorrhagic stroke patients also faster and better, improving survival and residual disability.

References

1. Fazio C, Carolei A (1976) Le emorragie cerebrali. Minerva Angiol 1:109-188
2. Mayer SA (2003) Ultra-early hemostatic therapy for intracerebral hemorrhage. Stroke 34:224-229
3. Takeya Y, Popper JS, Shimizu Y et al (1984) Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii, and California: incidence of stroke in Japan and Hawaii. Stroke 15:15-23
4. Bruno A, Carter S, Qualls C et al (1996) Incidence of spontaneous intracerebral hemorrhage among Hispanics and non-Hispanic whites in New Mexico. Neurology 47:405-408
5. Sacco RL, Boden-Albala B, Gan R et al (1998) Stroke incidence among white, black, and Hispanic residents of an urban community: the Northern Manhattan Stroke Study. Am J Epidemiol 147:259-268
6. Bruno A, Carter S (2000) Possible reason for the higher incidence of spontaneous intracerebral hemorrhage among Hispanics than non-Hispanic whites in New Mexico. Neuroepidemiology 19:51-52
7. Marini C, Totaro R, De Santis F et al (2001) Stroke in young adults in the community-based L'Aquila registry: incidence and prognosis. Stroke 32:52-56
8. Hamilton MG, Zabramski JM (1996) Spontaneous intracerebral hematoma. In: Tindall GT, Cooper PR, Barrow DL (eds) The practice of neurosurgery. Williams and Wilkins, Baltimore
9. Ariesen MJ, Claus SP, Rinkel GJ et al (2003) Risk factors for intracerebral hemorrhage in the general population: a systematic review. Stroke 34:2060-2065
10. Fisher CM (1971) Pathological observations in hypertensive cerebral hemorrhage. J Neuropathol Exp Neurol 30:536-550
11. Lin CH, Shimizu Y, Kato H et al (1984) Cerebrovascular disease in a fixed population of Hiroshima and Nagasaki. Stroke 15:653-660
12. Szatrowski TP, Peterson AV, Shimizu Y et al (1984) Serum cholesterol, other risk factors, and cardiovascular disease in a Japanese cohort. J Chron Dis 37:569-584

13. Iribarren C, Jacobs DR, Sadler M et al (1996) Low total serum cholesterol and intracerebral hemorrhagic stroke: is the association confined to elderly men? The Kaiser Permanente Medical Care Program. Stroke 27:1993-1998
14. Iso H, Jacobs DR, Wentworth D et al (1989) Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the Multiple Risk Factor Intervention Trial. N Engl J Med 320:904-910
15. Yano K, Reed DM, Maclean CJ (1989) Serum cholesterol and hemorrhagic stroke in the Honolulu Heart Program. Stroke 20:1460-1465
16. Segal AZ, Chiu RI, Eggleston-Sexton PM et al (1999) Low cholesterol as a risk factor for primary intracerebral hemorrhage: a case-control study. Neuroepidemiology 18:185-193
17. Klatsky AL, Armstrong MA, Friedman GD (1989) Alcohol use and subsequent cerebrovascular disease hospitalizations. Stroke 20:741-786
18. Monforte R, Estruch R, Graus F et al (1990) High ethanol consumption as risk factor for intracerebral hemorrhage in young and middle-aged people. Stroke 21:1529-1532
19. Thrift AG, Donnan GA, McNeil JJ (1999) Heavy drinking, but not moderate or intermediate drinking, increases the risk of intracerebral hemorrhage. Epidemiology 10:307-312
20. McCarron MO, Nicoll JA (2004) Cerebral amyloid angiopathy and thrombolysis-related intracerebral haemorrhage. Lancet Neurol 3(8):484-92
21. McCarron MO, Nicoll JA, Stewart J et al (1999) The apolipoprotein E å2 allele and the pathological features in cerebral amyloid angiopathy related hemorrhage. J Neuropathol Exp Neurol 58:711-718
22. Hill MD, Silver FL, Austin PC et al (2000) Rate of stroke recurrence in patients with primary intracerebral hemorrhage. Stroke 31:123-127
23. Bereczki D, Liu M, do Prado GF et al (2000) Cochrane report: a systematic review of mannitol therapy for acute ischemic stroke and cerebral parenchymal hemorrhage. Stroke 31:2719-2722
24. Yu YL, Kumana CR, Lauder IJ et al (1992) Treatment of acute cerebral hemorrhage with intravenous glycerol. A double-blind, placebo-controlled, randomized trial. Stroke 23:967-971
25. Poungvarin N, Bhoopat W, Viriyavejakul A et al (1987) Effects of dexamethasone in primary supratentorial intracerebral hemorrhage. N Engl J Med 316:1229-1233
26. Broderick JP, Adams HP, Barsan W et al (1999) Guidelines for the management of spontaneous intracerebral hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. Stroke 30:905-915
27. Morgenstern LB, Frankowski RF, Shedden P et al (1998) Surgical treatment for intracerebral hemorrhage (STICH): a single center randomized clinical trial. Neurology 51:1359-1363
28. Zuccarello M, Brott T, Derex L et al (1999) Early surgical treatment for supratentorial intracerebral hemorrhage: a randomized feasibility study. Stroke 30:1833-1839
29. Naff NJ, Carhuapoma JR, Williams MA et al (2000) Treatment of intraventricular hemorrhage with urokinase: effects on 30-day survival. Stroke 31:841-847
30. Brott T, Broderick J, Kothari R et al (1997) Early hemorrhage growth in patients with intracerebral hemorrhage. Stroke. 28:1-5
31. Fujii Y, Tanaka R, Takeuchi S et al (1994) Hematoma enlargement in spontaneous intracerebral hemorrhage. J Neurosurg 80:51-57
32. Hedner U, Ingerslev J (1998) Clinical use of recombinant FVIIa (rFVIIa). Transfus Sci 19:163-176
33. Hedner U (1998) Recombinant activated factor VII as a universal haemostatic agent. Blood Coagul Fibrinolysis 9:S147-S152

34. Mayer SA, Brun N, Broderick J et al (2004) Recombinant factor via for acute intracerebral hemorrhage. 5th World Stroke Congress, Vancouver 23–26 June 2004 (Abstract book, p 48)

Chapter 11

An introduction to Open Source software licensing and use in anaesthesia department

V. Lanza, M. Sajeva

The Open Source initiative is a real revolution for the scientific community of computer science, actually it points straight to the improvement of pure research to obtain better software usable by the whole community, but still protecting the intellectual rights. The key point does not mean only access to the source code or free software, but also the freedom to derive works from the original and to redistribute or sell them as new software or as component of a bigger project. The father of this idea is Richard Stallman [1], the founder of the GNU Project; it started in 1984 to develop a free software operating system named GNU.

GNU is the recursive acronym for "GNU's Not Unix", but now, commonly, it indicates all the software that is developed under the Open Source initiative. One of the most important software born under the wing of GNU initiative is the Linux Operative System, which is a real and fully functional Network Operative System that can be used for server installation instead of commercial software (e.g. Microsoft, SUN and Apple solutions). Linux is a Unix-like operative system and it is the OS (Operative System) most widely used by professionals for server installation. Most of the Internet server runs on Linux with Apache installed as Web server. The October 2003 Netcraft Web Server Survey [2] found that more than 64% of the web sites on the Internet are using Apache, thus making it more widely used than all other web servers combined.

The use of Open Source software in an anaesthesia department can improve the work flow, the efficiency and it can drop down the total cost of ownership (TCO) of the computer installation, requiring much less expenses in software licence. We will try to give the guidelines to discover what is Open Source software and how to use it in an anaesthesia department.

Type of licensing

We will introduce the most important kind of software and knowledge licenses available for the Open Source community. Every license has got pros and cons, and it is up to the developer to choose the one that fits his needs best.

1. *GPL (GNU General Public License)* – it is the basic license directly derived from the GNU project. The main peculiarity of GPL is that any software or library derived from a GPL project must be released under the GPL license too. It means

free access to the whole source code, that is no commercial software, with proprietary parts, can be produced from a GPL project. This means also that every GPL software will produce Open Source software. It is very restrictive, but it is conform to the original GNU project.

2. *LGPL (Lesser GNU General Public License)* – it is similar to the GPL, but it allows the release of non Open Source software or libraries from other Open Source project. That means that it is possible to derive commercial protected code from scientific project for free.
3. *BSD (Berkley Software Distribution)* – it is the most free and open license, which means that the developer can do whatever he prefers with binaries (executables) and with source code, but he has got to include the copyright and the disclaimer statements. It is a system that Microsoft and Apple use in their product portions of code released with BSD license.
4. *FDL (Free Documentation License)* – the Free Software Foundation has released a special license to protect the intellectual rights and favourite the release of free books and manual. The most famous example is the Wikipedia, the Free Encyclopaedia [3] available on the Internet in more than fifteen languages.

These are only the four most used licenses available under the Open Source initiative (Fig. 1). There are a lot more derived directly and made personal to satisfy the needs of the developer. It is up to the scientific community to choose the best for one's project.

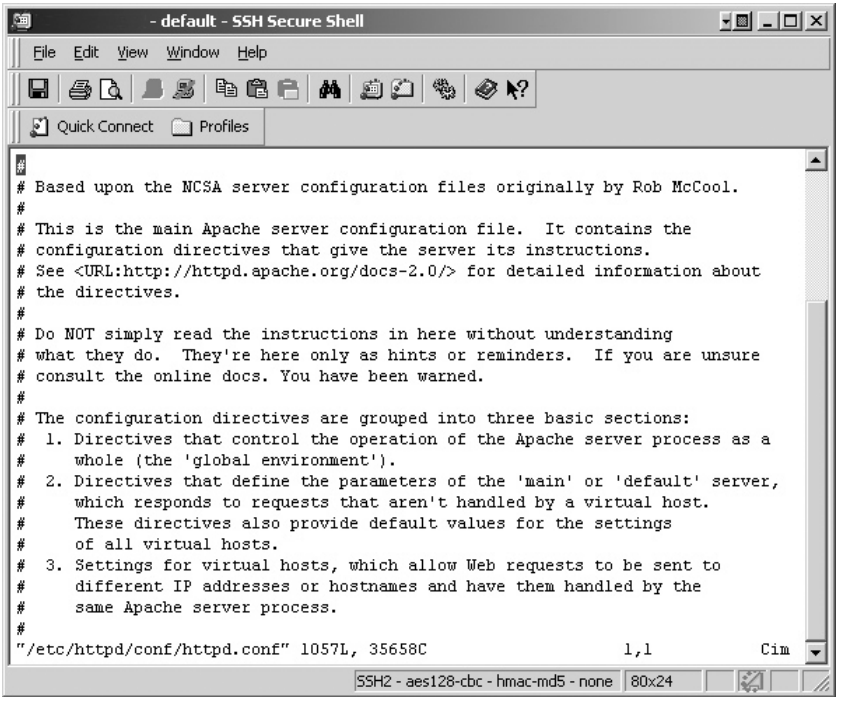

Fig. 1. The Open Source Initiative official website

What is Linux

Linux [4] is one of the most interesting Open Source projects; actually, it is the most widely used OS for server installation in universities and in enterprises. It was initially developed by Linus Torvalds, a young student at the University of Helsinki in Finland. The project started in 1991, but the 1.0 release of the kernel (the very heart of the OS) only occurred in 1994. The Linux kernel was released under the GNU General Public License and that allowed other developers to use the source code to make it better and to develop the rest of the OS. The current kernel version is 2.6 (released in December 2003), but development continues. The most interesting characteristics of the OS are functionality, adaptability and robustness, that is why the most important IT companies (IBM, SUN, HP and others) decided to use and support the development of this project.

The kernel needs other modules and libraries to be used as an OS, like the *file system*, the *IO system* (Input – Output), and so on. But what makes an OS attractive is the software equipment available to offer services.

The sum of OS plus a software bundle is named a *Distribution*, or a *Distro* (as hackers prefer to say). There are different *distros* of Linux available on the Internet, the most widespread is the Red Hat [5], which is a commercial product made explicitly for intensive server applications. *Red Hat* has an Open Source project available to the whole Linux community, named *Fedora* [6]. The main difference between Fedora and Red Hat *distros* is in the technical support offered by the company.

Fedora is a good distribution, easy to install and administer, and should be kept in mind for every installation project that does not require official certification. But this is not the only solution available: there are *distro* that fit on one floppy disk, made just to serve as a gateway firewall or as network routers.

Adaptability is the keyword that let Linux be used in every computer project.

Open Source software in anaesthesia

The adoption of Open Source solutions can improve the management and quality of every computer assisted activity, but it requires an initial investment in training for the system administrator as well as for the whole staff.

Open Source software can be used in anaesthesia departments easily: the most common start can be the installation of a Linux server as firewall/gateway to let the whole computer network share the Internet access in security. This kind of project only requires an obsolete PC (like an Intel Pentium-based computer) and it can be used with a single floppy Linux distro (e.g. Coyote Linux [7]). This kind of configuration lets you start a complete and powerful firewall just by using an unused component: download the *distro*, load it in a floppy disk and let your PC boot from the floppy itself. The configuration of the floppy requires some knowledge about TCP/IP protocols and networking, but not too much in depth.

Another interesting project could be the installation of a fully interactive

intranet based on a Linux server. Using a full Fedora free distribution, we could use Apache [8] as a web server with MySQL as database and PHP as script language to develop a dynamic intranet accessible from the whole department to register and read, for example, patients data.

If we do not want to become pro in computer and network administration, we can hire a professional that will install and train our staff to use the system. The TCO of the whole system will be much lower than buying software licenses that will need to be renewed every two years.

In the same way, if we want to start the development of a personalised service, like patient data recording, we can start by using another project under GPL license and customise it, making it much more comfortable to our needs.

The source for all the Open Source project is the Source Forge web site [10] (Fig. 2), where it is possible to find all registered projects of the developers community. It could be interesting to start a research by using the keyword "medical": we will find a lot of projects used all over the world in enterprises too.

It could seem a little hard for beginners to start the installation or to plan such a development of the computer infrastructure, but there could be other ways to start the approach to Open Source initiatives: for example, one could start to use *OpenOffice* instead of other commercial office suite software. *OpenOffice* [11] is a software suite made of a word processor, a spreadsheet, a presentation maker (and many other tools); what must be said is that the tools are very similar to the

Fig. 2. SourceForge.net is the most complete Open Source project repository

Microsoft Office suite, and the software is also compatible. Making the amount is simple: consider that every two years it is necessary to renew the license of the software tools to upgrade them to the latest version, with an estimated amount of about 500,00 euro per PC.

Introduction to the use of the Open Source solution in an anaesthesia department

The Open Source software can improve the computer network management in an anaesthesia department with many positive effects; we will only cite the three largest: (1) improvement of the system security due to access to the source code; (2) reduced TCO (Total Cost of Ownership) and reduced licensing fees; and (3) straight technical support from the scientific community of developers.

The use of the Open Source software in an anaesthesia department can improve the work flow and the efficiency of the computer network. We will try to give the guidelines to install a simple intranet server for an anaesthesia department using Open Source software. Our project supposes that the administrator does not have Unix or Linux skills; however, he must be a good computer user (we refer as training level to the ECDL, basic level) and he must have a small computer network working on the basis of the TCP/IP protocol (which is common in the Microsoft Windows environment). This knowledge will be enough to let him install and set-up a simple intranet server based on Linux, the most famous Open Source Operative System, with Apache as web server. This article could be helpful to the management too: actually, it shows how, with a very little economical investment, we can install a powerful intranet based on Open Source software, that is without spending money in software license.

Choosing the right software

The adoption of Open Source software in an anaesthesia department does not require specific skills for the system administrator; first of all, we have to plan the computer network infrastructure. In our example, we will plan to implement a small intranet server based on Linux and Apache as web server. We will suppose the existence of a small computer network based on the ethernet standard (IEEE 802.3) using the TCP/IP protocol; we will add a simple server to this system to offer advanced services as, for example, a simple web server.

Before talking about Linux, let us go back to the concept of *distros*. An OS is made by the *kernel*, the very heart of the OS itself, plus a subset of other software pieces that let the kernel "talk" to the other hardware components. For example, the *file system* is the software that lets the kernel access the storage peripherals and write data in *files*. Once we have a full OS running, like Linux, we need application programmes to offer services to our users. For example, if we want to offer an intranet service based on a web browser, we need a web server application running

on our server. Users will access the server using a common web browser, like Microsoft Internet Explorer o Netscape Navigator. In the same way, if we want a database to share information on our ICU patients, we will need to run an RDBMS server application to let our user access shared data.

A *distro* is the sum of the OS itself plus a set of software programmes. There are a lot of distributions available on the Internet, some commercial, and some for free.

We will base our installation on *Fedora Core 1* [1], which is the Open Source distribution (completely free) of Red Hat Linux [2] and Apache [3] as web server (included in the Fedora *distro*) to distribute hypertext documents over the network.

To start the implementation of our project we need a personal computer equipped with at least 64 megabyte of RAM, an Intel Celeron class processor, and a network interface card. This is the typical computer that we cannot use any more, not even to write down a document in WinWord, but this will be perfect as a server, if powered by Linux. If you have a better machine, it will run even better and you will have a faster server. The hard disk has to be 4 gigabytes at least: the full installation of Fedora needs about 4 gigabytes plus at least one gigabyte for virtual memory (*swap partition*) and user's data. All the software we need to do the installation is downloadable from the Internet, or may be obtained from several technical newspapers.

The installation of Fedora is quite simple: insert the first CD-ROM and let it boot up from the CD itself, then follow the screenshots. In Fig. 3, the disk partitio-

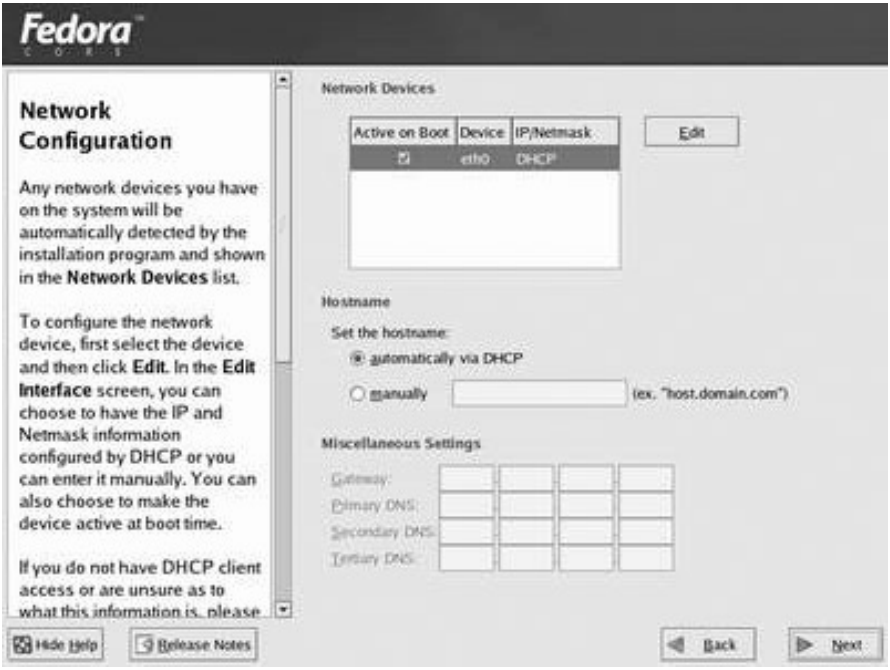

Fig. 3. The hard disk partition can be made automatically or using the Disk Druid tool

ning setup is shown; we can select the "*Automatically partition*" option to let the installation software choose the best partition for our hard disk. The most important part is the setup of the NIC (Network Interface Card). We will use the TCP/IP protocol to let hosts in the network share data and talk to each other. Each host has a unique codename, named IP address: we will give the server a private subnet class C address, 192.168.0.1, with 255.255.255.0 as netmask. Enter this data in the form shown in Fig. 4, and do not forget to disable any firewall option that will be proposed in the next screenshot.

After a few screenshots that let you choose the language, the time zone and password for the root, and the administrator of the server, the real installation of files in your PC will start.

At the end, the system will reboot and you will be asked to login entering your username (root) and password. The installation of the system is done, now we need only to setup the web server to start our anaesthesia intranet.

The web server installation

Apache is the most used web server [3] on the Internet and we are going to set it up for our anaesthesia intranet service. The setup itself is very simple although the configuration file of Apache is quite long: more than 1050 rows. Actually, we have to change the content of just one row to make it work.

Most of the configuration files in Linux can be found in the directory */etc*. The Apache configuration files are in the directory */etc/httpd/conf*. We will use a text

Fig. 4. The manual setting of the NIC let you choose the host name and the IP adress

editor to modify the configuration file: if you feel more comfortable with a GUI (Graphic User Interface), just click on the RedHat icon in the lower left corner and choose an editor, otherwise open a console window and use *VI*, the command line editor.

The use of VI could be harder at the beginning, but is a very powerful tool for the system administrator. Open up a command line editor and from the prompt type the following command:

```
]# vi /etc/httpd/conf/httpd.conf
```

the output should be similar to what is shown in Fig. 5. As we see, the length of the configuration file is more than 1050 rows, but we need to change only one statement.

VI has got three working modes, but we only need to know two of them: the *command mode* and the *insert mode*. When we load it, VI is in command mode; whatever key we press is intended as a command. The "/" key is the search

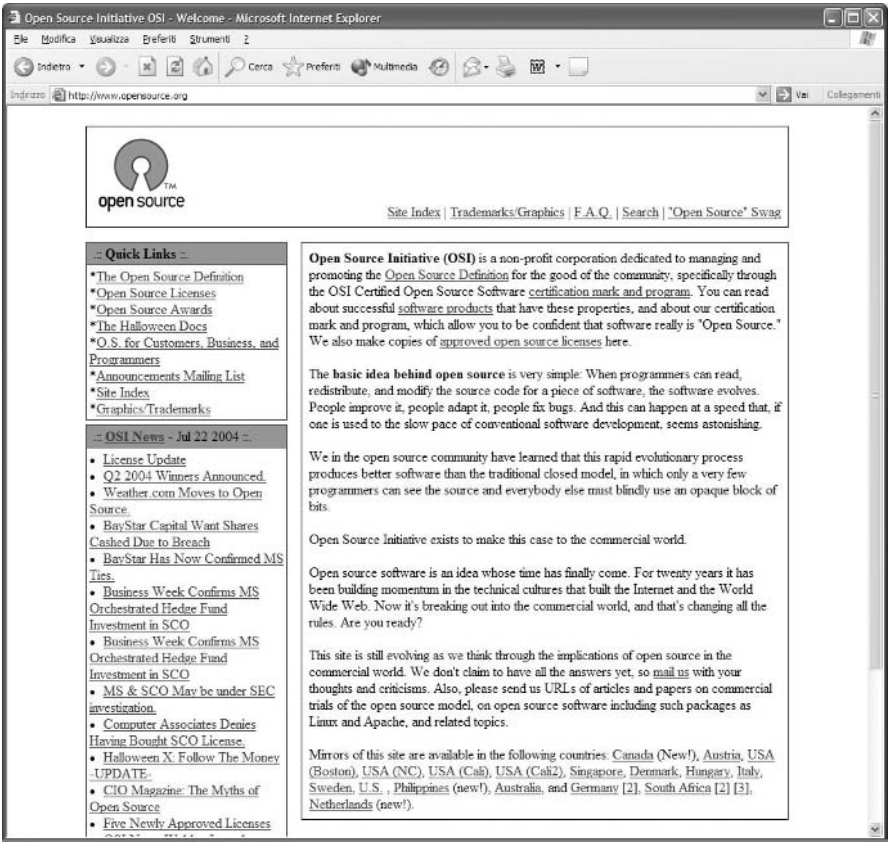

Fig. 5. The conFig.tion file httpd.conf it is longer than 1200 rows, but to make Apache works you need to change just a few

command, whatever string we type after it is used as the pattern-matching text. Let us type

```
/ServerName
```

the screenshot should change and it should show the following text marked:

```
# ServerName new.host.name:80
```

The "#" character is the remark command; it means that whatever is written after it is not evaluated by the Apache server. We have to delete the "#" character and type, instead of "new.host.name:80", the real name of the host or its IP address. If preferred, we can add the listening port; the default port for HTTP (the Web's protocol) is TCP 80, so we will not change it. To change the text, we have to switch the working mode of VI from *command mode* to *insert mode*, which allows us to edit the text. Let us move the cursor, with the arrow keys, near the *ServerName* command and type the letter "I"; now we should be able to read "--INSERT--" in the lower part of the screen. Change the statement as following

```
ServerName 192.168.0.1
```

To save the configuration file, we change the VI mode back to command, by typing once on the ESC key (we do not see the "--INSERT--" text in the lower part of the screen any longer). Let us type the following command:

```
:wq
```

which means write the file and then quit the editor. If we wanted to quit without saving our work, we can type

```
:q!
```

which means, just quit.

To be sure that the web server is running with the configuration file we just modified, we have to restart it:

```
]# service httpd restart

Stopping httpd:[ FAILED ]
Starting httpd:[ OK ]
```

The first row of the message means that the web server was not running, the second confirms that now the server is working.

To test that everything is correctly working we can open a web browser, like Mozilla if we are working on the same PC, or IE if we are working on another PC

of the network and type as URL the IP address of the server 192.168.0.1. The output should be similar to the one in Fig. 6.

To publish HTML documents on the intranet, all we have to do is to put them in the *Document Root* of the web server, the default Document Root is */var/www/html*. Whatever file will be moved to that directory, will be available for all the user on the LAN. The best way to make files easily available is to create an *index.htm* file to include links to the other files. A simple example of the index.htm file could be the following:

```
<html>
  <head>
    <title>ICU Intranet Home Pagetitle
  </head>
  <body>
      <h1>Welcome in the ICU Intraneth1
```

Fig. 6. This is what your browser will show if the conFig.tion of Apache is working good

```
    here you will find the most updated documents and
draft sheets.<br>
    <a href="cover.doc">Cover example for reportsa - a
WinWord cover to use in reports.<br>
    <a href="timetable.xls">The official timetablea</a>
<br>
<br>
<a href="mailto:sajevalanza@icu.it">Need any help? Wri-
te us an email!</a>
<hr>
  </body>
</html>
```

We have to copy all the text in a file and save it as *index.htm* in the */var/www/html* directory. If we do not feel comfortable with HTML tags language, we can use an editor like Macromedia Dreamweaver or Microsoft FrontPage that is much more user-friendly and will help us in writing the code.

Conclusions

EU member states are supporting the Open Source initiative suggesting the adoption of free software in government installation instead of commercial software. The latest national laws suggest adoption of Open Source solutions in educational structures as well, such as in schools and universities. It is clear that imprisoning knowledge with license fees does not allow any improvement nor any growth.

The project proposed in this article aims to show how simple the installation of an intranet based on Open Source OS could be. The use of Open Source does not require financial investments in either hardware or software, but only investments in the training of people to improve their computer skills. Hardware and software get obsolete very quickly. That does not happen with investments in training: Open Source is the key to improve the quality of our technical staff and of our computer environment.

References

1. Richard Stallman Home Page – http://www.stallman.org/
2. Netcraft Web Server Survey – http://news.netcraft.com/
3. Wikipedia, the Free Encyclopaedia – http://www.wikipedia.com/
4. Linux.org – http://www.linux.org/
5. Red Hat Corporation – http://www.redhat.com/
6. Fedora Project – http://fedora.redhat.com/
7. Coyote Linux – http://www.coyotelinux.com/
8. Apache Project – http://www.apache.org
9. Coyote Linux – http://www.coyotelinux.com/

10. Source Forge – http://www.sourceforge.net
11. OpenOffice.org – http://www.openoffice.org/
12. Tartamella M, Sajeva M, Vassallo M, Puccio L (2004) Amministrazione Avanzata di Server Linux. Springer – Verlag Italia, Milan

MICRODIALYSIS

Chapter 12

Lessons we have learnt from microdialysis in animals and humans

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Microdialysis provides the opportunity for simple and continuous monitoring of metabolic changes in tissues before they are reflected in the peripheral blood chemistry or in systemic physiological parameters. The method was developed more than 30 years ago for monitoring chemical events in the animal brain [1, 2] and has become an accepted scientific standard technique with more than 9000 published studies. In the late 1980s the possibilities for monitoring the human brain were first explored [3], and since then the technique has been used for biochemical monitoring of most human tissues. However, the clinical usefulness of the technique was delayed owing to lack of instruments suitable for clinical routine use, including bedside monitoring of relevant biochemical variables.

In 1995 CMA Microdialysis (Stockholm, Sweden) introduced a sterile microdialysis catheter, a simple microdialysis pump and a bedside biochemical analyser. The instrumentation was originally intended for subcutaneous and intramuscular use, but after slight modification the microdialysis catheter has also been used intracerebrally as an integrated part of routine multimodality monitoring. In this short review I will briefly discuss some principles and limitations of the microdialysis technique and present data from experimental studies in animals and clinical experience collected in various human tissues.

The microdialysis technique

The basic idea of microdialysis is to mimic the function of a blood capillary by positioning a thin dialysis tube in the tissue. The membranous wall of the tube allows free diffusion of water and solutes between the surrounding interstitial fluid and the perfused solution (perfusate). The concentration gradients between the interstitial fluid and the perfusate constitute the driving force for diffusion. The molecular weight of the molecules being sampled is limited by the pore size of the dialysis membrane (cut-off). The perfusate flows along the dialysis membrane slowly and at a constant speed, and the sample (dialysate) is collected and analysed biochemically.

The concentration of analytes achieved in the dialysate is dependent on the degree of equilibration between the perfusate and the interstitial fluid. This is

termed 'relative recovery' (recovery) and is defined as the dialysate/interstitial concentration ratio expressed as percentage [4]. Accordingly, the microdialysis technique does not give the absolute concentration of the biochemical variables studied unless it is calibrated in vivo. When clinical microdialysis is performed as a standardised routine technique (see below) this limitation is usually not significant. However, there are some underlying factors that it is important to recognise.

Factors affecting recovery in vivo

The three most important factors affecting recovery during clinical routine conditions are the area of the semipermeable membrane, the perfusion flow rate and the diffusion in the surrounding interstitial fluid. As expected, the recovery increases in proportion to the dialysis membrane area [8]. Compared with dialysis membranes used in most experimental studies the microdialysis catheters intended for clinical purposes are very large. The CMA/60 catheter, which is used in for example in subcutaneous tissue, has a 30-mm-long dialysis membrane and the CMA/70 catheter used in the brain, a membrane length of 10 mm. The diameter of both probes is about 0.6 mm, and the standard cut-off of the dialysis membrane (during clinical routine) is 20 kDa.

The standard perfusion flow rate used during clinical routine is 0.3 ml/min, which allows sampling every 30 min. Owing to the slow perfusion rate and the large dialysis membranes recovery is high: in vivo recovery for the intracerebral (CMA/70) catheter is approximately 70% for the biochemical variables used routinely (see below) [9]. (For the longer CMA/catheter it is approaching 90%.) If the perfusion rate is increased to permit more frequent sampling recovery decreases to about 30% at 1 ml/min [9].

The diffusion rate in the surrounding interstitial space is important and varies with the molecular weight of the studied analytes and size and tortuosity (prolongation of diffusion pathways due to cell membranes) of the interstitium. The recovery may thus vary between tissues and changes with the pathophysiological conditions. The problem has no significance for clinical routine, but is very relevant, for example when microdialysis is used for quantitative pharmacokinetic studies [10, 11]. The importance of the limitation imposed on diffusion by the surrounding interstitial space also explains why it is useless to perform in vitro calibration to compensate for the recovery in vivo.

Biochemical variables monitored during clinical routine

The biochemical variables used for routine monitoring during clinical conditions are chosen to cover important aspects of cerebral energy metabolism and to give indications of degradation of cellular membranes (Fig. 1). In normal conditions glucose is the sole substrate for cerebral energy metabolism. In the cytosol it is degraded to pyruvate (glycolysis) with a net yield of 2 ATP for each molecule of glucose. Owing to the redox conditions part of the pyruvate (py) is converted to

lactate (la). The la/py ratio reflects cytoplasmatic redox state, which can be expressed in terms of the lactate dehydrogenase equilibrium:

$$\frac{[NADH]\,[H^+]}{[NAD^+]} = \frac{[Lactate]}{[Pyruvate]} \times K_{LDH}$$

The la/py ratio thus gives information of tissue oxygenation. The major part of pyruvate enters the citric acid cycle in the mitochondria with a net yield of another 36 ATP. The relation between the citric acid cycle and the important excitatory transmitter glutamate is shown in Fig. 1. However, the glutamate level obtained by microdialysis does not reflect liberation of the transmitter exclusively. The intracellular concentration of glutamate is high and the concentration in the interstitial fluid probably often reflects release from leaky cells.

Since the brain does not contain any triglycerides (TG) a high level of intracerebral glycerol is considered to be a reliable indicator of degradation of the glycerophospholipids of cellular membranes and cell damage [5, 6]. In other tissues, and in particular in fat tissue, glycerol is mainly obtained from degradation of TG. Lipolysis is under sympathetic control through catecholamine receptors on the adipocytes, which are stimulated both by circulating catecholamines and by local

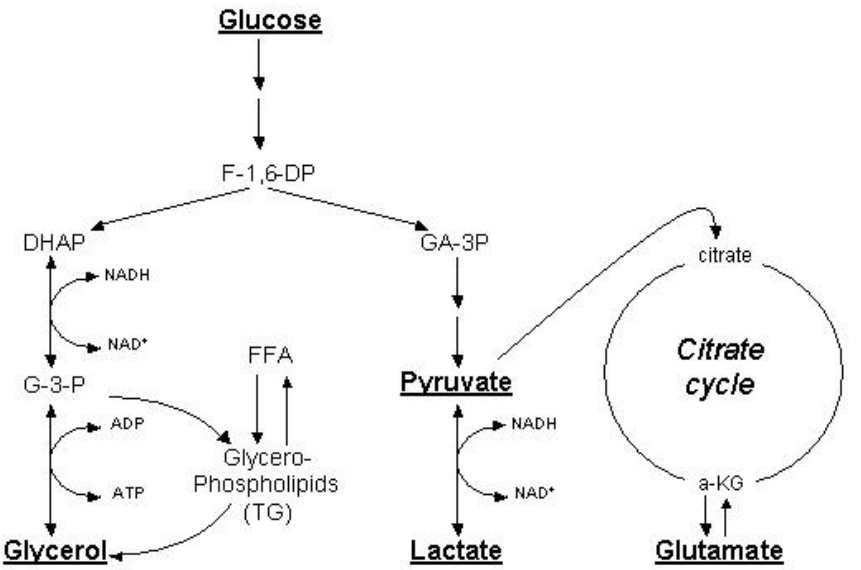

Fig. 1. Simplified diagram of intermediary metabolism of the glycolytic chain and its relation to the formation of glycerol and glycerophospholipids and to the citric acid cycle. *Underlined* metabolites are measured at the bedside with enzymatic techniques (*F-1,6-DP* fructose-1,6-diposphate, *DHAP* dihydroxyacetone-phophate, *GA-3P* glyceraldehyde-3-phosphate, *G-3-P* glycerol-3-phosphate, *FFA* free fatty acids, *TG* triglycerides, *a-KG* a-ketoglutarate)

noradrenergic nerve endings. The glycerol level in subcutaneous fat tissue may be used as an indicator of physical and of mental stress [7].

During clinical routine the biochemical variables are analysed with a CMA 600 Microdialysis Analyser (CMA Microdialysis, Stockholm, Sweden). This analyser uses enzymatic and colorimetric techniques. The reagent enzymatically oxidises the substrate, and hydrogen peroxide is formed. Peroxidase then catalyses the reaction between the hydrogen peroxide, 4-amino-antipyrine and phenol (3,5-dichloro-2-hydroxy-benzene sulfonic acid in the case of glycerol, and *N*-ethyl-*N*-(2-hydroxy-3-sulfonylpropyl)-*m*-toluidine in the case of pyruvate) to form red-violet quinoneimine or quinonediimine. The rate of coloured substance formation is proportional to the substrate concentration, which is photometrically measured at a wavelength of 546 nm.

Clinical microdialysis

The microdialysis technique has been used in most human tissues, as shown in Fig. 2. At this point I will here only briefly review some data from the tissues surrounded by frames in Fig. 2. Since microdialysis is an invasive technique, the tissue damage caused by the catheter and the possible complications are of great importance. These risks may be most obvious during intracerebral microdialysis, and the brain is also the organ in which we have most clinical experience.

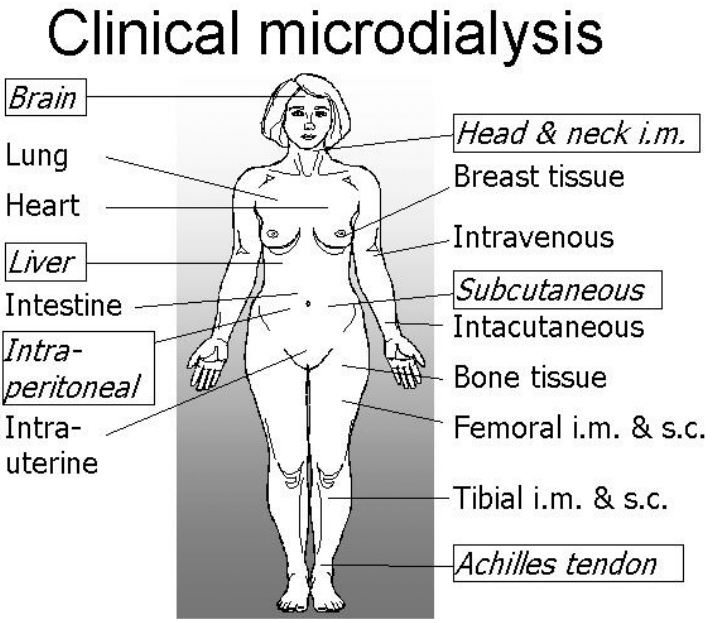

Fig. 2. Human tissues that have been studied with the microdialysis technique. Tissues within *frames* are discussed in the text

It is essential that the blood–brain barrier (BBB) remains intact during microdialysis, and many experimental studies have shown that this is the case [12, 13]. The initial tissue damage causes a disruption of the BBB that is visible <10 min after insertion, but the BBB appears to be intact again after 30 min [14]. Histological examinations have described the tissue reactions in the rat brain surrounding the microdialysis probe [15]. Within the first 2 days the neuropil is normal and only occasional haemorrhage surrounds the probe. On the 3rd day an astrocytic reaction is seen, using antiserum against glial fibrillary acidic protein. Fourteen days after implantation there are layers of reticulin-positive fibres surrounding the dialysis membrane. Similar reactions may occur in the human brain, but it should be underlined that, in contrast to the experimental situation, catheter insertion and all surgical procedures are performed under sterile conditions in the clinical situation. In addition, the relation between the sizes of the brain and of the probe is very different for rat and for human, and wide species variations exist, for example in the proportions of neurons to astrocytes.

We have used intracerebral microdialysis as a routine clinical monitoring technique in almost 300 patients (most of them with multiple intracerebral catheters), and we have not observed any complications of this technique.

Subcutaneous and myocutaneous microdialysis

Since the glucose concentration in the extracellular space of the subcutaneous adipose tissue closely mirrors the blood glucose concentration, microdialysis might be an ideal technique for frequent analysis of the glucose level. Subcutaneous or myocutaneous microdialysis may also be used for tissue monitoring after plastic surgery.

Subcutaneous

A reliable method for long-term, continuous in vivo monitoring of blood glucose concentrations in insulin-dependent diabetes has been sought for several decades. In 1993 Bolinder et al. [16] suggested subcutaneous microdialysis as a solution to this problem. Their studies showed that microdialysis could be used for continuous, long-term monitoring in diabetic patients during ordinary daily life and that the daily glucose profiles could be used for tailoring insulin therapy. In a follow-up study it was shown that the true diurnal variability was too great to be accurately reflected even by frequent self-monitoring of the blood glucose level [17].

The importance of careful control of the blood glucose level was recently emphasised by the observation that maintenance of a blood glucose level below 6 mmol/l significantly reduced mortality in intensive care patients [18, 19]. To investigate whether the subcutaneous glucose level also accurately reflect blood glucose levels during intensive care, we performed a study in 62 severely head-injured patients (2434 simultaneous analyses of glucose concentration in arterial blood and subcutaneous adipose tissue) [20]. With the techniques used in the study (perfu-

sion flow 0.3 μl/min; membrane length 30 mm), the recovery of glucose from subcutaneous adipose tissue has been shown to be between 0.79 [21] and 0.9 [22]. Since the ratio blood/plasma glucose concentration is approximately 0.9, we would expect that in ideal circumstances the interstitial glucose concentration would be equal to blood glucose concentration divided by 0.9 and, since recovery for glucose with the present technique is approximately 0.8, the glucose s.c./glucose blood ratio obtained would be close to 0.9. In many patients a very good correlation was obtained, as illustrated by two cases in Fig. 3.

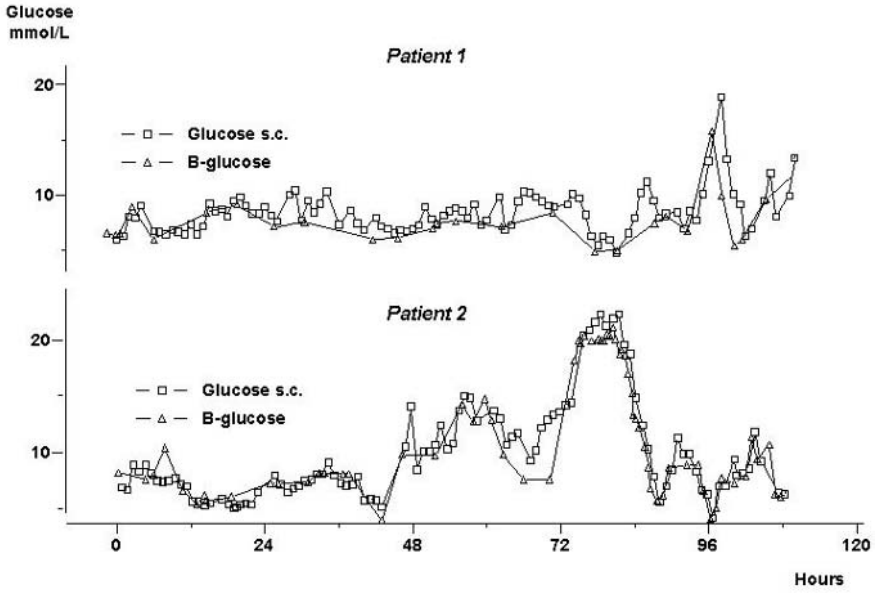

Fig. 3. Comparison of glucose level in subcutaneous fat tissue obtained by microdialysis and the simultaneous blood glucose levels in two patients during intensive care after severe traumatic brain injury

However, comparison of the average glucose concentration in blood (mean±SEM) and interstitial fluid of subcutaneous adipose tissue (mean±SEM) in all 62 patients during the first 24 h after start of intensive care (Fig. 4) showed that the glucose s.c. was significantly higher ($P<0.001$) during the period 6–7 h after the start than 1–2 h after the start, although the blood glucose concentration did not change significantly. The ratio glucose s.c./glucose blood increased slowly during the first few hours and was approximately 0.85 by 6–7 h after start of treatment. The ratio continued to increase slowly and was above 0.90 about 60 h after start of treatment.

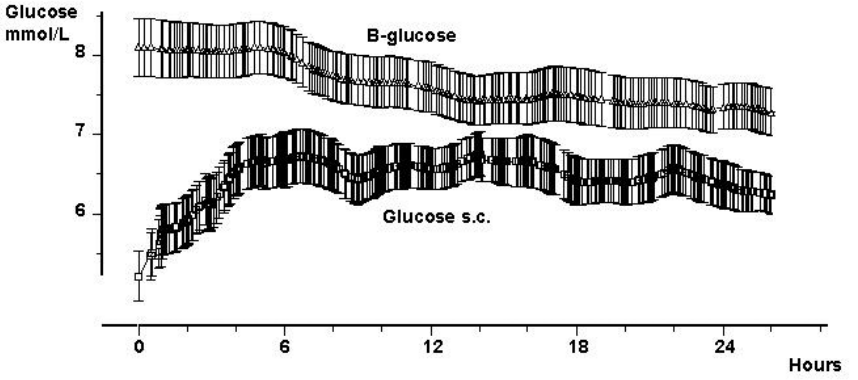

Fig. 4. Average glucose concentration (mean value±SEM) in blood (*B-glucose*) and interstitial fluid of subcutaneous adipose tissue (*Glucose s.c.*) in 62 patients during the first 24 h after the start of pharmacological treatment to counteract stress reaction and increased ICP

During the first few hours after trauma many patients were probably under sympathetic stress with peripheral vasoconstriction although their vital functions had been secured. We assume that our antistress/antihypertensive treatment protocol [23] affected the balance between local consumption rate and delivery of glucose. A close correlation between glucose s.c. and glucose blood, similar to that obtained in diabetic humans in normal conditions [16, 17], was not obtained until the initial stress reaction had been treated, as revealed by the decreases in MAP, lactate s.c. and glycerol s.c. (c.f. [20]).

Myocutaneous

Myocutaneous flaps have been increasingly used in reconstructive surgery. Despite technical advances and improved surgical skills 1–10% of free flaps fail, which is commonly due to postoperative thrombosis of the vascular pedicle. Röjdmark et al. [24] used microdialysis to study the biochemical changes induced during flap transfer. They defined the biochemical changes observed during ischaemia and suggested that the technique might be useful in postoperative flap surveillance. They also conducted a postoperative study of ten women previously treated for breast cancer who underwent reconstruction with transverse rectus abdominis or latissimus dorsi flaps [25]. The postoperative biochemical changes were monitored for 24 h, and the authors concluded that the microdialysis technique seemed to be well suited for continuous monitoring of tissue metabolism in myocutaneous flaps of different origin.

Recently, a microdialysis study demonstrated the changes of glucose, lactate, and pyruvate in an experimental model of microvascular flap during ischaemia and reperfusion [26]. The authors concluded that decreasing glucose levels and increa-

sing lactate concentrations were associated with arterial and venous occlusions from the first hour of ischaemia. In venous ischaemia, lactate concentrations remained lower than those in arterial ischaemia. The increase in la/py ratio and lactate/glucose ratio was related to ischaemia and also discriminated between arterial and venous occlusion.

Microdialysis of the liver

After liver transplantation some degree of clinical and biochemical dysfunction invariably occurs. Early detection of vascular complications, such as arterial and portal vein thrombosis, are especially important in the early transplantation period. In an experimental study in the pig, Nowak et al. [27] used intrahepatic microdialysis to study the levels of glucose, pyruvate, lactate and glycerol before surgery, during cold storage of the liver and during implantation and recirculation. After cold perfusion glucose, lactate and glycerol levels increased, whereas pyruvate rapidly decreased. During cold storage glucose and glycerol levels increased, lactate remained stable and pyruvate levels were undetectable. After portal reperfusion glucose, lactate and glycerol continued to increase for about 60 min, slowly normalizing thereafter. The la/py ratio calculated initially increased but remained stable during cold storage. During rewarming it showed an accelerated increase, but after reperfusion the la/py ratio rapidly normalised.

Knowledge of these metabolic patterns during experimental conditions was used to interpret changes obtained in ten consecutive patients undergoing whole-organ orthotopic liver transplantation [28]. The authors concluded that the microdialysis procedure was easy to perform and safe and described the metabolic profiles reflecting recovery of the liver graft from ischaemia-reperfusion injury.

Intraperitoneal microdialysis

The intestinal tract and the intraperitoneal cavity are of considerable interest during intensive care. A suitable monitoring technique would be valuable for more than diagnosis of disorders of the visceral organs and for postsurgical surveillance. During shock and multiorgan failure splanchnic ischaemia is a major contributory component. Microdialysis of the intestinal wall has been performed in many experimental studies and most of these experiences were recently reviewed and the data extended in a doctoral thesis [28]. However, microdialysis of the intestinal wall would probably be difficult to perform in clinical conditions.

On the basis of experimental studies, intraperitoneal microdialysis (IPM) was recently suggested as a possible clinical method [30]. In a pig model, intestinal ischaemia was induced by occlusion either of the superior mesenteric artery or of arcus vessels supplying a 30-cm-long small bowel segment. The authors concluded that IPM might also be a good monitoring technique for the early detection of intestinal ischaemia in clinical conditions.

The IPM technique was subsequently introduced for biochemical monitoring after major abdominal surgery, and the results have been presented in a series of publications [31–35]. Although the number of patients studied is still limited and the data must be regarded as preliminary, IPM seems to have the potential for becoming an important technique in clinical routine monitoring and in further clinical scientific investigations.

Intracerebral microdialysis

The majority of clinical studies utilising microdialysis have been performed in the brain. As mentioned above, the biochemical variables used during routine monitoring have been chosen to cover important aspects of cerebral energy metabolism (glucose, pyruvate, lactate), to indicate excessive interstitial levels of excitatory transmitter substance (glutamate) and to give indications of degradation of cellular membranes (glycerol). Most basic principles of cerebral energy have been known for decades [35]. However, it might be useful to review how the levels of these measured biochemical variables vary during experimental, transient cerebral ischaemia when the microdialysis technique is used for sampling.

Fig. 5A shows changes in the intracerebral levels of glucose and lactate and in the la/py ratio after the induction of cerebral ischaemia. In Fig. 5B the changes in the la/py ratio are compared with the simultaneous changes in the levels of glutamate and glycerol. In this experimental study transient brain ischaemia was induced in fetal lambs in utero by occlusion of the umbilical cord followed by resuscitation after cardiac standstill (Amer-Wåhlin et al., paper in preparation). The microdialysis technique was identical to that used during clinical conditions except that the perfusion rate was increased (1.0 μl/min) to allow frequent sampling (which explains the basal levels of the biochemical variables). Induction of ischaemia caused an almost instantaneous increase in the la/py ratio shortly afterwards, followed by an increase in the glutamate level. Glucose, pyruvate, and glutamate rapidly recovered after resuscitation, but the levels of lactate and glycerol continued to be elevated.

These data are of importance for the interpretation of our clinical findings. The la/py ratio, reflecting the redox state of the cytoplasm, will increase immediately when delivery of oxygen is insufficient and will rapidly return to a near-normal level on reoxygenation. The lactate level rapidly increases during ischaemia but remains elevated when circulation is restituted. Glycerol, the indicator of degradation of cellular membranes, increases relatively slowly during energy failure and remains elevated for some time when energy metabolism is normalised. The interstitial glucose level, finally, reflects the balance between delivery from the blood capillaries and the cellular uptake.

It is important to realise that the microdialysis technique gives biochemical information only on a small volume surrounding the catheter. However, the regional differences in blood flow and energy metabolism are considerable in most pathophysiological conditions, and most adverse secondary events primarily affect

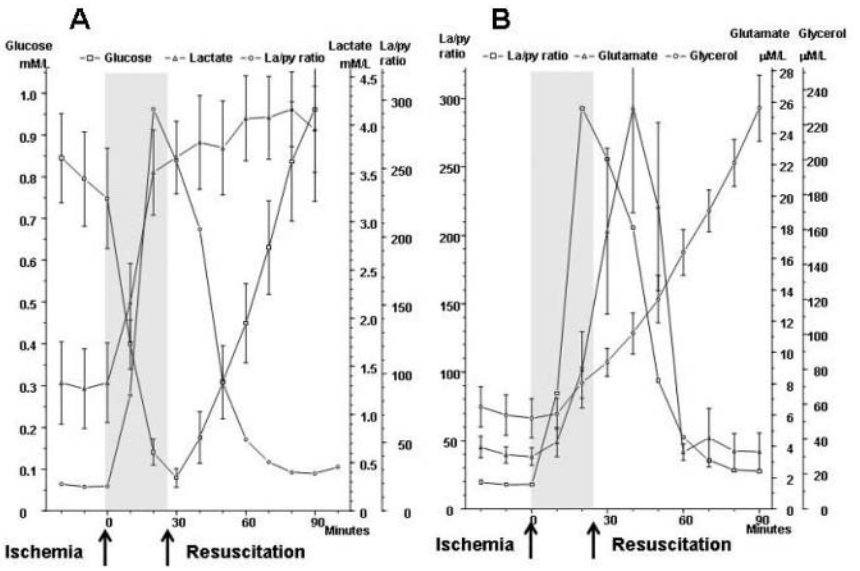

Fig. 5 Changes in intracerebral biochemistry during transient global cerebral ischaemia
A Levels of glucose and lactate (mean±SD), and the lactate/pyruvate (la/py) ratio
B Ratio of lactate to pyruvate and levels of glutamate and glycerol (mean±SD)

the sensitive penumbra zones surrounding focal lesions [36]. The fact that microdialysis is a regional technique may thus be regarded as an advantage, providing the positioning of the catheters can be visualised in relation to the focal injuries. Since the CMA/70 catheter has a thin gold thread placed in the tip of the probe it can be visualised on routine CT-scanning (Fig. 6). This gold thread does not interfere with MR scanning (but the perfusion pumps must naturally be disconnected and removed during the scan).

Intracerebral microdialysis has been introduced in many neurosurgical centres, and the number of published scientific studies is approaching 700. In a subsequent short review I will discuss some of the experience collected in these studies.

Other aspects of clinical microdialysis and the potential for clinical research

As illustrated in Fig. 2, microdialysis has been used in various human tissues, most frequently to investigate or monitor energy metabolism as one part of clinical routine. However, microdialysis is an open technique, permitting sampling of practically all stable biochemical compounds provided they can pass the dialysis membrane. The technique can also be used to deliver substances to the interstitial fluid from the perfusate. For routine purposes, catheters with a membrane cut-off

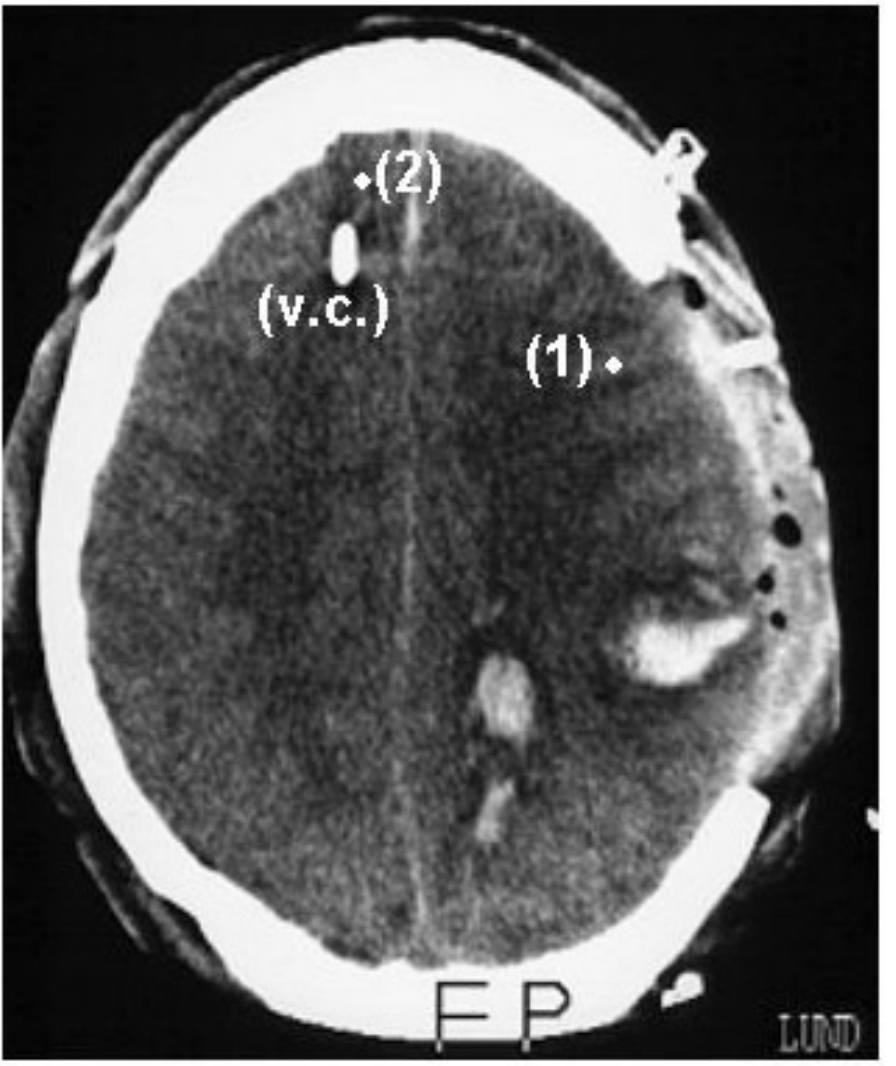

Fig. 6. Postoperative CT scan illustrating positioning of one microdialysis catheter in a 'worse' position (*1*) in the penumbra zone close to superficial contusions after evacuation of an acute subdural haematoma and removal of the bone flap. One microdialysis catheter is placed in the contralateral hemisphere – a 'better' position (*2*) – close to the ventricular catheter (*v.c.*)

of 20 kDa are used, but 100-kDa catheters are available for clinical purposes, and these also allow the study of larger molecules (e.g. cytokines). When these catheters are used some technical precautions, such as addition of colloids to the perfusate, must be taken to avoid interstitial loss of the perfusing fluid [37].

That use of the microdialysis technique can sometimes lead to quite unexpected clinical discoveries is illustrated by a study of patients with chronic Achilles tendi-

nosis [38]. In this study the authors found high levels of glutamate but no signs of inflammation and no increase in prostaglandin E2 in patients with chronic Achilles tendon pain. Surprisingly, a subsequent study showed that eccentric training relieved the pain but did not decrease the glutamate level in the tendon [39].

The microdialysis technique has great potential for clinical scientific studies. This fact is illustrated by the possibilities of measuring the interstitial concentrations of various drugs and even performing quantitative pharmacokinetic studies. The brain may seem to the most difficult tissue for such investigations, but owing to the BBB and the wide functional differences in different regions, it is perhaps also the most challenging target. Two recent publications have shown that it is possible to accomplish such pharmacokinetic studies [10, 11].

References

1. Ungerstedt U, Pycock CH (1974) Functional correlates of dopamine neurotransmission. Bull Schweiz Akad Med Wiss 1278:1-5
2. Ungerstedt U (1991) Microdialysis – principles and application for studies in animal and man. J Intern Med 230:365-373
3. Meyerson BA, Linderoth B, Karlsson H et al (1990) Extracellular measurements in the thalamus of parkinsonian patients. Life Sci 46:301-308
4. Ungerstedt U, Herrera-Marschitz M, Jungnelius U et al (1982) Dopamine synaptic mechanisms reflected in studies combining behavioural recordings and brain dialysis. In: Kotisaka M et al (eds) Advances in dopamine research. Pergamon Press, New York, pp 219-231
5. Ungerstedt U, Bäckström T, Hallström Å et al (1997) Microdialysis in normal and injured human brain. In: Kinney JM, Tucker HN (eds) Physiology stress and malnutrition. Functional correlates, nutritional intervention. Lippincott–Raven, Philadelphia New York, pp 361-374
6. Hillered L, Valtysson J, Enblad P et al (1998) Interstitial glycerol as a marker for membrane phospholipid degradation in the acutely injured human brain. J Neurol Neurosurg Psychiatry 64:486-491
7. Hagström-Toft E, Arner P, Wahrenberg H et al (1993) Adrenergic regulation of human tissue metabolism in situ during mental stress. Endocrinol Metab 76:392-398
8. Ungerstedt U (1984) Measurement of neurotransmitter release by intracranial dialysis. In: Marsden CA (ed) Measurement of neurotransmitter release in vivo. Wiley, New York, pp 8-107
9. Hutchinson PJ, O' Connell MT, Al-Rawi PG et al (2000) Clinical cerebral microdialysis: a methodological study. J Neurosurg 93:37-43
10. Tunblad K, Ederoth P, Gärdenfors A et al (2004) Altered blood-brain barrier transport of morphine in experimental meningitis studied with microdialysis. Acta Anaesthesiol Scand 48:294-301
11. Ederoth P, Tunblad K, Bouw R et al (2004) Blood-brain barrier transport of morphine in patients with severe brain trauma. Br J Clin Pharmacol 57:427-435
12. Blasberg RG, Fenstermacher JD, Patlack CS (1983) Transport of α-aminobutyric acid across brain capillary and cellular membranes. J Cereb Blood Flow Metab 3:8-12
13. Hamberger A, Nyström B (1984) Extra- and intracellular amino acids in the hippocampusduring development of hepatic encephalopathy. Neurochem Res 9:1181-1192

14. Benveniste H, Drejer J, Shousboe A et al (1984) Elevation of the extracellular concentrations of glutamate and aspartate in rat hippocampus during transient cerebral ischemia monitored by intracerebral microdialysis. J Neurochem 43:1369-1374
15. Benveniste H, Diemer NH (1987) Cellular reactions to implantation of a microdialysis tube in the rat hippocampus. Acta Neuropathol (Berl) 74:234-238
16. Bolinder J, Ungerstedt U, Arner P (1993) Long-term continuous glucose monitoring with microdialysis in ambulatory insulin-dependent diabetic patients. Lancet 342:1080-1085
17. Bolinder J, Hagstrom-Toft E, Ungerstedt U et al (1997) Self-monitoring of blood glucose in type I diabetic patients: comparison with continuous microdialysis measurements of glucose in subcutaneous adipose tissue during ordinary life conditions. Diabetes Care 20:64-70
18. Van den Berghe G, Wouters P, Weekers F et al (2001) Intensive insulin therapy in critically ill patients. N Engl J Med 345:1359-1367
19. Van den Berghe G, Wouters PJ, Bouillon R (2003) Outcome benefit of intensive insulin therapy in critically ill: insulin dose versus glycemic control. Crit Care Med 31:359-366
20. Lourido J, Ederoth P, Sundvall N et al (2002) Correlation between blood glucose concentration and glucose level in subcutaneous adipose tissue evaluated with microdialysis during neuro intensive care. Scand J Clin Lab Invest 62:285-292
21. Rosdahl H, Hamrin K, Ungerstedt U et al (1998) Metabolite levels in human skeletal muscle and adipose tissue studied with microdialysis at low perfusion flow. Am J Physiol 274:E936-E945
22. Moberg E, Hagstrom-Toft E, Arner P (1997) Protracted glucose fall in subcutaneous adipose tissue and skeletal muscle compared with blood during insulin-induced hypoglycaemia. Diabetologia 40:1320-1326
23. Grände PO, Asgeirsson B, Nordström CH (2002) Volume targeted therapy of increased intracranial pressure: the Lund concept unifies surgical and non-surgical treatments. Acta Anaesthesiol Scand 46:929-941
24. Röjdmark J, Hedén P, Ungerstedt U (1998) Microdialysis—a new technique for free flap surveillance: methodological description. Eur J Plast Surg 21:344-348
25. Röjdmark J, Blomqvist L, Malm M et al (1998) Metabolism in myocutaneous flaps studied by in situ microdialysis. Scand J Plast Reconstruct Hand Surg 32:27-34
26. Setälä LP, Korvenoja EMJ, Härmä MA et al (2004) Glucose, lactate, and pyruvate response in an experimental model of microvascular flap ischemia and reperfusion: a microdialysis study. Microsurgery 24:223-231
27. Nowak G, Ungerstedt J, Wernerman J et al (2002) Metabolic changes in the liver graft monitored continuously with microdialysis during liver transplantation in a pig model. Liver Transplant 8:424-432
28. Nowak G, Ungerstedt J, Wernerman J et al (2002) Clinical experiences in continuous graft monitoring with microdialysis early after liver transplantation. Br J Surg 89:1169-1175
29. Sommer T (2004) Microdialysis in the assessment of regional intestinal ischemia. Doctoral thesis, Center of Sensory-motor Interaction, Aalborg University, Denmark
30. Ungerstedt J, Nowak G, Ericzon BG et al (2003) Intraperitoneal microdialysis (IPM): a new technique for monitoring intestinal ischemia studied in a porcine model. Shock 20:91-96
31. Jansson K, Ungerstedt J, Jonsson T et al (2003) Human intraperitoneal microdialysis: increased lactate/pyruvate ratio suggests early visceral ischemia. A pilot study. Scand J Gastroenterol 38:1007-1011
32. Jansson K, Redler B, Truedsson L et al (2004) Intraperitoneal cytokine response after

major surgery: higher postoperative intraperitoneal versus systemic cytokine levels suggest the gastrointestinal tract as a major source of the postoperative inflammatory reaction. Am J Surg 187:373-377
33. Jansson K, Redler B, Truedsson L et al (2004) Postoperative on-line monitoring with intraperitoneal microdialysis (IPM) is a sensitive clinical method for measuring increased anaerobic metabolism that correlates to cytokine response. Scand J Gastroenterol 39:434-439
34. Jansson K, Strand I, Redler B et al (2004) Results of intraperitoneal microdialysis depend on the location of the catheter. Scand J Clin Lab Invest 64:63-70
35. Siesjö BK (1978) Brain energy metabolism. Wiley, Chichester New York Brisbane
36. Ståhl N, Schalén W, Ungerstedt U et al (2003) Bedside biochemical monitoring of the penumbra zone surrounding an evacuated acute subdural haematoma. Acta Neurol Scand 108:211-215
37. Rosdahl H, Hamrin K, Ungerstedt U et al (2000) A microdialysis method for the in situ investigation of the action of large peptide molecules in human skeletal muscle: detection of local metabolic effects of insulin. Int J Biol Macromol 28:69-73
38. Alfredson H, Thorsen K, Lorentzon R (1999) In situ microdialysis in tendon tissue: high levels of glutamate, but not prostaglandin E_2 in chronic Achilles tendon pain. Knee Surg Sports Traumatol Arthrosc 7:378-381
39. Alfredsson H, Lorentzon R (2003) Intratendinous glutamate levels and eccentric training in chronic Achilles tendinosis: a prospective study using microdialysis technique. Knee Surg Sports Traumatol Arthrosc 11:196-199

Chapter 13

Secondary brain injury – does microdialysis have a role?

M. Smith

Traumatic brain injury (TBI) is the leading cause of mortality in the first four decades of life, and the incidence of significant morbidity, even in milder forms of injury, is high. TBI is therefore a huge socio-economic problem, because most of the people it affects are adults in their most productive years and it contributes massively to the prevalence of long-term disability. There have been marked improvements in the treatment of patients with severe TBI over the last decade, which have led to reductions in both mortality and morbidity. Advances in management have been achieved in the pre-hospital setting, in the A&E department and in the intensive care unit, although it is difficult to pinpoint exactly at which points of the management pathway the advances have made the greatest contribution to improved outcome. However, secondary brain injury has a significant adverse effect on outcome and prevention, and its recognition and treatment are crucial to the successful management of TBI.

Pathophysiology of severe TBI

Head injury is a heterogeneous diagnosis encompassing a wide range of pathologies, including diffuse axonal injury, focal contusions and space-occupying haematomas. Primary brain injury is the direct result of mechanical trauma applied at the moment of impact and causes variable degrees of irreversible cell damage attributable to physical disruption of neurones or axons (Table 1). It cannot be treated by medical intervention, although early evacuation of an expanding intracranial mass lesion reduces morbidity and mortality. Secondary brain injury begins from the moment of primary traumatic injury and develops during the subsequent minutes, hours and days, causing further neuronal damage and worsening the ultimate neurological deficit. It represents additional insults to the 'at risk' neuronal tissue and is essentially ischaemic in nature.

Secondary brain injury can usefully be divided into two components – secondary brain damage and secondary brain insults [1]. Secondary brain damage occurs following activation by the primary injury of an auto-destructive cascade of ionic, metabolic and immunological changes that render the brain more susceptible to secondary insults and ultimately results in irreversible neuronal damage or death. The causes of secondary brain damage include the release of excitotoxic amino acids such as glutamate and aspartate, production of oxygen free radicals and

Table 1. Primary and secondary brain injury

Causes of primary brain injury	Causes of secondary brain injury	
	Intracranial	Extracranial
Diffuse axonal injury	Expanding haematomas	Systemic hypotension
Haemorrhagic contusions and lacerations	Brain swelling	Hypoxaemia
Extradural haematoma	Seizures	Hypercapnia and hypocapnia
Subdural haematoma		Hyperthermia
Traumatic subarachnoid haemorrhage		Hyperglycaemia and hypoglycaemia
		Disturbances of blood coagulation

increased production of lactate and hydrogen ions [2]. The final common pathway of these processes is the entry of calcium into cells, with consequent cellular swelling and cell death. Because the brain is located inside the rigid cranium, such swelling results in an increase in intracranial pressure (ICP) and a reduction in cerebral perfusion pressure (CPP). This leads to a further reduction in oxygen delivery and worsening cerebral ischaemia, causing increased acidosis and further glutamate and free radical release, thereby setting up a vicious cycle of ischaemic injury.

Secondary brain insults arise from both systemic and intracranial changes (Table 1) that initiate or propagate pathophysiological processes and cause fatal damage to neurones already rendered susceptible to injury by the primary insult. Systemic hypotension and hypoxaemia are major causes of secondary brain injury and are primary determinants of adverse outcome after TBI [3]. Profound changes occur in CBF after TBI, and up to one third of patients sustain significant cerebral hypoperfusion in the first few hours after injury [4]. Pressure autoregulation may also be obtunded or abolished, making CBF dependent on systemic blood pressure and rendering the brain susceptible to damage at both high and low pressures. In particular, systemic hypotension is a potentially lethal complication after TBI [5]. Secondary brain insults are largely preventable or treatable and can be manipulated by clinicians throughout their course [6].

Secondary brain injury is therefore a major determinant of the cerebral ischaemic burden after TBI, which is the dominant factor determining neurological outcome. Regional and global cerebral ischaemia have been detected after brain trauma both during intensive care management [7] and, in 90% of patients, at post-mortem examination [8].

Intensive care management after TBI

The aim of intensive care management of TBI is to restore and maintain the brain's normal physiological environment in order to prevent or treat secondary ischaemic brain injury. The vicious cycle of secondary brain damage and secondary insults develops rapidly, and the goal of treatment is to reverse or prevent cerebral ischaemia so as to prevent further ischaemic neuronal damage. In the absence of pharmacological neuroprotective strategies, the maintenance of systemic physiology, which involves ICP- and CPP-guided therapy, is of crucial importance. Specialist neurocritical care should be available for all patients with severe TBI and is likely to improve outcome [9].

The delivery of targeted neurocritical care after TBI depends on the ability to monitor pathophysiological changes at and around the site of injury, and also in remote regions where compensatory changes may occur. Regional and global changes in cerebral haemodynamics and oxygenation frequently follow head injury [7, 8] and often go undetected by many monitoring techniques. A major problem with conventional monitors is that they are 'reactive' or 'reflective'—i.e. they signal functional changes *after* they have occurred, when significant secondary brain injury is already established. The challenge for clinicians is to develop and establish monitoring techniques that deliver relevant 'predictive' information within a clinically useful time-scale, so that potential windows for targeted treatment may be identified and exploited. Early detection of biochemical markers of ischaemia by microdialysis may offer such potential after TBI.

Cerebral microdialysis and secondary brain injury

Cerebral microdialysis is a well-established laboratory tool that is increasingly used for bedside monitoring to provide on-line analysis of brain tissue biochemistry after TBI [10–12]. The cellular pathology that occurs after TBI is reflected in metabolic changes in brain extracellular fluid (ECF), and microdialysis measures early biochemical markers of cerebral ischaemia and therefore has the potential to monitor the processes of secondary injury [13]. It may allow the identification of patients at risk of developing secondary injury and guide therapy within clinically useful time-scales, thereby potentially reducing secondary brain damage and improving outcome [14]. Conventional bedside microdialysis with commercially available equipment (e.g. CMA Microdialysis, Solna, Sweden) allows measurement of ECF lactate, pyruvate, glucose, glycerol and glutamate concentrations, thus providing an on-line profile of brain tissue biochemistry at the bedside.

The biochemical changes that accompany cerebral ischaemia have been well described, and particular importance attaches to the change in the redox state of the cell as evidenced by changes in the lactate-to-pyruvate ratio (LP ratio). After TBI, a high LP ratio has been found to be correlated with the severity of clinical symptoms and fatal outcome [11, 15], and it is a more reliable marker than lactate concentration alone [16]. The LP ratio is also independent of catheter recovery in

vivo [17] and is therefore a prime candidate for use as an early biomarker of ischaemia. Cerebral ischaemia is also paralleled by a decrease in ECF glucose and an increase in glutamate and glycerol concentrations [18, 19].

Several clinical studies have demonstrated the presence of abnormal LP ratio and of abnormal glucose, glycerol and glutamate levels following severe TBI, with wide variations in microdialysis variables not only between different subjects but also within individual subjects over time [10–12, 15]. An early study reported 25-fold increases in LP ratio and glutamate concentration after brain injury [10], and it has since been demonstrated that such variations reflect the high and changing levels of metabolic activity within the injured brain [20].

As discussed previously, cerebral ischaemia results in failing cellular metabolism and subsequent release of excitotoxic amino acids, production of oxygen free radical and tissue acidosis. If unchecked, these changes will lead to further cellular swelling and a vicious circle of worsening cerebral ischaemia causing increasing tissue acidosis and further excitotoxic and peroxidative damage. Microdialysis might therefore be expected to detect ischaemia-induced changes in brain biochemistry *before* changes can be detected by more conventional monitoring techniques. It has recently been demonstrated that, as well as being associated with intracranial hypertension, a rise in LP ratio often *precedes* its development [12]. In other words, the LP ratio not only reflects the cerebral ischaemia that follows elevations in ICP and reductions in CPP, but also detects biochemical markers of ischaemia at the cellular level *before* the onset of intracranial hypertension. Even in the presence of adequate cerebral perfusion, damaged neurones are unable to utilise energy substrates adequately, because of mitochondrial failure [21, 22]. In such circumstances, a high LP ratio might signify the inability of the damaged mitochondria to utilise the aerobic metabolic pathway fully and so to maximise the efficient extraction of energy from the available pyruvate, thus reflecting a shift toward the energy-inefficient fermentation pathway producing lactate. In a recent study, LP ratio >25 and glycerol >100 μmol/l were able to predict a subsequent rise in ICP during the next 3 h [12]. Because intracranial hypertension is known to be associated with poor outcome after TBI, these findings support previous work that has demonstrated a relationship between abnormal microdialysis variables and adverse outcome [11]. The site of catheter placement is important. Microdialysis data from a catheter placed in 'at risk' tissue is able to detect biochemical deterioration before an increase in ICP, whereas data from a catheter placed in 'normal' brain usually observes biochemical changes after the increase in ICP [15]. The detection of an abnormal LP ratio by microdialysis in the penumbral region, in the presence of normal ICP, should not therefore be interpreted exclusively as an established and irreversible ischaemic change. It might also reflect an early manifestation of mitochondrial impairment that precedes, rather than follows, widespread cellular swelling and intracranial hypertension.

Some episodes of intracranial hypertension occur as a result of mechanical events, such as coughing, nursing interventions, physiotherapy or the expansion of an intracranial haematoma or hydrocephalus. Obviously such events cannot be predicted by brain biochemical monitoring and may explain why rises in ICP can

be positively predicted by high LP ratios in only 53% of cases [12]. Cerebral microdialysis does not therefore replace the standard investigation of sudden elevations in ICP, such as CT scanning. However, in the absence of mechanical or surgically remedial causes of intracranial hypertension, microdialysis demonstrates impending ischaemia after TBI with reasonable specificity [12]. A recent study in patients with subarachnoid haemorrhage (SAH) showed that microdialysis was also able to predict the occurrence of a delayed ischaemic deficit with 75–90% sensitivity and specificity, on average 11 h before its clinical appearance [24].

Despite recent data highlighting the predictive value of microdialysis, one study found no correlation between interstitial glycerol concentration and secondary events, such as intracranial hypertension and low CPP, in 15 TBI patients [23]. However, this study did demonstrate that glycerol concentrations <150 μmol/l were associated with favourable outcomes whilst a peak glycerol concentration >150 μmol/l had a positive predictive value of 100% for unfavourable outcome. The authors conclude that measuring glycerol is not useful for the early detection of secondary adverse events, but suggest that the positive predictive value of peak glycerol 150 μmol/l for an unfavourable outcome is an indicator the severity of parenchymal damage. A rise in ECF glycerol concentration occurs following breakdown of glycerol-phospholipids in cell membranes and indicates that tissue ischaemia has already progressed to cell damage. Although high glycerol values do reflect the severity of ischaemic damage and indicate that some neurones are already dead, they should not be interpreted as meaning that there is no scope for intervention to prevent further damage. If the microdialysis probe is correctly placed in the penumbra, rises in glycerol concentration whilst the ICP is still normal suggest that the biochemical damage is spreading outward from the epicentre and is affecting the area where the probe is implanted. If unchecked, the damage will progressively extend to neighbouring areas and will eventually result in diffuse swelling detectable by ICP monitoring. It is therefore possible that rises in glycerol concentration in the penumbra predict diffuse secondary changes later occurring on a global level.

Although a recent study has failed to demonstrate a predictive element in elevation of glutamate concentration after TBI [12], previous work in patients with SAH has demonstrated that glutamate is a sensitive indicator of impending ischaemia [25]. The failure to demonstrate a predictive effect of rises in glutamate concentrations after TBI might be related to the very wide variation in glutamate concentrations between and within individuals, as well as to selection of an inappropriate threshold value. Glutamate is a well-known marker of ischaemic damage and has a crucial role in provoking cell death by opening calcium channels. Intuitively, therefore, it seems it should be an attractive biomarker for prediction of secondary deterioration after TBI.

Novel biomarkers

Cerebral microdialysis is a method that might also allow measurement of proteins, neurotransmitters, cytokines and other inflammatory markers from brain ECF. Protein S100B is released following astrocyte disintegration, and changes in plasma S100B concentration have been correlated with rises in ICP and adverse clinical outcome after brain injury [26]. It has recently been demonstrated that measurement of brain ECF S100B by microdialysis using conventional microdialysis catheters is practical and reliable [27]. In this pilot study, brain ECF S100B (eS100B) concentrations were 'event related', and mean daily eS100B concentration was a sensitive predictor of mortality. Temporal profiles of brain eS100B concentration might therefore provide additional clinical information, and measurement of eS100B using microdialysis warrants further investigation as a clinical tool. As well as having the potential to become a major neuromonitoring tool, microdialysis might also provide a unique opportunity for clinical neuroscientific research.

Conclusions

Cerebral microdialysis is able to detect changes in brain tissue biochemistry that are associated with secondary brain injury after TBI. Recent evidence suggests that it might also have the potential to provide an early warning of secondary cerebral deterioration, thereby potentially allowing the opportunity to deliver targeted therapy *before* irreversible neuronal damage occurs. The measurement of other biomarkers of brain injury, such as S100B and novel inflammatory markers, might allow new applications to be developed. Further work on the testing and application of microdialysis in the clinical arena is warranted but, in the meantime, microdialysis provides useful additional information within the context of multimodality monitoring after brain injury.

References

1. Maas AI, Dearden M, Servadei F et al (2000) Current recommendations for neurotrauma. Curr Opin Crit Care 6:281-292
2. Teasdale GM, Graham DI (1998) Craniocerebral trauma: protection and retrieval of the neuronal population after injury. Neurosurgery 43:723-738
3. Chesnut RM, Marshall LF, Klauber MR (1993) The role of secondary brain injury in determining outcome from severe head injury. J Trauma 34:216-222
4. Bouma GJ, Muizelaar JP, Choi SC et al (1991) Cerebral circulation and metabolism after severe traumatic brain injury: the elusive role of ischemia. J Neurosurg 75:685-693
5. Chesnut RM (1997) Avoidance of hypotension: conditio sine qua non of successful severe head-injury management. J Trauma 42:S4-S9
6. Maas AI, Dearden M, Teasdale GM et al (1997) EBIC guidelines for management of severe head injury in adults. European Brain Injury Consortium. Acta Neurochir (Wien) 139:286-294

7. Jones PA, Andrews PJD, Midgley S et al (1994) Measuring the burden of secondary insults in head injured patients during intensive care. J Neurosurg Anesthesiol 6:4-14
8. Graham DI, Ford I, Adams JH, et al (1989) Ischemic brain damage is still common in fatal non-missile head injury. J Neurol Neurosurg Psychiatry 52:346-350
9. Patel HC, Menon DK, Tebbs S et al (2002) Specialist neurocritical care and outcome from head injury. Intensive Care Med 28:547-553
10. Persson L, Hillered L (1992) Chemical monitoring of neurosurgical intensive care patients using intracerebral microdialysis. J Neurosurg 76:72-80
11. Hutchinson PJ, al-Rawi PG, O'Connell MT et al (2000) On-line monitoring of substrate delivery and brain metabolism in head injury. Acta Neurochir Wien Suppl 76:431-435
12. Smith M, Belli A, Sen J et al (2004) Prediction of secondary brain injury during neurocritical care: the role of cerebral microdialysis. In: Klaus S, Bahlmann L (eds) Microdialysis—monitoring tissue chemistry in intensive care medicine. Pabst Science Publishers, Lengerich, pp 45-55
13. Reinstrup P, Stahl N, Mellergard P et al (2000) Intracerebral microdialysis in clinical practice: baseline values for chemical markers during wakefulness, anesthesia and neurosurgery. Neurosurgery 47:701-710
14. Menon DK (1999) Cerebral protection in severe brain injury; physiologic determinants of outcome and their optimisation. Br Med Bull 55:226-58
15. Stahl N, Mellergard P, Hallstrom A et al (2001) Intracerebral microdialysis and bedside biochemical analysis in patients with fatal traumatic brain lesions. Acta Anaesthesiol Scand 45:977-985
16. Persson L, Valtysson J, Enblad P et al (1996) Neurochemical monitoring using intracerebral microdialysis in patients with subarachnoid haemorrhage. J Neurosurg 84:606-16
17. Hillered L, Persson L (1999) Theory and practice of microdialysis—prospects for future clinical use. Acta Neurochir Wien Suppl 75:3-6
18. Peerdeman SM, van Tulder MW, Vandertop WP (2003) Cerebral microdialysis as a monitoring method in subarachnoid hemorrhage patients, and correlation with clinical events. A systematic review. J Neurol 250:1079-1085
19. Del Arco A, Segovia G, Fuxe K et al (2003) Changes in dialysate concentrations of glutamate and GABA in the brain: an index of volume transmission mediated actions? J Neurochem 85:23-33
20. Hutchinson PJ, Gupta AK, Fryer TF et al (2002) Correlation between cerebral blood flow, substrate delivery and metabolism in head injury: a combined microdialysis and triple oxygen positron emission tomography study. J Cereb Blood Flow Metab 22:735-745
21. Verweij BH, Muizelaar JP, Vinas FC et al (2000) Impaired cerebral mitochondrial function after traumatic brain injury in humans. J Neurosurg 93:815-820
22. Verweij BH, Muizelaar JP, Vinas FC et al (2000) Impaired cerebral mitochondrial function after traumatic brain injury in humans. J Neurosurg 93:815-820
23. Peerderman SM, Girbes AR, Polderman KH et al (2003) Changes in interstitial glycerol concentration in head-injured patients; correlation with secondary events. Intensive Care Med 29:1825-1828
24. Skjoth-Rasmussen J, Shultz M, Kristensen SR et al (2004) Delayed neurological deficit detected by an ischemic pattern in the extracellular metabolites in patients with aneurysmal subarachnoid hemorrhage. J Neurosurg 100:8-15
25. Nilsson OG, Brandt L, Ungerstedt U et al (1999) Bedside detection of brain ischaemia using intracerebral microdialysis: subarachnoid haemorrhage and delayed ischaemic deterioration. Neurosurgery 45:1176-1785
26. Petzold A, Green AJ, Kier G et al (2002) Role of serum S100B as an early predictor of

high intracranial pressure and mortality in brain injury: a pilot study. Crit Care Med 30:2705-2710
27. Sen J, Belli A, Petzold A et al (2003) Brain extracellular fluid S-100B levels correlates with mortality in acute brain injury. Neurosurgery 53:482

Chapter 14

Liver graft monitoring with intrahepatic microdialysis

G. Nowak

Liver transplantation has become a standard therapy for many patients with various liver diseases after the declaration by the National Institutes of Health in the USA in 1983, that "liver transplantation is a therapeutic modality for end-stage liver disease that deserves broader application" [1]. In Europe, more than 4000 liver transplants are performed each year, and already more than 100,000 transplants have been carried out so far [2, 3]. Despite an improvement in liver preservation and surgery, the problem of graft dysfunction still persists [4]. In fact, liver function after transplantation is determined not only by the quality of the donor organ or recipient-related factors, but also by factors associated with the transplantation procedure. In general, liver transplantation consists of two operations: liver procurement from the donor and liver implantation in the recipient. Organ procurement has become standardized and is based on in situ organ perfusion, in which the liver is perfused with cold preservation solution in the donor. The period between harvesting the organ and transplantation of the graft into the recipient involves ischaemia since there is no blood and oxygen supply during this period [5]. Two types of ischaemia occur during transplantation: (1) cold ischaemia, when the liver graft is harvested from the donor and kept cool to reduce its metabolic rate; and (2) warm ischaemia, during implantation in the warm environment before proper re-vascularisation of the graft in the recipient. Because of the double blood supply in the liver (i.e. portal vein and hepatic artery), the process of liver reperfusion can also be divided into two parts, portal and arterial reperfusion.

The ischaemic liver injury that occurs during liver preservation is almost invariably connected to clinical and biochemical liver dysfunction occurring early after procurement. At the time of organ reperfusion during the recipient operation, additional injury occurs to the ischaemic liver, known as reperfusion injury. These two events are usually referred to as ischaemia–reperfusion injury and contribute to post-transplant primary graft dysfunction, which ranges from minor, insignificant abnormalities to primary graft non-function. The incidence of primary graft non-function varies widely depending on the definition used [6]. Commonly used definitions of primary graft non-function are death or re-transplantation within 2 weeks after liver transplant [7]. The reported incidence of primary graft dysfunction, including non-function, after liver transplantation is as high as 23% of patients [7, 8]. Although patients with primary graft dysfunction usually steadily improve with conservative treatment, increased morbidity, prolonged intensive care [6], and an increased incidence of subsequent graft rejections are still observed in these

patients [9]. Moreover, up to 30% of patients with graft dysfunction need re-transplantation within the first 3 months after transplantation [4, 8, 10], which increases the demand on an already small pool of donor organs. Therefore, early detection and monitoring of complications such as primary graft non-function is of great clinical importance [11].

Another major cause of patient morbidity and mortality early after transplantation is caused by vascular complications, such as thrombosis of the hepatic artery or of the portal vein. Hepatic artery thrombosis occurs in 2–24% of transplanted patients and is more often observed in children than in adults [12, 15]. The incidence of this complication depends not only on the surgical technique used but also on the duration of graft preservation and graft rejection [16, 17]. The clinical presentation of arterial thrombosis may range from fulminating hepatic failure to late biliary complications [18, 19]. An untreated arterial thrombosis may result in further complications, such as sepsis, hepatic necrosis, coagulopathy, bile leaks or biliary abscesses. However, in some instances, especially in children, arterial thrombosis may occur without any symptoms. Most adult patients require re-transplantation, whereas children often develop arterial collaterals to the liver with sufficient arterial blood supply [17]. Portal vein thrombosis is a rare complication, occurring in 1–2% of all patients, but in up to 10% of children [13, 14, 20]. Although successful surgical intervention with good long-term outcome is possible in case of vascular thrombosis in the transplanted liver, early detection of these complications is essential. Therefore, since ischaemia–reperfusion injury and post-transplant vascular complications have an impact on hepatic metabolism, intrahepatic microdialysis technique may be ideal for monitoring the transplanted liver and identifying post-transplant complications.

One of the most important aspects of hepatic transplantation is the ability of the liver to regenerate energy-rich compounds, such as adenosine triphosphate, after transplantation [21, 22]. The major source of metabolic energy for cells both in the presence and absence of oxygen is glucose. Under physiological conditions during glycolysis, glucose is metabolised into pyruvate resulting in energy production. In the presence of oxygen, pyruvate enters the citric acid cycle. During ischaemia lactate is produced from pyruvate in order to maintain anaerobic glycolysis with low energy production [23]. Therefore, monitoring of lactate and pyruvate levels reveals whether aerobic metabolism is occurring or not [24]. Glycerol is an end product of lipolysis in adipose tissue and it is also an indicator of membrane disintegration during such events as ischaemia [25, 26]. Loss of energy leads to an influx of calcium and an activation of phospholipases, which split glycerol away from the cell membrane. Oxygen-derived free radicals also contribute to this membrane damage [27]. It has been shown that during brain or skin flap ischaemia, when supplies of glucose and oxygen are diminished, tissue lactate and glycerol increase, while glucose and pyruvate decrease [26, 28-30].

Intrahepatic microdialysis technique

Usually, two microdialysis catheters are used, one intrahepatic catheter and one subcutaneous reference catheter. The reason for using two catheters is to distinguish local metabolic changes in the monitored liver (intrahepatic catheter) and systemic changes (reference catheter reflecting changes in the blood).

The reference catheter is inserted subcutaneously in the adipose tissue over the left or the right pectoral area. This is done by lifting a skin fold with one hand and pushing the microdialysis catheter, resting inside a steel slit cannula introducer, through a hole in the skin made by the needle. The introducer is withdrawn while the catheter is held firmly in place. The catheter is secured with two thin sutures. For implantation of intrahepatic microdialysis catheter, a plastic guider with a steel cannula is used. The point of insertion of this cannula in the liver can differ but usually includes segment IV. After removal of the steel cannula, the microdialysis catheter is inserted into the plastic guider, which is then removed by splitting it. A secure suture is made on the cuff, surrounding the inflow and outflow tube, and fixed to the falciform ligament or to the margin of the liver to prevent movements of the membrane. Intrahepatic catheter tubes are led out through the middle portion of the abdominal incision or via a tunnel in the abdominal wall.

Microdialysis catheters are perfused with perfusion solution (Ringer solution) using microinfusion pumps at a flow rate of 0.3 μl/min. At least 20–25 min of perfusion is considered necessary to flush the microdialysis catheter, after which the collection of samples starts. Microvials are changed at a minimum of 20-min intervals in order to collect enough fluid for basic analyses, including glucose, lactate, pyruvate and glycerol. Intrahepatic microdialysis was carried out for over 9 days without the occurrence of any complications related to the technique. The vials with the collected microdialysis perfusate are placed in an analyser, which contains spectrophotometric assay. Analyte-specific enzymatic reagents that mix with the sample and results in oxidative formation of hydrogen peroxide-are used. The most frequently used method allows measurements of pyruvate between 10 and 1500 μmol/l; therefore concentrations below 10 μmol/l should be recorded as 10 μmol/l. This estimation is made in order to calculate the lactate/pyruvate ratio during prolonged ischaemia.

Intrahepatic microdialysis was used to monitor metabolic changes in a liver graft during different stages of transplantation in a pig liver transplantation model [31]. This study showed that warm ischaemia and subsequent reperfusion seem to be the most harmful periods for the liver, as reflected by an accelerated increase in glucose and glycerol levels and an increased lactate/pyruvate ratio. High intrahepatic glucose levels during ischaemia appear to be a liver-specific event reflecting glycogen degradation in hepatocytes. A clinical study with intrahepatic microdialysis monitoring after liver transplantation showed that the procedure is easy to perform and safe for the patient [32]. Interestingly, the same reported suggested that intrahepatic microdialysis can aid in the detection of ischaemic complications early after transplantation. However, our not-published observation of positive correlation between systemic glucose and intrahepatic lactate/pyruvate ratio indi-

cates that ischaemia-like changes can also appear under hyperglycaemic conditions during the first 2 days after transplantation.

Methods based on monitoring of liver-graft metabolism are attractive because liver metabolic recovery after transplantation is considered to be a sensitive indicator of liver function and has a direct correlation with both the survival rate of liver grafts and good transplant outcome in humans [33, 34]. Primary graft nonfunction following liver transplantation is manifested by hepatic cytolysis with rapidly rising transaminases, absence of bile production, a severe liver-related coagulation deficit, and high lactate levels. Primary graft dysfunction is a borderline syndrome with either complete recovery or causing graft complications eventually leading to re-transplantation. The prediction of these events at the time of cold storage, intra-operatively, or as early as possible postoperatively is important. A wide variety of functional and morphological techniques have been developed to accomplish this goal [35, 36]. Although blood liver-function tests after transplantation have been studied experimentally and clinically, there are only a limited number of reports on the metabolic changes in the liver graft itself [37]. Apart from bile secretion studies, none of the current methods has the ability to monitor liver metabolism continuously or to monitor the metabolism of the graft without repeated biopsies, patient exposure to X-radiation, or repeated examinations requiring highly qualified personnel.

There are several advantages to using microdialysis to study liver metabolism during transplantation. Microdialysis allows changes in metabolites to be studied directly in the organ, regardless of whether the organ circulation is intact or not. Moreover, liver-graft monitoring with microdialysis can be started in the donor before organ as to whether a liver should be accepted for transplantation or not. Monitoring with microdialysis can also be continued during and after transplantation. This would be of particular interest in the case of marginal livers, such as fatty livers, old donors, or in a situation in which ischaemic injury has been severe. Post-transplant monitoring can be easily performed for several days from one single puncture in the liver graft. Metabolic changes in the tissue may be detected by microdialysis before they are reflected in peripheral blood chemistry. Bedside analysis also provides quick information, which could be of crucial importance in case of early hepatic metabolic failure.

It has been shown that the interstitial glucose concentration indicates the amount of glucose available in the tissue as a reflection of plasma concentration [38]. Therefore, glucose concentration in the tissue depends on local blood flow and glucose uptake into the tissue [38]. This mechanism would explain glucose decrease in the very early stage of cold ischaemia, since blood flow is interrupted in the transplant. However, the subsequent increase in glucose levels in the liver observed during ischaemia appears to be a liver-specific reaction. The increase in glucose levels at the beginning of cold ischaemia is followed by a stabilization, which seems to be independent of the length of the cold ischaemia. During warm ischaemia, the increase in glucose accelerates and is even more pronounced in livers with a long cold ischaemia. This would indicate not only a difference in the effect of cold and warm ischaemia on liver metabolism but also the impact of warm

ischaemia injury during liver implantation. The increase in glucose during ischaemia is explained by glycogen degradation, especially during warm ischaemia and early after reperfusion [39-41].

The post-reperfusion decrease in glucose is most likely due to recovery of the mechanism controlling glycogenolysis or utilization of glucose by the cells. However, the decrease could also be explained in part by a simple wash-out effect, in which the intrahepatic glucose is flushed to the systemic circulation when blood flow is restored [42]. In clinical studies, this has been described as a post-reperfusion hyperglycaemia and is seen early after reperfusion [43]. Interestingly, the described decrease in intrahepatic glucose levels occurs approximately at the time of the liver-graft re-arterialisation and underlines the importance of oxygenation in the recovery process. Therefore, a more rapid arterialisation of the transplanted liver might reduce glucose leakage from the hepatocytes during transplantation. However, further studies on the effect of the sequence of arterial and portal reperfusion, are necessary.

In relation to glucose metabolism, a commonly used indicator of tissue ischaemia is lactate. During cold ischaemia, aerobic and anaerobic glycolysis seems to be halted, as reflected by low and stable lactate levels and undetectable pyruvate levels. During warm ischaemia, an increase in lactate concentration is observed with undetectable pyruvate levels indicating anaerobic glucose metabolism. After portal reperfusion, there is an increase in lactate levels, which together with low pyruvate levels indicates continuous anaerobic glycolysis. The aerobic glucose metabolism seems to increase at the time of liver arterialisation, as reflected by decreasing lactate and increasing pyruvate levels. During the anhepatic time, lactate levels in the reference tissue increase followed by a decrease and normalization after arterial reperfusion. These findings in the reference tissue correspond to the lactate measurements in the blood, which are commonly used to monitor liver-metabolism recovery after liver transplantation.

Despite the use of lactate as an indicator of metabolism, it is important to emphasize that lactate alone is probably not a good marker of ischaemia. Lactate levels may not only be related to hypoxia and ischaemia but also to hypermetabolism [24]. In fact, hypermetabolism is seen after reperfusion, as indicated by higher levels of pyruvate early after arterial reperfusion than before cold perfusion. Interestingly, higher pyruvate levels are also observed in the reference tissue after the anhepatic phase, with normalization after arterial reperfusion. Thus, since hypermetabolism results in an increase in both lactate and pyruvate levels, the lactate/pyruvate ratio seems to be a more appropriate marker of ischaemia. During cold ischaemia, there is a rapid increase in the lactate/pyruvate ratio followed by stabilization. This has been interpreted as a short period of anaerobic glycolysis, which then is effectively inhibited by cooling. During warm ischaemia, the anaerobic glycolysis increases again, as demonstrated by the increased lactate/pyruvate ratio. However, the rapid decrease after reperfusion implies restoration of aerobic conditions, even if the decrease in the lactate level is delayed. This decrease is observed at the time of portal reperfusion in livers with short cold ischaemia, and with a 40-min delay corresponding to arterial reperfusion in livers after long cold ischaemia.

Previous studies in other tissues have shown that not only the lactate/pyruvate ratio but also the levels of glycerol are good markers of ischaemia [44, 45]. The most likely source of glycerol is from damaged cell membranes; another possible source is the intracellular fat. However, this seems to be less likely, since hypoxia results in accumulation of intracellular fat in hepatocytes. A constant increase of intrahepatic glycerol during cold storage indicates a continuous time-dependent injury to the cell membranes. Once warm ischaemia starts, the cell damage accelerates since glycerol increases more rapidly. This acceleration is more pronounced during a long cold-ischaemia time. Thus, the events at warm ischaemia and reperfusion are, to a large extent, the result of damage during cold ischaemia. This supports the theory that cold preservation increases the sensitivity of the liver to warm-ischaemia injury in a time-dependent manner [46-49].

In summary, studies with intrahepatic microdialysis during liver transplantation strongly demonstrate the need to keep both cold- and warm-ischaemia times as short as possible due to continuous injury to the liver during cold ischaemia and acceleration of this injury during warm ischaemia. Since warm ischaemia is an unavoidable step in liver transplantation, other protective methods must be introduced, such as isolation of the liver graft from the surrounding warm environment during implantation or keeping temperatures low by continuous cold perfusion of the graft. The changes in glucose metabolism during transplantation provide evidence that arterial reperfusion may be important to improve the recovery of oxidative glycolysis. Therefore, liver-graft arterialisation before portal reperfusion should be considered, especially in livers with a long cold-ischaemia time. Moreover, microdialysis is a useful tool for experimental and clinical studies on ischaemia–reperfusion injury as well as for evaluation of new preservation solutions and different pretreatment protocols. Microdialysis is a safe and reliable method to clinically monitor liver function for several days after liver transplantation. However, further studies are necessary for better evaluation of microdialysis as a method for detection and monitoring of post-transplant complications, such as arterial and portal thrombosis.

References

1. EASL (1984) National Institute of Health Consensus Development Conference Statement: Liver Transplantation. June 20-23, 1983. Hepatology 4:107-110
2. (2003) 2002 OPTN/SRTR Annual Report
3. European Liver Transplant Registry
4. Strasberg SM, Howard TK, Molmenti EP et al (1994) Selecting the donor liver: risk factors for poor function after orthotopic liver transplantation. Hepatology 20:829-838
5. Jamieson NV (1991) Review article: improved preservation of the liver for transplantation. Aliment Pharmacol Ther 5:91-104
6. Clavien PA, Harvey PR, Strasberg SM (1992) Preservation and reperfusion injuries in liver allografts. An overview and synthesis of current studies. Transplantation. 53:957-978
7. Chazouilleres O, Calmus Y, Vaubourdolle M et al (1993) Preservation-induced liver injury. Clinical aspects, mechanisms and therapeutic approaches. J Hepatol 18:123-134

8. Ploeg RJ, D'Alessandro AM, Knechtle SJ et al(1993) Risk factors for primary dysfunction after liver transplantation - a multivariate analysis. Transplantation 55:807-813
9. Howard TK, Klintmalm GB, Cofer JB et al (1990) The influence of preservation injury on rejection in the hepatic transplant recipient. Transplantation 49:103-107
10. Mor E, Klintmalm GB, Gonwa TA et al (1992) The use of marginal donors for liver transplantation. A retrospective study of 365 liver donors. Transplantation 53:383-386
11. Lemasters JJ, Bunzendahl H, Thurman RG (1995) Reperfusion injury to donor livers stored for transplantation. Liver Transpl Surg 1:124-138
12. Abbasoglu O, Levy MF, Vodapally MS et al (1997) Hepatic artery stenosis after liver transplantation--incidence, presentation, treatment, and long term outcome. Transplantation 63:250-255
13. Langnas AN, Marujo W, Stratta RJ et al (1991) Vascular complications after orthotopic liver transplantation. Am J Surg 161:76-82
14. Wozney P, Zajko AB, Bron KM et al (1986) Vascular complications after liver transplantation: a 5-year experience. AJR Am J Roentgenol 147:657-663
15. Settmacher U, Stange B, Haase R et al (2000) Arterial complications after liver transplantation. Transpl Int 13:372-378
16. Mor E, Schwartz ME, Sheiner PA et al (1993) Prolonged preservation in University of Wisconsin solution associated with hepatic artery thrombosis after orthotopic liver transplantation. Transplantation 56:1399-1402
17. Imagawa DK, Busuttil RW (1996) Technical problems: vascular. In: Busuttil RW, Klintmalm GB (eds) Transplantation of the liver, 1st edn. WB Saunders, Philadelphia, pp 626-632
18. Drazan K, Shaked A, Olthoff KM et al (1996) Etiology and management of symptomatic adult hepatic artery thrombosis after orthotopic liver transplantation (OLT). Am Surg 62:237-240
19. Margarit C, Hidalgo E, Lazaro JL et al (1998) Biliary complications secondary to late hepatic artery thrombosis in adult liver transplant patients. Transpl Int 11 1:S251-S254
20. Lerut J, Tzakis AG, Bron K et al(1987) Complications of venous reconstruction in human orthotopic liver transplantation. Ann Surg 205:404-414
21. Chavez-Cartaya RE, Metcalfe S, Ramirez-Romero P et al (1994) Rat liver blood flow after ischemia and reperfusion. The effects of the platelet-activating factor antagonist WEB-2170 and of removing circulating leukocytes. Transplantation 57:1440-1444
22. Inomoto T, Tanaka A, Awane M et al (1996) Changes in glucose transporter 2 and carbohydrate-metabolizing enzymes in the liver during cold preservation and warm ischemia. Transplantation 61:869-874
23. Hickman R, Rose-Innes C, Tyler M et al (1992) Energy charge as an indication of liver viability. A comparison of changes in livers that remained intact with those subjected to autografting. Transplantation 53:540-545
24. Harken AH (1976) Lactic acidosis. Surg Gynecol Obstet. 142:593-606
25. Goodman JC, Gopinath SP, Valadka AB et al (1996) Lactic acid and amino acid fluctuations measured using microdialysis reflect physiological derangements in head injury. Acta Neurochir Suppl (Wien) 67:37-39
26. Hillered L, Valtysson J, Enblad P et al (1998) Interstitial glycerol as a marker for membrane phospholipid degradation in the acutely injured human brain. J Neurol Neurosurg Psychiatry 64:486-491
27. Suzuki M, Yamaki T, Takeuchi H et al (2001) Hemodynamic patterns of phosphatidylcholine hydroperoxide and hyaluronic acid during hepatic ischemia-reperfusion. J Hepatobiliary Pancreat Surg 8:161-168

28. Hillered L, Persson L, Ponten U et al (1990) Neurometabolic monitoring of the ischaemic human brain using microdialysis. Acta Neurochir (Wien) 102:91-97
29. Rojdmark J, Blomqvist L, Malm M et al (1998) Metabolism in myocutaneous flaps studied by in situ microdialysis. Scand J Plast Reconstr Surg Hand Surg 32:27-34
30. Marklund N, Salci K, Lewen A et al (1997) Glycerol as a marker for post-traumatic membrane phospholipid degradation in rat brain. Neuroreport 8:1457-1461
31. Nowak G, Ungerstedt J, Wernerman J et al (2002) Metabolic changes in the liver graft monitored continuously with microdialysis during liver transplantation in a pig model. Liver Transpl 8:424-432
32. Nowak G, Ungerstedt J, Wernerman J et al (2002) Clinical experience in continuous graft monitoring with microdialysis early after liver transplantation. Br J Surg 89:1169-1175
33. Lanir A, Jenkins RL, Caldwell C et al (1988) Hepatic transplantation survival: correlation with adenine nucleotide level in donor liver. Hepatology 8:471-475
34. Sumimoto K, Inagaki K, Yamada K et al (1988) Reliable indices for the determination of viability of grafted liver immediately after orthotopic transplantation. Bile flow rate and cellular adenosine triphosphate level. Transplantation. 46:506-509
35. Knoop M, Haller G, Langrehr JM et al (1995) The effect of temporary hepatic ischemia on liver surface pH and potassium ion activity in the rat. Langenbecks Arch Chir 380:58-61
36. Tokuka A, Tanaka A, Kitai T et al (1994) Interrelationship of oxygen supply by hepatic artery and portal vein: rapid analysis of ischemia-reflow-induced changes in hepatic oxygenation in experimental and clinical subjects by tissue near-infrared spectroscopy. Eur Surg Res 26:342-352
37. Jujo H, Tanaka K, Masumoto H et al (1987) Metabolic changes of the isograft after orthotopic liver transplantation in the rat. Transplant Proc 19:1088-1090
38. Hovda DA, Lee SM, Smith ML et al (1995) The neurochemical and metabolic cascade following brain injury: moving from animal models to man. J Neurotrauma 12:903-906.
39. Cywes R, Greig PD, Morgan GR et al (1992) Rapid donor liver nutritional enhancement in a large animal model. Hepatology 16:1271-1279
40. Cywes R, Greig PD, Sanabria JR et al (1992) Effect of intraportal glucose infusion on hepatic glycogen content and degradation, and outcome of liver transplantation. Ann Surg 216:235-246
41. Imamura H, Dagenais M, Giroux L et al (1995) Cold ischemia-reperfusion injury of the liver. Role of the liver donor nutritional status in rats. Transplantation 60:14-19
42. Bradley AL, Sika M, Becker YT et al (1998) Net hepatic glucose output is normal on postoperative day 1 after liver transplantation. Am Surg 64:255-258
43. Khoury GF, Klandorf H, Brems J et al (1989) Pancreatic hormonal responses to hyperglycemia during orthotopic liver transplantation in man. Transplantation 47:891-893
44. Hillered L, Persson L (1999) Neurochemical monitoring of the acutely injured human brain. Scand J Clin Lab Invest Suppl 229:9-18
45. Nilsson OG, Brandt L, Ungerstedt U et al (1999) Bedside detection of brain ischemia using intracerebral microdialysis: subarachnoid hemorrhage and delayed ischemic deterioration. Neurosurgery 45:1176-1184
46. Vajdova K, Smrekova R, Mislanova C et al (2000) Cold-preservation-induced sensitivity of rat hepatocyte function to rewarming injury and its prevention by short-term reperfusion. Hepatology 32:289-296
47. Vreugdenhil PK, Rankin MA, Southard JH (1997) Cold storage sensitizes hepatocytes to oxidative stress injury. Transpl Int 10:379-385
48. Adam R, Bismuth H, Diamond T et al (1992) Effect of extended cold ischaemia with UW solution on graft function after liver transplantation. Lancet 340:1373-1376

49. Deschenes M, Belle SH, Krom RA et al (1998) Early allograft dysfunction after liver transplantation: a definition and predictors of outcome. Transplantation 66:302-310

Chapter 15

Myocardial metabolism during open heart surgery, assessed with microdialysis

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Worldwide nearly 1 million patients per year undergo coronary artery bypass grafting. As revealed by several outcome studies [1, 2], most patients benefit from this procedure. However, in a growing subset of patients the course after surgery is prolonged and mortality is rather high, at 30–35%; nearly 50% of the costs related to all cardiac surgery are accounted for by this subset [2]. Consequently, this type of surgery is a heavy burden on the healthcare system, and methods of early detection and – ideally – rapid treatment of patients at risk of developing complications are of pivotal importance. There is no doubt that the myocardium and the surgical procedure – especially the use of cardiopulmonary bypass – have key roles in the development of postoperative organ dysfunction [3]. But in most circumstances, monitoring is focused on global myocardial function and systemic haemodynamics. While the use of transoesophageal echocardiography allows assessment of functional changes in contractility [4, 5] and a pulmonary artery catheter may give additional and continuous information on cardiac output and mixed venous saturation, little is known about what happens in the myocardium. In a few centres a coronary sinus catheter is placed, but owing to variations in myocardial venous drainage [6] analysis of coronary sinus blood is a rather unspecific method of determining metabolism in an area of interest, and especially in regions that are subjected to revascularisation. We were interested to find whether it was possible to monitor myocardial metabolism in the specific area of revascularisation during open coronary artery bypass graft (CABG) procedures using the microdialyis technique. A commercially available microdialysis catheter (CMA 70, CMA/Microdialysis AB, Sweden) was placed in the apical region of the beating heart for direct assessment of the distal area of the left descending artery [7, 8]. We chose to analyse the course of myocardial metabolism in patients undergoing standard CABG procedures with CBP (on-pump) and in patients scheduled for CABG without extracorporeal circulation (off-pump). Myocardial lactate and pyruvate concentrations were analysed semicontinuously, and the lactate-to-pyruvate ratio (LP ratio) – as a marker of the myocardial redox or oxygenation status – was calculated [9]; these were compared with the metabolite concentrations in the systemic circulation.

Methods

Patients

Following approval by the local ethical committee and provision of informed, written consent, 29 patients (mean age 64±8 years) with coronary artery disease (CAD) and a left ventricular ejection fraction (LVEF) of more than 40% were enrolled in the study. Twelve of the patients had a history of myocardial infarction. Cardiovascular risk factors were: hypertension (n=17), diabetes mellitus (n=8), former or current smoking habit (n=12), hypercholesterolaemia (n=10) and family history of cardiovascular diseases (n=8). Demographic data and cardiovascular risk factors did not differ between the two groups. Patients underwent CABG with one to three venous grafts and the left internal mammary artery (LIMA) for revascularisation of the left anterior descending coronary artery (LAD). On-pump procedures were performed in 17 patients and off-pump procedures, in 12.

Anaesthesia

Anaesthesia was induced with etomidate (0.3–0.5 mg·kg $^{-1}$) and sufentanil (0.5–1 μg·kg $^{-1}$) and maintained with continuous infusions of propofol (5–8 mg·kg $^{-1}$ h $^{-1}$) and sufentanil (0.5–1 μg·kg $^{-1}$ h $^{-1}$). Muscle relaxation was achieved with pancuronium bromide (0.1 mg·kg $^{-1}$). All patients were mechanically ventilated in a pressure-controlled mode (PEEP = 5 cmH_2O, with level of pressure control = 15 cmH_2O, FiO_2 = 0.5). The respiratory rate was adjusted until normocapnia was achieved.

In the on-pump group pure oxygen was given immediately before CPB. During CPB ventilation was stopped. After CPB a lung recruitment manoeuvre (two 20-s inflations to give 45 mmHg) was performed and ventilation was restarted in the same mode as before CPB. The patients in the off-pump group were continuously ventilated according to the pressure-controlled mode described above.

Each patient was equipped with a radial arterial line, a central venous line, and an automated pulmonary artery catheter for continuous determination of mixed venous oxygen saturation and semicontinuous measurement of cardiac output and right ventricular ejection fraction (Vigilance; Edwards Lifescience, Baxter, Unterschleissheim, Germany). Intraoperative fluid management was adjusted so as to achieve and maintain central venous pressure between 8 and 12 mmHg and a pulmonary artery capillary occlusion pressure (PAOP) between 15 and 18 mmHg. Volume replacement was performed with Ringer's solution and gelatin polysuccinate, as appropriate. Arterial blood samples were collected during the observation period for blood gas analysis and microdialysis measurements. Nasopharyngeal and rectal temperature were measured continuously throughout the observation period. Routine cardiopulmonary bypass grafting was performed in moderate hypothermia (32°C nasopharyngeal) with a membrane oxygenator (Hilite; Medos, Stolberg, Germany) and a roller pump (Stöckert, Munich, Germany). The pump was primed with 1,430 ml Ringer's solution, 250 ml 20% mannitol and 20 ml 8.4% (1 M) sodium bicarbonate. Patients were completely heparinised according to body

weight, the dose being 300 IU/kg body weight. Activated clotting time was kept longer than 450 s. Aortic and two-stage venous cannulation was performed, and after cross-clamping the heart was arrested using antegrade blood cardioplegia (cold induction) as described by Buckberg [10, 11], which was repeated every 20 min (cold reinfusion) and followed by a 'hot shot' for 3 min before the cross-clamp was removed. Mean arterial blood pressure (MAP) during CPB was maintained at 60–80 mmHg. Vasopressors (norepinephrine) were administered if necessary.

Surgical and microdialysis procedure

After a median sternotomy a longitudinal pericardotomy was performed. Before preparation of the LIMA the myocardial microdialysis catheter (CMA 70, CMA/Microdialysis AB, Sweden) was inserted almost parallel to the LAD in the apical region on the beating heart. To this end, a venous cannula was inserted tangentially through the myocardial wall. The tip of the microdialysis catheter was then inserted into the distal end of the cannula, and retraction of the cannula made it possible to place the catheter tip in its final position in the myocardium, where it was sutured with 5/0 prolene. The inlet of this double-lumen microdialysis catheter was connected to a battery-driven infusion pump (CMA 107 pump, CMA/Microdialysis AB, Sweden) and constantly perfused with lactate-free Ringer's solution at a flow rate of 2 µl/min. The microdialysis probes used had a membrane length of 10 mm and a molecular cut-off of 20 kDa. Interstitial fluid was sampled via the outlet in microvials, and stored at –75°C for subsequent analysis of lactate and pyruvate.

Experimental design

In the on-pump group, microvials were changed every 15 min until the start of CPB. The last vial was changed directly before cross-clamping of the aorta. During CPB, interstitial fluid was sampled at the end of each 20-min cardioplegia period and immediately before removal of the cross-clamp. After CPB, microvials were again changed every 15 min. In the off-pump group, before the anastomosis was constructed microvials were also changed at 15-min intervals. The last vial was changed immediately before the LAD was reopened. During reperfusion, vials were changed in the same 15-min mode as before. Microdialysis catheters were removed before chest closure and inspected for blood dryness before the patient was transferred to the intensive care unit.

Statistical analysis

Results are presented as mean±SEM. Data were analysed nonparametrically by the Wilcoxon signed-rank test for within-group differences and differences between myocardium and systemic metabolites. A p-value under 0.05 was considered statistically significant.

Results

Use of the microdialysis catheters involved no such complications as bleeding, infections or arrhythmias. The insertion procedure took less than 2 min. None of the patients showed clinical or enzymatic signs of myocardial ischaemia. The course of the systemic metabolism and haemodynamics showed no significant changes in the off-pump group, but there were significant increases in heart rate (due to the pacer) and cardiac output after CPB in the on-pump group. In contrast to blood levels, the results of myocardial microdialysis showed tremendous changes during the observation period in both groups.

Immediately after insertion we observed that myocardial LPR values in both groups were rather higher than blood values [33±8 vs 13±4 (on-pump); 39±9 vs 14±4 (off-pump); p.05]. In the on-pump group this parameter decreased to the normal range before cross-clamping. During the cardiopulmonary bypass, the myocardial LPR increased again, up to 27±5 (p.05 vs before CPB), followed by a sharp decrease to very low values during reperfusion.

In the off-pump group the LPR remained high after insertion and during preparation of the LAD. During reperfusion or revascularisation the LPR decreased tremendously, to 6±3 (p.05 vs before). Myocardial pyruvate increased exponentially after anastomosis in both groups. In contrast, myocardial lactate increased slightly in the on-pump group and dropped slightly in the off-pump group, recovering normal values.

Discussion

This study was designed to determine the course of the levels of metabolites related to energy metabolism in myocardial tissue during open heart surgery performed with use of the microdialysis technique. We did not observe any complications, such as infection or bleeding, connected with insertion of the microdialysis catheter. The catheter membrane is very vulnerable, but after it was retracted from the myocardium we did not detect any membrane ruptures; the microdialysis catheters were still intact and no material remained in the heart.

Directly after insertion of the microdialysis catheter into the beating heart we observed a high LPR. This phenomenon can be explained by the destruction of myocardial tissue. The fast decrease of the LPR to normal values until cross-clamping was performed may have been caused by the initial flushing of the microdialysis catheter and the high perfusion rate of 2 µl/ min, which enabled rapid wash-out of the interstitial space [12, 13]. Owing to the prolonged preparation trauma and the use of a myocardial tissue stabiliser in the off-pump group, the LPR remained high until anastomosis of the LAD. The second LPR peak extending up to the third application of blood cardioplegia in the on-pump group might be interpreted as a sign of myocardial tissue dysoxia [5]. In clinical studies the effect of cardioplegia on the myocardial LPR only has been determined from coronary sinus blood samples [5, 12]. Kennergreen et al. compared myocardial lactate and glucose

concentrations with arterial and coronary sinus blood measurements during open heart surgery including CPB [14, 15]. Interestingly, these authors observed no essential differences in the biochemistry of arterial and coronary sinus blood. In their study coronary sinus blood was taken before and after CPB, but not while it was in progress. The relative changes in the myocardial lactate concentrations were comparable to those recorded in our study.

In particular, we focused our interest on the myocardial pyruvate concentration, which increased sharply after coronary anastomosis in both groups. Actually this was a very short period for monitoring the reperfusion biochemistry. However, for safety reasons we chose to withdraw the microdialysis catheter before closing the chest. In contrast to Kennergren's study – in which the catheter was left in place for a longer period – this may limit our data interpretation, but may also allow for the treatment of potential bleedings in the area of insertion. A comparable course of myocardial pyruvate to that observed in our study has been reported by Zemgulis et al. in an animal model of myocardial ischaemia. After CPB these authors observed a larger increase of the myocardial pyruvate in nonischaemic than in ischaemic areas [16]. Their microdialysis measurements were continued until 60 min after CPB. One explanation for this tremendous increase in pyruvate may be that the pyruvate dehydrogenase (PDH) enzyme complex was inhibited in this situation. A possible explanation for this phenomenon in turn is that the increase in free radical formation induced by the extracorporeal circulation may have effected injury to the myocardial PDH complex during reperfusion, with consequent uncoupling of glycolysis and glucose oxidation [17–19].

Using the ^{13}C nuclear magnetic resonance (NMR) technique, Lewandowski documented a decrease in pyruvate oxidation in postischaemic hearts [8]. He confirmed results published by Kobayashy et al., who performed an in vitro assay of the PDH enzyme complex and determined that 45% of the PDH was inactive during the first 2 min of myocardial reperfusion [20]. After continued reperfusion, PDH activity normalised to control levels. This suggests that the PDH inhibition was reversible. A rapid increase in the mitochondrial ATP/ADP ratio and the increased availability of ATP as substrate for PDH kinase coupled with continued high levels of NADH and acetyl CoA – which stimulates PDH kinase activity – have been discussed as agents of the early inactivation of PDH during reperfusion. It is of note that both these groups studied isolated hearts: the results obtained in this model may be very different from the clinical situation, especially with respect to the measures used to reduce myocardial oxygen consumption during aortic cross-clamping, i.e. hypothermia and blood cardioplegia.

Gore et al. performed a comparative assessment of the lactate and pyruvate metabolism in septic patients and in healthy volunteers using stable isotope tracer methodology and indirect calorimetry [21]. Their interest was focused on the effect of the administration of dichloracetate (DCA), which is known to increase pyruvate oxidation when oxygen is available. In their group of severely septic patients they observed a marked acceleration of glycolysis, with a combined accumulation of pyruvate and lactate. They concluded that in sepsis the accumulation of lactate was not a result of limitations in tissue oxygenation, but the consequence of a marked

increase in pyruvate. We observed a similar metabolic constellation after CPB. In our study the slightly increased myocardial lactate could be interpreted as a limitation on the consumption of oxygen. This contrasts with improved oxygen consumption in the off-pump group, which is associated with a decrease in myocardial lactate after anastomosis.

At present the myocardial microdialysis technique is a rather new device technology. Therefore, it is very difficult to interpret the biochemical data in the clinical context, especially in relation to functional myocardial changes. In our study we examined only patients in whom left ventricular ejection fraction was normal. There were no complications during the clinical course in either group. The patients showed no electroencephalographic, enzymatic or functional signs of myocardial infarction after the CABG procedure. It would, however, be very interesting to compare our biochemical results with analogous results recorded in patients with a low left ventricular ejection fraction or a low cardiac output syndrome. Microdialysis may also be found to offer diagnostic and therapeutic options when the effects of different cardioplegia solutions on myocardial metabolism and with regard to situations in which patients are difficult to wean from CPB are analysed.

Conclusion

A commercially available catheter was used in a clinical trial of myocardial microdialysis. The myocardial lactate and pyruvate concentrations and the lactate-to-pyruvate ratio, as a sensitive marker of the myocardial redox status, showed profound changes in both off-pump and on-pump patients. These microdialysis data have to be interpreted in the context of a variety of clinical implications, and a great deal of effort needs to be invested to determine the precise role of microdialysis in CABG procedures and find whether it is possible to improve our clinical management of open heart surgery patients using this new technology.

References

1. Khan NE, De Souza A, Mister R, Flather M et al (2004) A randomized comparison of off-pump and on-pump multivessel coronary-artery bypass surgery. N Engl J Med 350:21-28
2. Calafiore AM, Di Mauro M, Canosa C et al (2003) Myocardial revascularization with and without cardiopulmonary bypass: advantages, disadvantages and similarities. Eur J Cardiothorac Surg 24:953-960
3. Kuhn C, Muller-Werdan U, Schmitt DV et al (2000) Improved outcome of APACHE II score-defined escalating systemic inflammatory response syndrome in patients post cardiac surgery in 1996 compared to 1988-1990: the ESSICS-study pilot project. Eur J Cardiothorac Surg 17: 30-37
4. Isgro F, Skuras JA, Kiessling AH, et al. (2002) Survival and quality of life after a long-term intensive care stay. Thorac Cardiovasc Surg 50: 95-99

5. Bashour CA, Yared JP, Ryan TA et al (2000) Long-term survival and functional capacity in cardiac surgery patients after prolonged intensive care. Crit Care Med 28: 3847-3852
6. Lüdinghausen M (1987) Clinical anatomy of cardiac veins. Surg Radiol Anat 16:159-168
7. Hultman J, Ronquist G, Hansson HE et al (1986) Myocardial energy metabolism during mitral valve replacement. Thorac Cardiovasc Surg 34:351-355
8. Lewandowski ED, Damico LA, White LT et al (1995) Cardiac responses to induced lactate oxidation: NMR analysis of metabolic equilibria. Am J Physiol: 269:160-168
9. Opie LH, Mansford KR (1971) The value of lactate and pyruvate measurements in the assessment of the redox state of free nicotinamide-adenine dinucleotide in the cytoplasm of perfused rat heart. Eur J Clin Invest 1:295-306
10. Buckberg GD (2001) Cardioplegia solutions—unproven herbal approach versus tested scientific study. Semin Thorac Cardiovasc Surg 13:52-55
11. Kato NS, Buckberg GD (1992) New intraoperative cardioprotective strategies for myocardial protection. Curr Opin Cardiol 7:959-967
12. Ungerstedt U (1991) Microdialysis—principles for studies in animals and man. J Intern Med 230:365-373
13. Bolinder J, Hagström E, Ungerstedt U et al (1989) Microdialysis of subcutaneous adipose tissue in vivo for continuous glucose monitoring in man. Scand J Clin Lab Invest 49:465-474
14. Kenergren C, Mantovani V, Lönnroth P et al (1999) Monitoring of extracellular aspartate aminotransferase and troponin T by microdialysis during and after cardioplegic heart arrest cardiology. 92:162-170
15. Kennergren C, Mantovani V, Strindberg L et al (2002) Myocardial interstitial glucose and lactate before, during and after cardioplegic heart arrest. Am J Physiol Endocrinol Metab 284: 88-94
16. Zemgulis V, Ronquist G, Bjerner T et al (2001) Energy-related metabolites during and after induced myocardial infarction with special emphasis on the reperfusion injury after extracorporeal circulation. Acta Physiol Scand 171: 129-143
17. Schoder H, Knight RJ, Kofoed KF et al (1998) Regulation of pyruvate dehydrogenase activity and glucose metabolism in post-ischaemic myocardium. Biochim Biophys Acta 27: 62-72
18. Bunger R, Swindall B, Brodie D et al (1993) Pyruvate attenuation of hypoxia damage in isolated working guinea-pig heart. Int J Biochem 25: 725-729
19. Parolin, ML, Spriet LL, Hultman E et al (2000) Regulation of glycogen phosphorylase and PDH during exercise in human skeletal muscle during hypoxia. Am J Physiol Endocrinol Metab 278: 522-534
20. Kobayashi K, Neely JR (1983) Effects of ischemia and reperfusion on pyruvate dehydrogenase activity in isolated rat hearts J Mol Cell Cardiol 15:359-367
21. Gore DC, Jahoor F, Hibbert JM, De Maria EJ (1996) Lactic acidosis during sepsis is related to increased pyruvate production, not deficits in tissue oxygen availability. Ann Surg 224:97-100

CLINICAL PHARMACOLOGY

Chapter 16

The journey of a drug to the target site: what is decisive?

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In clinical pharmacology there is probably no term that is more frequently used to describe the concentration of a drug in a tissue than tissue penetration. Concentrations of anti-infectives in tissues at the target site are decisive for the microbial and clinical success of chemotherapy. Many chemical and physical characteristics, such as the molecular weight, the pH value and the octanol/water partition coefficient, exert an important impact on the penetration of antimicrobial agents into various tissues. The velocity of diffusion and drug equilibration depends on the surface areas of the respective compartments. In addition, active transport mechanisms, e.g. P-glycoprotein (P-gp), result in the generation of a concentration gradient between compartments. Blood perfusion is also a very important determinant that may delay or impair complete plasma to tissue equilibration.

Background

In the antimicrobial therapy of infections, the "hardly assessable compartment" is another term that is frequently used. However, it is completely unclear when this term is applied appropriately. Because of this uncertainty, we would like to define "hardly assessable compartment" at the beginning: The hardly assessable compartment is a well-defined anatomic space in which the distribution and the concentration of a drug may be expected to be homogenous. Nevertheless, the concentration of an antibiotic in this defined compartment is either too low or borderline to eradicate bacteria, despite the administration of standard dosages and effective plasma concentrations. Subsequently, in antimicrobial chemotherapy as well as in therapies using other drugs, there is one basic principle that has to be considered: In order to achieve an effective drug action, it is necessary that the concentration of the drug at the target site is sufficiently high. In the case of a bacterial infection, the dosage of the antimicrobial agent should be high enough that its concentration at the infected site reaches therapeutically active levels.

In general, drugs are transported in the blood stream to the target organ. The unbound fraction of the drug is able to cross the capillary membrane and diffuse into the fluid of the interstitial space of the tissue [1]. Thus, it is only the free drug fraction that penetrates into tissues and exerts a pharmacological effect. From the interstitial space fluid (ISF), the drug permeates the cell membranes to reach the

cytoplasm where it may target the cell organelles. The transport of the drug from the blood to the target site as well as its elimination are affected by numerous factors. The challenge in the adequate dosing of pharmaceutical agents arises from the fact that the concentration of a drug at the target site is not known in most cases and measurement of the time-concentration profile in the infected tissue is, in most circumstances, not available in routine settings [2].

Many factors that markedly affect the tissue penetration of drugs have been identified, and are of chemical, physical and physiological natures [3]. Most importantly, the size and the weight of the molecule, its lipophilicity, the extent of plasma protein binding, the pH value in body fluids as well as the characteristics of the capillary wall are decisive. In addition, blood perfusion of the organ, degree of vascularisation, and the presence or absence of active transport mechanisms also play relevant roles in drug penetration. Furthermore, it should be noted that other physiological determinants, such as heart rate, organ function, concomitant medication and therapeutic interventions, may substantially affect the tissue and plasma pharmacokinetics in compromised patients.

Chemical properties of drugs

The molecular weight and the molecular size determine the velocity of drug penetration. The smaller the drug is, the faster diffusion will occur by crossing biological membranes. The molecular size of an antibiotic may vary extensively (Table 1). The molecule teicoplanin, for example, has a molecular weight that is around ten-fold greater than that of fosfomycin. Teicoplanin, therefore, does not penetrate physiological barriers as fast as fosfomycin. However, the diffusion of drugs in the human body does not strictly follow Fick's laws of diffusion. While very small molecules like oxygen excellently diffuse, according to the law of Fick, larger molecules penetrate membranes much slower than predicted.

Table 1. Chemical properties of different antibiotics

Substance	Molecular weight	Plasma protein binding (%)	pK_a
Fosfomycin	180	~0	1.5-6.4
Beta-lactams	300-600	10-95	2-8
Ciprofloxacin	331	~30	8.8
Gentamicin	450	~25	3.5-5.5
Vancomycin	1449	10-50	Not available
Teicoplanin	1993	95	9-12.5

One possible explanation for this discrepancy between smaller and larger molecules in their diffusion properties can be explained by differences in their lipophilicity. The lipophilicity of a drug is commonly defined by the octanol/water partition coefficient. The higher this parameter, the greater the octanol fraction and lipophilicity of the drug. This is of particular interest in the penetration of the central nervous system, where the drug has to cross the blood-brain barrier. The

blood-brain barrier consists of several layers of lipid membranes and the vascular endothelia [2, 4]. Lipophilic drugs, therefore, are able to reach the central nervous system much more easily than hydrophilic drugs.

Another parameter that affects tissue penetration is the extent of plasma protein binding (PPB). The percentage of PPB may vary from 0% to almost 100% and is of great importance with respect to the drug's pharmacokinetics because only the unbound, non-plasma protein bound fraction of a drug is able to pass the central compartment and diffuse into the ISF. Antibiotics that exert no PPB reach concentrations in tissues that are almost identical to total plasma levels. This has been observed for fosfomycin after a period of around 20 min after the end of the infusion [5]. In contrast, moxifloxacin, for example, exerts a PPB of around 50-60% [6]. Consequently, the tissue levels of moxifloxacin are around a half of those measured in the plasma. With these considerations in mind, it needs to be pointed out that the PPB of a drug may differ between extensively individuals and may completely diverge from values reported in the literature. Joynt et al. demonstrated that the extent of the PPB of ceftriaxone depends on the total drug concentration in plasma [7]. With increasing concentrations in plasma, the unbound fraction of ceftriaxone increased simultaneously. This effect was much more pronounced in critically ill patients [8]. In septic patients suffering from hyperalbuminaemia the PPB varied from 10% to 90% [7]. The reported value for PPB for ceftriaxone in the literature is 90%. This extreme discrepancy between the reported values and the measured values in the critically ill highlights the need for individual measurement of PPB if the appropriate drug concentration and drug dosage is to be achieved in the therapy of compromised patients.

The degree of the PPB also determines the penetration of the drug in the central nervous system. This was recently pointed out in a report published by Pfausler et al. [9]. In this study, patients presenting catheter-associated ventriculitis and scheduled to undergo extraventricular drainage received fosfomycin four times a day. Specimens from the liquor and plasma were taken at defined time points and their concentrations were compared using the area under the concentration versus time curve (AUC), i.e. a well-accepted parameter that describes tissue penetration. The tissue AUC was related to the plasma AUC, and it was demonstrated that the ratio of the two is around 0.25 under steady-state conditions. This illustrates that 25% of the concentration in the plasma is able to penetrate the blood-brain barrier. The extent of penetration of fosfomycin into the liquor did not change although the overall condition of the patient improved greatly during the treatment period. This underlines the fact that penetration of this very hydrophilic compound into the central nervous system is unexpectedly high and cannot be exclusively explained by the presence of capillary leakiness, which might be present during ventriculitis. In contrast, vancomycin exerts a PPB of ≈ 25%, and was not able to sufficiently penetrate the blood-brain barrier and to enrich in the liquor even though the study populations were comparable [10].

Keeping all of these chemical and physical properties of the drug in mind, we can summarise by stating that the penetration of an antimicrobial agent into the liquor can be predicted by its molecular size, lipophilicity and PPB. Based on these

parameters, the calculated values of drug penetration corresponded with the in vivo measured concentrations in liquor with a coefficient of correlation of 0.9 [4].

Other chemical determinants that are important for the penetration of a drug are its pK_a and pH value at the target site. Most drugs are available either as a weak base or as a weak acid. The pK_a determines the pH at which half of the drug is present in the ionised or non-ionised form. The dissociation characteristics markedly affect the pharmacokinetics of drugs because weak acids enrich in an alkaline milieu and weak bases in an acid milieu. This can be explained as follows: the permeability of cell membranes depends on the grade of dissociation of the drug. Non-dissociated or non-ionised drugs may penetrate lipid membrane much more easily than ionised drugs. If a base permeates a cell membrane and reaches an acid compartment, than this drug dissociates and is present as a cation. As a result, the ionised form of the drug is not able to redistribute or cross the lipid membrane and, therefore, accumulates at defined sites. Also, the pH value may differ between different body fluids. It is most likely that concentrations of antibiotics differ substantially between compartments because of this ion-trapping phenomenon. For antibiotics, it should be considered that the target site has an acid milieu in most cases and thus an accumulation of weak bases is expected.

Diffusion and surface-area-to-volume ratio

The velocity of diffusion is markedly affected by the chemical properties of the compound as well as by the surface area to volume ratio of the compartments involved (Fick's law). If the surface area of a compartment is relatively large, than drug equilibration between compartments take place very rapidly. Under these conditions, it is possible that complete drug equilibration occurs between the plasma compartment and tissues without marked delay. Changes of drug concentrations in serum are closely paralleled by the drug concentration profile in tissue. However, it is only the unbound drug fraction [11-13] that is able to cross the capillaries and thus equilibrate with the interstitium of the compartment (Fig. 1). The AUC_{serum} and $AUC_{interstitium}$ are almost identical, and thus the ratio is about 1.

The sphere is a geometric body with the lowest surface area, when its volume is predefined. A spherical abscess, therefore, has the lowest surface to volume ratio of all geometric bodies and thus equilibration of drugs between external compartments and the abscess fluid will occur very slowly. More importantly, it is not only the geometric form but also the absolute surface area and size of the spherical abscess that has to be considered in the drug equilibration process. The larger the diameter of the abscess, the longer the distance that an antibiotic molecule has to pass per diffusion. Therefore, it is most likely that, even within the abscess, a concentration gradient of the antibiotic is present. This gradient may be even more pronounced if the antibiotic is degraded or consumed by the bacteria in the presence of β-lactamases. The C_{max} in the abscess fluid is most likely lower than the C_{max} in plasma even when the drug is administered several times and a steady-state condition is reached. The ratio $AUC_{abscess}$ to AUC_{serum} is thus significantly less than 1 (Fig. 2).

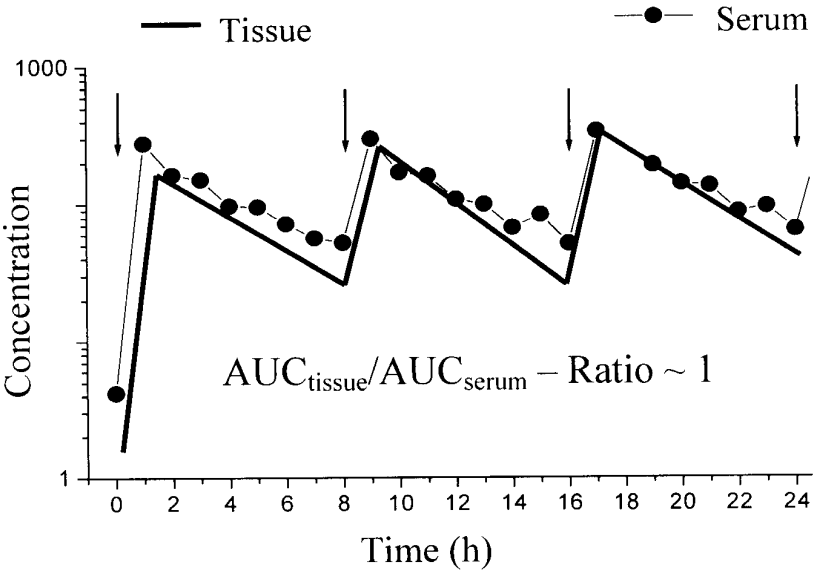

Fig. 1. Time-concentration profiles of a drug for serum and tissue. Representing an example of a large surface area to volume ratio. The drug was administered three times a day (arrows)

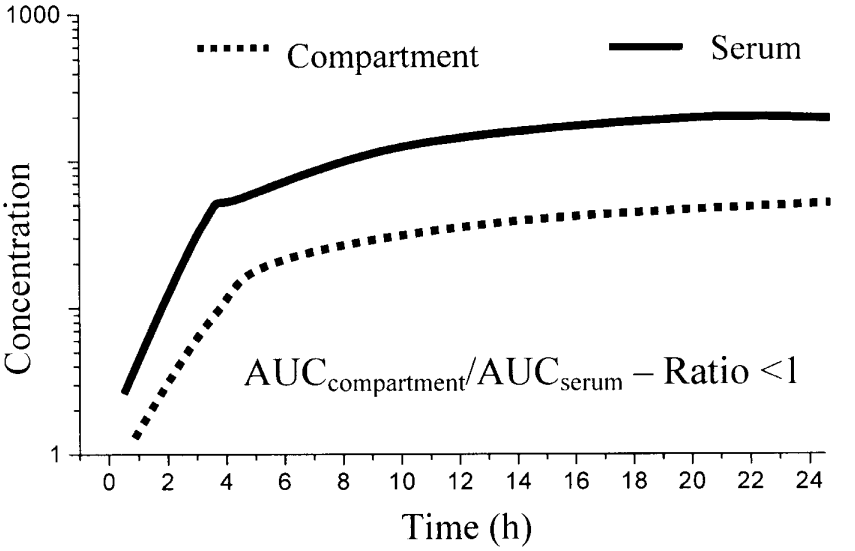

Fig. 2. Depicts the time-concentration profile of a drug for serum during continuous infusion in the presence of the permanent activity of a transport mechanism. Tissue concentrations are lower as compared to the central compartment, despite steady state conditions

Blood flow

Blood flow exerts an important role on the pharmacokinetics of a drug, particularly if blood circulation to the peripheral site is blunted, as in patients with peripheral arterial occlusive disease [13]. Ciprofloxacin was administered to these patients proximal and distal to the stenotic arteria of the affected limb. Concentrations of ciprofloxacin in the comprised, ischemic limb were significantly lower than in healthy tissue. All patients were scheduled to undergo percutaneous transluminal angioplasty (PTA) to improve blood perfusion of the lower limb. After PTA of the afflicted stenotic artery, blood perfusion was significantly improved in all patients, with blood perfusion parameters being comparable to those of the healthy contralateral side. The concentrations at the infected ischemic site were almost identical to the time-concentration profile determined in the healthy tissue. These results have been strongly confirmed by subsequent studies using vasopressors such as norepinephrine [14]. In another study in septic patients, it was shown that the concentration versus time profiles of piperacillin in muscle and subcutaneous adipose tissue were significantly lower in patients receiving potent vasopressors than in healthy controls [11]. Taken together, these data provide circumstantial evidence that tissue concentrations of antibiotics depend on the presence of potent vasoactive drugs and on blood flow to peripheral sites.

Active transport mechanisms

Recently, the relevance of physiological transport mechanisms in the pharmacokinetics of drugs has been discussed, and membrane P-gp is considered to play an eminent role [15]. This protein is an ATP-dependent nonspecific efflux pump encoded by the multidrug resistance gene (*mdr*) [16]. P-gp is able to nonspecifically transport drugs from the intracellular space out of the cell. The pump is located on the membranes of various organs, including those with elimination functions, such as the liver, the kidney and the intestine [17], and is present in high amounts in the capillary endothelium.

Schinkel et al. tested the relevance of P-gp in knockout- ($mdr^{-}/^{-}$) and wild-type ($mdr^{+}/^{+}$) mice [18]. In P-gp knockout mice, concentrations of tested drugs were significantly higher than in wild-type. For example, the concentrations in brain of digoxin in P-gp-negative mice were around 24 fold higher than in the wild-type. This effect was particularly pronounced for the central nervous system, because of the presence of the blood-brain barrier and the high level of expression of P-gp on endothelial cells of brain capillaries [19-21].

From this it might be concluded that P-gp is able to form a concentration gradient between two different compartments. Fig. 2 shows schematically how tissue and plasma concentrations are expected to be in the presence of active-transport mechanisms. Despite continuous intravenous administration of a drug, the concentrations in tissues will not reach corresponding serum concentrations because the drug will be permanently pumped back from the interstitium into the

serum. Thus, a concentration gradient between tissue and plasma is present despite steady-state conditions.

P-gp activity, however, shows very high inter- and intra-individual variability. In addition, it was recently shown that the activity of P-gp might vary depending on the presence of inflammation. Stress (oxidative, physical or inflammatory) has been shown to extensively modify the activity of P-gp [20, 22]. Thus, P-gp in intensive care patients is most likely activated, resulting in very low drug concentrations in tissues. This most probably explains why concentrations of piperacillin were up to ten-fold lower in both skeletal muscle and subcutaneous adipose tissue compared to free plasma concentrations. In contrast, in healthy controls, plasma concentrations were identical to tissue concentrations and complete plasma to tissue equilibration was observed for the free drug fraction of piperacillin [11].

Changes in tissue concentrations due to inflammation

Inflamed tissue is not comparable to healthy tissue because of the presence of hyperaemia, dolour, tumour, redness and impaired function. In a very recently published study, the concentration versus time profile of moxifloxacin was measured in patients suffering from soft-tissue infections [23]. These data were compared to the time-concentration profiles determined in healthy tissue. The moxifloxacin concentrations in inflamed tissue were higher than in healthy tissue of the contralateral side. Moxifloxacin is a weak substrate for P-gp and is therefore only eliminated from the tissue by this pump to a very low extent. The high concentrations of moxifloxacin in inflamed tissue are, therefore, most likely due to hyperaemia and the increased permeability of the infected tissue. In a diabetic subgroup, however, a completely opposite result was obtained. The concentration versus time profile in the diabetic subgroup was higher in healthy tissue than in the inflamed contralateral side. This discrepancy between diabetic and the non-diabetic patient populations can probably be explained by the presence of diabetic angiopathy syndrome. Thus, vascular pathology is present in almost each long-term diabetic patient and can be detected long before ulcer and infection of soft tissue occurs. The low concentration of moxifloxacin at the infected site was the result of impaired blood perfusion of the limbs in the diabetic group.

This study highlights two important facts. Firstly, pharmacokinetic data derived from healthy tissue cannot be transferred uncritically to inflamed tissue. Secondly, diseases may substantially alter the pharmacokinetics of antimicrobial drugs in target tissues.

Recommendations by regulatory affairs

In the course of the development and approval of antimicrobials and other drugs, many questions have to be addressed, and collected data have to be submitted to governmental regulatory affairs departments. Chief among these are data regar-

ding the efficacy of the drug, the effect of sub-inhibitory concentrations, the development of resistance and toxicological characteristics. In addition, the tolerability and the pharmacokinetics of the drug in plasma and tissues have to be reported. These data are collected in different phases during drug development and include in vitro tests, animal testing and, finally, phase I studies in humans. The European Agency for the Evaluation of Medicinal Products (EMEA) and the US Food and Drug Administration (FDA) are responsible for drug approval and monitoring. Both institutions have established guidelines for the industry aiming at providing clear instructions with respect to carrying out clinical trials and making drugs and antibiotics as effective as possible. These institutions currently recommend that concentrations of antimicrobial agents must be determined at the site of infection. In addition, it is advocated that pharmacokinetic data obtained in humans must be evaluated with regard to pharmacodynamic effects. This means that the efficacy of the pharmacokinetic data derived in vivo have to be tested in vitro on clinically relevant bacteria. This combined pharmacokinetic/pharmacodynamic (PK/PD) approach allows testing of whether the time-concentration profile determined in tissues and plasma is effective in eradicating bacteria at the target site. The /PD approach, therefore, might also be used to optimise drug dosages in vivo.

Perspectives

The time-concentration profile of an antimicrobial agent at the target site is important for the microbial and clinical efficacy of chemotherapy. However, the pharmacokinetics of a drug in the human body are modified by many factors, such as chemical, physical, physiological and pathological conditions. In most cases, it is not possible to consider all of these parameters simultaneously. Thus, the EMEA and FDA currently recommend that the time-concentration profile of an antibiotics should be determined in tissue instead of plasma. Only knowledge of concentrations of antibiotics at the relevant site will allow the prediction of microbial and clinical efficacy and provides a rational basis for tailoring antibiotic treatment regimes.

References

1. Renkin EM (1978) The microcirculatory society Eugene M. Landis award lecture. Transport pathways through capillary endothelium. Microvasc Res 15:123-135
2. Nau, R, Prange, HW (1996) Estimation of steady state antibiotic concentration in cerebrospinal fluid from single-dose kinetics. Eur J Clin Pharmacol 49:407-409
3. Barza, M, Cuchural, G (1985) General principles of antibiotic tissue penetration. J Antimicrob Chemother 15:A59-A75
4. Nau, R, Sorgel, F, Prange, HW (1998) Pharmacokinetic optimisation of the treatment of bacterial central nervous system infections. Clin Pharmacokinet 35:223-246

5. Joukhadar, C, Klein, N, Dittrich, P et al (2003) Target site penetration of fosfomycin in critically ill patients. J Antimicrob Chemother 51:1247-1252
6. Siefert, HM, Domdey-Bette, A, Henninger, K et al (1999) Pharmacokinetics of the 8-methoxyquinolone, moxifloxacin: a comparison in humans and other mammalian species. J Antimicrob Chemother 43:B69-B76
7. Joynt, GM, Lipman, J, Gomersall, CD et al (2001) The pharmacokinetics of once-daily dosing of ceftriaxone in critically ill patients. J Antimicrob Chemother 47:421-429
8. Popick, AC, Crouthamel, WG, Bekersky, I (1987) Plasma protein binding of ceftriaxone. Xenobiotica 17:1139-1145
9. Pfausler, B, Spiss, H, Beer, R et al (2003) Treatment of staphylococcal ventriculitis associated with external cerebrospinal fluid drains: a prospective randomized trial of intravenous compared with intraventricular vancomycin therapy. J Neurosurg 98:1040-1044
10. Pfausler, B, Haring, HP, Kampfl, A et al (1997) Cerebrospinal fluid (CSF) pharmacokinetics of intraventricular vancomycin in patients with staphylococcal ventriculitis associated with external CSF drainage. Clin Infect Dis 25:733-735
11. Brunner, M, Pernerstorfer, T, Mayer, BX et al (2000) Surgery and intensive care procedures affect the target site distribution of piperacillin. Crit Care Med 28:1754-1759
12. Joukhadar, C, Frossard, M, Mayer, BX et al (2001) Impaired target site penetration of beta-lactams may account for therapeutic failure in patients with septic shock. Crit Care Med 29:385-391
13. Joukhadar, C, Klein, N, Frossard, M et al (2001) Angioplasty increases target site concentrations of ciprofloxacin in patients with peripheral arterial occlusive disease. Clin Pharmacol Ther 70:532-539
14. Bernards, CM, Kopacz, DJ (1999) Effect of epinephrine on lidocaine clearance in vivo: a microdialysis study in humans. Anesthesiology 91:962-968
15. Cordon-Cardo, C, O'Brien, JP, Boccia, J et al (1990) Expression of the multidrug resistance gene product (P-glycoprotein) in human normal and tumor tissues. J Histochem Cytochem 38:1277-1287
16. Leveille-Webster, CR, Arias, IM (1995) The biology of the P-glycoproteins. J Membr Biol 143:89-102
17. Bertilsson, PM, Olsson, P, Magnusson, KE (2001) Cytokines influence mRNA expression of cytochrome P450 3A4 and MDRI in intestinal cells. J Pharm Sci 90:638-646
18. Schinkel, AH, Wagenaar, E, van Deemter, L et al (1995) Absence of the mdr1a P-Glycoprotein in mice affects tissue distribution and pharmacokinetics of dexamethasone, digoxin, and cyclosporin A. J Clin Invest 96:1698-1705
19. Fromm, MF (2000) P-glycoprotein: a defense mechanism limiting oral bioavailability and CNS accumulation of drugs. Int J Clin Pharmacol Ther 38:69-74
20. Felix, RA, Barrand, MA (2002) P-glycoprotein expression in rat brain endothelial cells: evidence for regulation by transient oxidative stress. J Neurochem 80:64-72
21. Loscher, W, Potschka, H (2002) Role of multidrug transporters in pharmacoresistance to antiepileptic drugs. J Pharmacol Exp Ther 301:7-14
22. Sarkadi, B, Muller, M, Hollo, Z (1996) The multidrug transporters--proteins of an ancient immune system. Immunol Lett 54:215-219
23. Joukhadar, C, Stass, H, Muller-Zellenberg, U et al (2003) Penetration of moxifloxacin into healthy and inflamed subcutaneous adipose tissues in humans. Antimicrob Agents Chemother 47:3099-3103

Chapter 17

The pharmacokinetics and pharmacodynamics of antimicrobial agents in intensive care unit patients as assessed by microdialysis

V. Kulemann, C. Joukhadar

Traditionally, microdialysis was used to monitor time-concentration courses against a baseline. For example, the time-concentration profile of glucose and lactate could be followed over periods of several hours and days. For many years, however, absolute concentrations could not be measured because calibration of the microdialysis probe was not possible . Nevertheless, this approach was sufficient to characterise metabolic disorders and, in particular, to monitor ischaemia during neurosurgery. The latter was achieved in brain trauma patients by taking into account the "Lund concept", which has been shown to significantly improve survival of intensive care patients as brain ischaemia may be detected earlier by use of microdialysis technique than by routine brain pressure measurement. This, however, has come under debate in recent years [1].

In the chemotherapeutic management of patients, evaluating relative changes in the amount of a drug against a baseline is insufficient because knowledge of the absolute tissue concentrations of a drug is considered to be essential for the overall pharmaceutical treatment of intensive care patients. This is clearly highlighted in many textbooks, which state that "to achieve a desired effect of a pharmaceutical agent, its concentration at the target site must be sufficiently high". Similarly, the ability to measure absolute plasma and tissue concentration of an antibiotic is important for the successful therapy of microbial infections. Nonetheless, microbiology societies and many microbiology journals still recommend to their members and readers that blood levels of an antibiotic should exceed the minimal inhibitory concentration (MIC) for a certain time period. This is a misconception, as blood concentrations are in most cases not identical to target site concentrations. Many clinical reports have clearly shown that tissue penetration is substantially impaired in cases of infections of the skin, eye, urinary tract, liver and central nervous system.

Microdialysis is a probe-based method to measure the time-concentration profile of antimicrobial agents in target tissues. The probe can be inserted into tissues without need for special skills. This method has a very high reproducibility and allows for the description of the time-concentration course of the unbound and microbiologically active drug fraction of an antibiotic at the target site. Microdialysis, therefore, fulfils current recommendations of the Food and Drug Admi-

nistration (FDA) and European Agency for the Evaluation of Medical Products (EMEA).

Healthy volunteers

Microdialysis was initially employed to study the basic principles of drug tissue penetration in healthy volunteers. In general, it was found that only the free fraction of an antibiotic is able to pass the capillary membrane and to equilibrate with the interstitial-space fluid (ISF) of soft tissues in healthy volunteers. This was demonstrated for almost all classes of antimicrobial agents. For instance, moxifloxacin [2, 3] was recently demonstrated to penetrate excellently into soft tissues. The total plasma concentrations of moxifloxacin were approximately twice as high as the free fraction of moxifloxacin in plasma. However, only the free fraction was able to completely equilibrate with the interstitium of skeletal muscle and subcutaneous adipose tissue within 2 h after intravenous drug administration. Moxifloxacin and other fluoroquinolones, such as levofloxacin [4] and ciprofloxacin [5–7], were demonstrated to equilibrate rapidly with the ISF of soft tissues if the free fraction of the antibiotic is taken into consideration. Thus, knowledge of the free fraction of an antibiotic allows establishment of the optimum dosage and dosing regimen needed to adequately treat infections with clinically relevant bacteria.

Another study using the ß-lactam antibiotic cefixime has greatly confirmed what was shown for the flouroquinolones. Total plasma concentrations were significantly higher than those of the free fraction of this antibiotic. The plasma protein binding (PPB) of cefixime [8] is around 80% and thus the total plasma fraction was significantly higher than the free fraction. The unbound fraction was able to completely equilibrate with the interstitium with an AUC_{tissue} to $AUC_{free\ plasma}$ ratio of around one. This parameter clearly indicates that drug tissue penetration is complete for the free fraction.

Another class of antibiotics that has recently received much attention is the ketolides. The first member of this class to be marketed was telithromycin, which was approved in 2001 for the therapy of upper respiratory tract infections and infections of the ear and throat. It was speculated that telithromycin could be used for the treatment of soft-tissue infections since ketolides are closely related to the class of macrolides. The ability of telithromycin to penetrate soft tissues was therefore tested in a recent study, and the authors were able to show that only the unbound fraction of telithromycin was able to cross the capillary membrane and equilibrate with the interstitium. The PPB, however, of telithromycin is around 80%, and thus only 20% of the total drug fraction was readily available in the interstitium. The drug concentration of telithromycin at the target site was very low. Regarding the MIC in the treatment of infections, it thus becomes clear why the time-concentration profile of an antibiotic might be too low to successfully eradicate bacteria involved in soft-tissue infections. This most probably is an explanation for the dramatic increase in resistance of *Streptococcus pneumonia* and other gram-positive bacteria against macrolide antibiotics in the last ten years. The

subinhibitory tissue concentrations of macrolides and ketolides and the subsequent high resistance rates have resulted in the fact that macrolides are no longer the first choice in the treatment of soft-tissue infections [9].

Patients

Based on the first findings derived from healthy volunteers, additional data on the effectiveness of microdialysis were collected in patients. The results showed that, in particular, the pharmacokinetic profile of antimicrobial agents was substantially altered in intensive care patients as this patient population suffers from many substantial organ disorders and receives a large number of concomitant medications [10]. One of the first studies testing the penetration properties of antimicrobial agents in intensive care patients was performed in 2000 [11]. In this study, the authors tested the ability of piperacillin to penetrate into soft tissues in patients scheduled to undergo aortic valve surgery. The time-concentration profiles determined in this patient population were compared to those of healthy controls (Fig. 1). As known from previous studies, complete equilibration of the free fraction of piperacillin was detected in soft tissues in healthy controls. In contrast, the time-concentration profile of free piperacillin in the interstitium of skeletal muscle was approximately four to five fold lower than the free concentrations in plasma. A

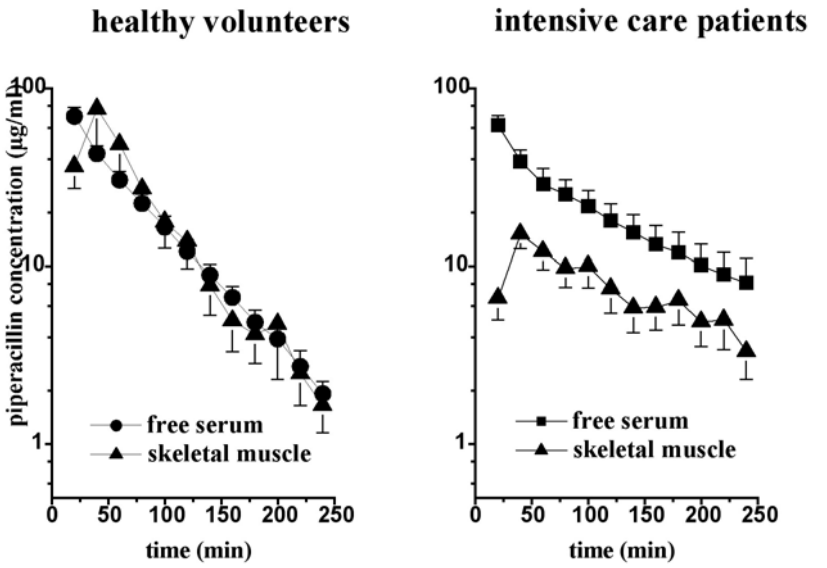

Fig. 1. Concentration versus time profiles of free piperacillin in plasma and the interstitium of skeletal muscle in healthy volunteers (*left*) and patients scheduled to undergo aortic valve surgery (*right*)

concentration gradient was present over the entire observation period of 4 h, indicating that diffusion is not the only process responsible for the equilibration between two compartments in septic patients.

The data reported in this population were confirmed by several other studies using imipenem [12], cefpirome [13], fosfomycin [14] and levofloxacin [15] and showed that, compared to healthy controls, drug tissue penetration in septic shock patients might be substantially prolonged and delayed. In addition, it was shown that concentrations of antimicrobial agents are substantially lower in septic shock patients than in healthy controls, which is particularly important for antimicrobial agents that exert concentration-dependent antimicrobial killing.

Pharmacokinetic/pharmacodynamic model

From these data it might be speculated that the concentration of antimicrobial agents at the target site is too low in septic shock patients to adequately kill clinically relevant bacteria. Indeed, the clinician is faced with the problem that drug penetration might be impaired in septic shock patients, but it is unclear how dosing regimens have to be modified to adequately kill pathogens at the target site of infection. Therefore, what the clinician is really interested in is not the pharmacokinetics of an antimicrobial agent at the target site but rather the effect, i.e. antimicrobial killing, of an antibiotic at the infection site. Hence, the use of a combined pharmacokinetic/pharmacodynamic (PK/PD) model, which links pharmacokinetic data of an antibiotic to its effects, is needed [16].

The combined PK/PD model consists of three steps (Fig. 2). The first step involves a description of the time-concentration course of the antimicrobial agent at the target site. This is best illustrated by a case study [15]. The pharmacokinetics of the model drug levofloxacin were determined in both plasma and the interstitium of soft tissues of critically ill patients after a single intravenous dose of 500 mg. The time-concentration profiles of levofloxacin in the two compartments were measured in each patient. As expected, moderate inter-individual variability was detected for the plasma compartment. However, variability between individuals was much more pronounced with respect to the time-concentration courses in soft tissues. For some individuals, very high concentrations were detected while in others the time-concentration profiles were very low, indicating that penetration of levofloxacin in these patients was insufficient. After correlation of these concentration profiles in plasma and soft tissues with the MIC, it became clear that for all of the patients dosing was sufficient for the plasma compartment, whereas for the tissue compartment the dose was in some cases insufficient.

In step two of the PK/PD model, a strain of *Staphylococcus aureus* is exposed exactly to the time-concentration profiles determined in plasma and in the interstitium. As expected from the plasma pharmacokinetics, bacterial killing in the plasma compartment was nearly complete in all individuals. For the tissue compartment, however, the bacteria were eradicated in those patients who had very high concentrations in tissues, but in other patients almost no inhibition of bacte-

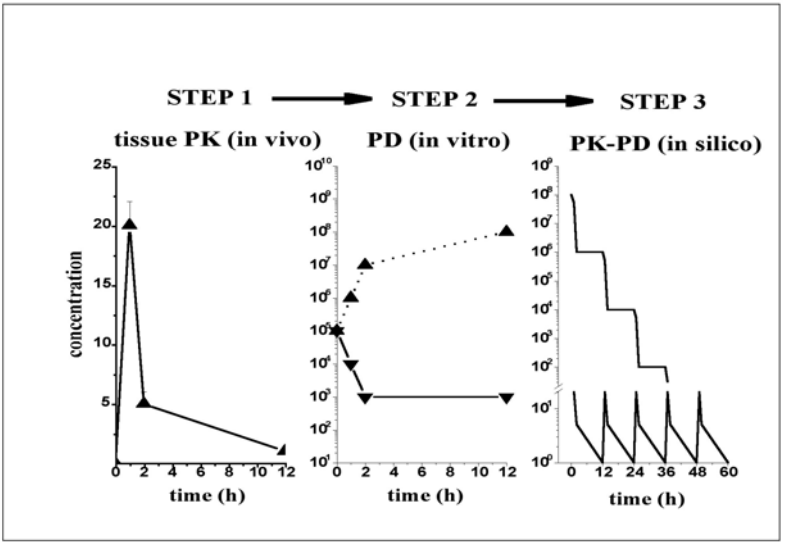

Fig. 2. The general concept of the combined in vivo PK/in vitro PD approach applied in an experiment

rial growth was detected over the simulation period of 8 h. These data show that antimicrobial dosing in the latter group of patients was insufficient and highlighted the need for appropriate dosing and dosing regimens of antimicrobial agents in septic shock patients. This is of particular importance for patients that have an increased volume of distribution or receive other medications that might substantially impair blood perfusion to peripheral sites. Thus, in critically ill patients a higher antimicrobial daily dosing and a higher initial or starting dose is recommended in order to adequately cover pathogenic bacteria at the site of infection.

Increasing the daily dose is of eminent importance for antibiotics that exert concentration-dependent antimicrobial killing, as is the case for aminoglycosides and flouroquinolones. Thus, an increase in the daily dose is associated with an increase of the concentration in tissues and thus with enhanced bacterial killing. From a recent meta-analysis using the penetration ratios of several antibiotics and the sepsis and organ failure assessment score (SOFA), it was expected that this, in turn, would improve clinical outcome. A correlation between the penetration of antibiotics into tissue and the SOFA score indicated that patients suffering from severe sepsis had the lowest tissue concentrations of antibiotic whereas penetration was improved in those patients with less severe disease. Hence, patients that would particularly benefit from adequate concentrations of antibiotics at the target site are those with the lowest tissue concentrations. Increasing the daily dose or shortening the dosing intervals might achieve this goal. Nonetheless, it should be kept in mind that an increase of the daily dose might be associated with untoward effects when antimicrobial agents with a narrow therapeutic window are prescribed.

In the third step of the PK/PD model, the information derived from the in vivo pharmacokinetics and the in vitro pharmacodynamic simulations is applied with the aid of a computer simulation program. Information about bacterial growth and growth inhibition rates allows for the simulation of bacterial killing over time after multiple doses of antibiotic. In the example presented in Fig. 2 (right panel, step three), complete bacterial eradication is obtained after administration of the fourth dosage of antibiotic.

This dynamic simulation provides a rational approach to describe and predict pharmacodynamics at the relevant target site. Some recent publications reported a microdialysis in-vivo PK/in-vitro PD model [16, 17], based on a previously described modified E_{max}-model, that may be used to predict drug effects at the site of drug action. The data were analysed with the integrated PK/PD model employing an E_{max} relationship to link unbound ciprofloxacin concentrations to bacterial kill rates [16]. These experiments showed that pharmacodynamic success or failure of antimicrobial therapy may be due to pharmacokinetic variability at the target site. Using such combined in-vivo PK/in-vitro PD approaches provides strong support for this type of modelling procedure and may also support their optimisation, thereby replacing current concepts for establishing dosing guidelines of select tissue infections.

References

1. Stahl N, Ungerstedt U, Nordstrom CH (2001) Brain energy metabolism during controlled Reduction of cerebral perfusion pressure in severe head injuries. Intensive Care Med 27:1215-1223
2. Joukhadar C, Stass H, Muller-Zellenberg U et al (2003) Penetration of moxifloxacin into healthy and inflamed subcutaneous adipose tissues in humans. Antimicrob Agents Chemother 47:3099-3103
3. Muller M, Stass H, Brunner M et al (1999) Penetration of moxifloxacin into peripheral compartments in humans. Antimicrob Agents Chemother 43:2345-2349
4. Bellmann R, Kuchling G, Dehghanyar P et al (2004) Tissue pharmacokinetics of levofloxacin in human soft tissue infections. Br J Clin Pharmacol 57:563-568
5. Brunner M, Stabeta H, Moller JG et al (2002) Target site concentrations of ciprofloxacin after single intravenous and oral doses. Antimicrob Agents Chemother 46:3724-3730
6. Joukhadar C, Klein N, Frossard M et al (2001) Angioplasty increases target site concentrations of ciprofloxacin in patients with peripheral arterial occlusive disease. Clin Pharmacol Ther 70:532-539
7. Muller M, Brunner M, Hollenstein U et al (1999) Penetration of ciprofloxacin into the interstitial space of inflamed foot lesions in non-insulin-dependent diabetes mellitus patients. Antimicrob Agents Chemother 43:2056-2058
8. Liu P, Muller M, Grant M et al (2002) Interstitial tissue concentrations of cefpodoxime. J Antimicrob Chemother 50 Suppl:19-22
9. Huovinen P (1999) Antibiotic usage and the incidence of resistance. Clin Microbiol Infect 5 4:S12-S16
10. Joukhadar C, Frossard M, Mayer BX et al (2001) Impaired target site penetration of

beta-lactams may account for therapeutic failure in patients with septic shock. Crit Care Med 29:385-391
11. Brunner M, Pernerstorfer T, Mayer BX et al (2000) Surgery and intensive care procedures affect the target site distribution of piperacillin. Crit Care Med 28:1754-1759
12. Tegeder I, Schmidtko A, Brautigam L et al (2002) Tissue distribution of imipenem in critically ill patients. Clin Pharmacol Ther 71:325-333
13. Joukhadar C, Klein N, Mayer BX et al (2002) Plasma and tissue pharmacokinetics of cefpirome in patients with sepsis. Crit Care Med 30:1478-1482
14. Joukhadar C, Klein N, Dittrich P et al (2003) Target site penetration of fosfomycin in critically ill patients. J Antimicrob Chemother 51:1247-1252
15. Zeitlinger MA, Dehghanyar P, Mayer BX et al (2003) Relevance of soft-tissue penetration by levofloxacin for target site bacterial killing in patients with sepsis. Antimicrob Agents Chemother 47:3548-3553
16. Delacher S, Derendorf H, Hollenstein U et al (2000) A combined in vivo pharmacokinetic-in vitro pharmacodynamic approach to simulate target site pharmacodynamics of antibiotics in humans. J Antimicrob Chemother 46:733-739
17. Zeitlinger MA, Marsik C, Georgopoulos A et al (2003) Target site bacterial killing of cefpirome and fosfomycin in critically ill patients. Int J Antimicrob Agents 21:562-567

PERIOPERATIVE MEDICINE

Chapter 18

Anaesthetic effects on regional cerebral blood flow and metabolism: three contemporary reasons to care

M.T. Alkire, J. Miller

A basic understanding of how anaesthesia affects cerebral blood flow and cerebral metabolism is readily available as common textbook material [1]. In general, most anaesthetic agents decrease cerebral metabolism in a dose-dependent manner with variable effects on cerebral blood flow [2]. Despite a basic understanding of the cerebral effects of anaesthetics, the study of anaesthetic effects on cerebral blood flow and metabolism remains a productive area of research with continued importance from both a clinical neuroanaesthesia and a mechanism of anaesthesia frame of reference. This field of study is approaching a revolutionary phase that is partly technology driven (i.e. higher resolution scanners, agent-specific ligands, newer imaging methodology), but which is also a direct result of the plethora of data that now exists regarding the effects of various agents on cerebral blood flow and metabolism. This large literature allows conclusions to be drawn that encompass integrated observations about various specific agents and across various classes of agents. This article, therefore, will not attempt a comprehensive review of the entire literature [2], rather it will focus on integrating some general observations into a cohesive theoretical framework with the aim of providing additional insights. Three contemporary reasons to care about the study of anaesthetic effects on cerebral blood flow and metabolism can be organised as relating to: (1) the documented commonalities among agents, (2) the documented differences between agents, and (3) the detailed effects related to specific agents. These reasons are expanded upon more fully below.

Commonalities

Commonalities exist between agents and classes of agents in how they affect regional cerebral blood flow and regional cerebral metabolism. These commonalities allow the general conclusions that most anaesthetics depress cerebral metabolism, although exceptions like ketamine exist [3-5], and that most intravenous anaesthetics decrease cerebral blood flow, whereas most inhalational agents tend to increase cerebral blood flow [1]. Common regional effects, in many cases, may suggest a shared underlying mechanism of action. Ori and colleagues noted early on that one of the only common regional metabolic

effects seen among the various agents was that they all caused metabolic suppression of the somatosensory cortex [6].

For the anaesthetic end-point of loss of consciousness in humans, a more recent case has been made for a common effect of most, if not all, agents on thalamic metabolism/blood flow and thalamo-cortical-corticothalamic connectivity [6-8]. This commonality has led to the development of the "thalamic consciousness switch" hypothesis of anaesthetic-induced unconsciousness [7]. When this idea was originally developed, it took into account a regional metabolic or blood-flow effect on the thalamus that was observed in humans as a sign of a common overlapping effect between various agents, including lorazepam [9], midazolam [10], propofol [11], isoflurane and halothane [7]. Further study has remained consistent with the thalamic overlap effect and has shown replications of propofol's thalamic effects [12, 13], along with the addition of an overlapping thalamic effect for sevoflurane [14]. Given that the majority of the PET signal originates from synaptic activity and that the thalamus receives a large afferent input from the cerebral cortex, the actual site of mechanistic overlap among agents is likely to be displaced from the thalamus and actually reside in the cerebral cortex [6]. The reduced thalamic metabolism during anaesthesia likely reflects a drug-induced decrease in cortico-thalamic activity. Such an idea fits well with electrophysiological studies [15], and with one study on the metabolic effects of enflurane in the rat, in which enflurane's metabolic effects on the thalamus were unilaterally prevented by ipsilateral cortical ablation [16].

However, it may not be simply a quantitative reduction in thalamic or cortical-thalamic metabolic activity that is key to anaesthetic effects on consciousness [2]; rather, it may be that anaesthetics work to prevent coordinated communication between the thalamus and the cortex. Such an idea was supported by a recent functional and effective connectivity analysis of inhalational anaesthesia [8]. Using a path analysis approach, it was determined that anaesthetic-induced unconsciousness in humans is associated with a functional change in thalamocortical connectivity, such that the thalamus and cortex no longer effectively interact with one another at the point of anaesthetic-induced unresponsiveness.

Other common regional effects are seen between groups of agents. For instance, there seems to be a strong tendency for most agents to suppress metabolism or blood flow in the cerebellum. This is more commonly associated with inhalational agents, especially isoflurane, halothane [8, 17, 18] and sevoflurane [13, 14]. When commonality among agents is looked at with higher resolution, other common regional effects emerge. Some of them are detailed below.

Differences

Differences exist between agents and classes of agents in how they affect regional cerebral blood flow and regional cerebral metabolism. These differences are evident even within agents of similar types that have presumed similar mechanisms of action. Such differences might imply different mechanisms of action between

agents. For example, Veselis and colleagues recently demonstrated that roughly equivalent sedative and hypnotic doses of propofol and thiopental, two agents thought to share a common cellular gamma-aminobutyric acid (GABA)-ergic mechanism of action, actually have differential effects on regional cerebral blood flow [12]. Thiopental had a marked effect on the cerebellum, whereas propofol did not. Additionally, propofol had a marked effect on the thalamus and frontal lobes that thiopental did not. These differential effects suggest either differential mechanisms of action on neuronal activity for each drug or some differential effect on local flow/metabolism coupling. It is interesting to note that thiopental did not show a regionally selective decrease of thalamic blood flow, as might have been expected from the above discussion on the "thalamic consciousness switch" hypothesis. The thiopental observations were, however, based on a relatively small sample size and await confirmation in a larger study. Nonetheless, metabolic activity within the thalamus, as well as within the rest of the brain, was likely greatly reduced for these subjects, so a lack of a specific regional thalamic effect does not imply that thalamic activity failed to be suppressed by the anaesthetic. In other words, thiopental essentially still "turned off" the thalamus, but in a manner consistent with how it also affected the rest of the brain.

These regional metabolic and blood flow differences between agents might ultimately prove to be one of their most important properties. An innovative future therapeutic potential is suggested by these differential effects that might be of clinical advantage. For example, the head-injured patient is often sedated with either propofol or midazolam. As it turns out, propofol reduces regional cerebral blood flow the most in the occipital lobe [11], whereas midazolam reduces regional cerebral blood flow the most in the frontal lobes [10]. This differential regional blood-flow effect between agents raises the possibility that one agent might be more beneficial than another depending on the type and location of a brain injury. For instance, perhaps midazolam would be the better agent for sedating a patient with a frontal head injury, in order to provide a regional luxury perfusion state. Conversely, perhaps propofol would be the better agent for such a patient, in order to minimise the chance of localised oedema formation or a regional hyperglycolysis.

Given the differential effects on blood flow and metabolism, it also would seem to follow that specific agents could have utility as carrier substances to allow for the anaesthetising of specific defined brain regions or, perhaps more importantly, for the delivery of specific treatment regiments. It can be envisioned that chemotherapeutic agents could be regionally distributed to the specific site of a tumour, depending on the location of the tumour and on the specific carrier agent (i.e. anaesthetic) selected. Granted, much work will need to be done in order to make these concepts a reality, but the potential for this therapeutic approach to anaesthetic drugs would seem to exist.

Details (or what in the world is that pesky interpeduncular nucleus doing?)

The differential regional effects evident between agents occur in particular detailed patterns. Understanding these detailed patterns can offer clues to the underlying cellular mechanisms of action for each agent, especially when the agent-specific patterns overlap with the specific regional distribution of a known receptor system. For example, propofol's regional cerebral metabolic effects are correlated with the regional cerebral distribution of GABA receptors [19]. Isoflurane's regional metabolic effects do not follow the distribution of the GABA-ergic system, but rather they are inversely related to the acetylcholine muscarinic system [19]. As new imaging ligands become available, there will likely be a rapid expansion in the number of studies that link anaesthetic mechanisms with specific receptors. This receptor approach has already been partly used to suggest a link between GABA-ergic receptor changes and isoflurane anaesthesia [20].

A further example regarding the details of the effects underlying various anaesthetic agents is provided by the well described metabolic sparing or increased metabolic response of the habenulo-interpenducular system, as seen with most agents in animal studies. The interpeduncular nucleus (IPN) is a group of cells in the midbrain tegmentum located between the cerebral peduncles. The IPN has many connections, including projections to the hippocampus [21-23], septum [24-26], entorhinal cortex [25], raphe nuclei [26, 27], dorsal/ventral tegmental regions[28], zona incerta in rats, and to the dorsal thalamus in cats. The IPN receives reciprocal connections from these structures as well as afferents from the habenula, the pedunculopontine and laterodorsal tegmental nuclei [29]. Thus, the IPN can modulate an array of neurotransmissions, including the aminergic transmitters. The IPN is also thought to be responsible for maintenance of certain phases of sleep, including generation of the hippocampal theta rhythm [30]. The IPN contains an abundance of cholinergic activity, indeed some of the highest of any brain region. The metabolic sparing effect on the IPN has been seen with a wide range of agents, including: chloral hydrate [31], barbiturates [31], ketamine [3-5], etomidate [32], ether [31], isoflurane [6, 33], halothane [34, 35], enflurane [16] and sevoflurane [36]. Two agents that do not spare IPN metabolism are propofol [37], and althesin [38]. The majority of cholinergic activity in the IPN is mediated through nicotinic receptors (nAChRs), located both pre- and postsynaptically. The presynaptic nAChRs are located, at least in part, on axon afferents from the medial habenula [39]. There is also evidence that a substantial portion of these are presynaptic nAChRs on intrinsic GABA-ergic neurons [40]. Given that the genes expressed in the medial habenula and IPN include those known to constitute nAChRs inhibited by various anaesthetics [41], it seems possible that anaesthetic inhibition of the presynaptic nAChRs leads to a decrease in a GABA-mediated efflux inhibition within the IPN. This then causes a disinhibition within the IPN that is then reflected as an increase in localised metabolism during exposure to anaesthetics. This example of an integrative holistic approach to understanding the interactions of anaesthetics with discrete neuroanatomical and physiological subsystems is illustrative of how a detailed reductionist approach to the problem of

anaesthetic effects on cerebral blood flow and metabolism might eventually help elucidate the underlying mechanisms of anaesthesia.

In summary, continued study of the cerebral metabolic and blood flow effects of anaesthetics will lead not only to a better clinical understanding of the anaesthesiologist's "tools of the trade", but also to further insights into anaesthetic mechanisms of action, the potential therapeutic utility of anaesthetic agents and a detailed understanding of the systems through which anaesthetics mediate their effects.

References

1. Drummond JC , Patel P (2000) Cerebral blood flow and metabolism. In: Miller RD (ed) Anaesthesia. Churchill-Livingstone, New York. pp.1203-1256
2. Heinke W, Schwarzbauer C (2002) In vivo imaging of anaesthetic action in humans: approaches with positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). Br J Anaesth 89:112-122
3. Crosby G, Crane AM, Sokoloff L (1982) Local changes in cerebral glucose utilization during ketamine anaesthesia. Anesthesiology 56:437-443
4. Davis DW, Mans AM, Biebuyck JF et al (1988) The influence of ketamine on regional brain glucose use. Anesthesiology 69:199-205
5. Freo U, Ori C (2004) Effects of anaesthesia and recovery from ketamine racemate and enantiomers on regional cerebral glucose metabolism in rats. Anesthesiology 100:1172-1178
6. Ori C, Dam M, Pizzolato G et al (1986) Effects of isoflurane anaesthesia on local cerebral glucose utilization in the rat. Anesthesiology 65:152-156
7. Alkire MT, Haier RJ, Fallon JH (2000) Toward a unitary theory of narcosis: Brain imaging evidence for a thalamocortical switch as the neurophysiologic basis of anaesthetic-induced unconsciousness. Consciousness & Cognition 9:370-386
8. White NS, Alkire MT (2003) Impaired thalamocortical connectivity in humans during general-anaesthetic-induced unconsciousness. Neuroimage 19:402-411
9. Volkow ND, Wang GJ, Hitzemann R et al (1995) Depression of thalamic metabolism by lorazepam is associated with sleepiness. Neuropsychopharmacology 12:123-132
10. Veselis RA, Reinsel RA, Beattie BJ et al (1997) Midazolam changes cerebral blood flow in discrete brain regions: an H2(15)O positron emission tomography study. Anesthesiology 87:1106-1117
11. Fiset P, Paus T, Daloze T et al (1999) Brain mechanisms of propofol-induced loss of consciousness in humans: a positron emission tomographic study. J Neurosci 19:5506-5513
12. Veselis RA, Feshchenko VA, Reinsel RA et al (2004) Thiopental and propofol affect different regions of the brain at similar pharmacologic effects. Anesth Analg 99:399-408
13. Kaisti KK, Langsjo JW, Aalto S et al (2003) Effects of sevoflurane, propofol, and adjunct nitrous oxide on regional cerebral blood flow, oxygen consumption, and blood volume in humans. Anesthesiology 99:603-613
14. Kaisti KK, Metsahonkala L, Teras M et al (2002) Effects of surgical levels of propofol and sevoflurane anaesthesia on cerebral blood flow in healthy subjects studied with positron emission tomography. Anesthesiology 96:1358-1370
15. Angel A (1993) Central neuronal pathways and the process of anaesthesia. Br J Anaesth 71:148-163
16. Nakakimura K, Sakabe T, Funatsu N et al (1988) Metabolic activation of intercortical and corticothalamic pathways during enflurane anaesthesia in rats. Anesthesiology 68:777-782

17. Alkire MT, Haier RJ, Shah NK et al (1997) Positron emission tomography study of regional cerebral metabolism in humans during isoflurane anaesthesia . Anesthesiology 86:549-557
18. Alkire MT, Pomfrett CJ, Haier RJ et al (1999) Functional brain imaging during anaesthesia in humans: effects of halothane on global and regional cerebral glucose metabolism. Anesthesiology 90:701-709
19. Alkire MT, Haier RJ (2001) Correlating in vivo anaesthetic effects with ex vivo receptor density data supports a GABAergic mechanism of action for propofol, but not for isoflurane. Br J Anaesth 86:618-626
20. Gyulai FE, Mintun MA, Firestone LL (2001) Dose-dependent enhancement of in vivo GABAa-benzodiazepine receptor binding by isoflurane. Anesthesiology 95:585-593
21. Baisden RH, Hoover DB, Cowie RJ (1979) Retrograde demonstration of hippocampal afferents from the interpeduncular and reuniens nuclei. Neurosci Lett 13:105-109
22. Groenewegen HJ, Steinbusch HW (1984) Serotonergic and non-serotonergic projections from the interpeduncular nucleus to the ventral hippocampus in the rat. Neurosci Lett 51:19-24
23. Wirtshafter D, Asin KE, Lorens SA (1986) Serotonin-immunoreactive projections to the hippocampus from the interpeduncular nucleus in the rat. Neurosci Lett 64:259-262
24. Vertes RP, Fass B (1988) Projections between the interpeduncular nucleus and basal forebrain in the rat as demonstrated by the anterograde and retrograde transport of WGA-HRP. Exp Brain Res 73:23-31
25. Shibata H, Suzuki T (1984) Efferent projections of the interpeduncular complex in the rat, with special reference to its subnuclei: a retrograde horseradish peroxidase study. Brain Res 296:345-349
26. Montone KT, Fass B, Hamill GS (1988) Serotonergic and nonserotonergic projections from the rat interpeduncular nucleus to the septum, hippocampal formation and raphe: a combined immunocytochemical and fluorescent retrograde labelling study of neurons in the apical subnucleus. Brain Res Bull 20:233-240
27. Maciewicz R, Foote WE, Bry J (1981) Excitatory projection from the interpeduncular nucleus to central superior raphe neurons. Brain Res 225:179-183
28. Groenewegen HJ, Ahlenius S, Haber SN et al (1986) Cytoarchitecture, fiber connections, and some histochemical aspects of the interpeduncular nucleus in the rat. J Comp Neurol 249:65-102
29. Woolf NJ, Butcher LL (1985) Cholinergic systems in the rat brain: II. Projections to the interpeduncular nucleus. Brain Res Bull 14:63-83
30. Valjakka A, Vartiainen J, Tuomisto L et al (1998) The fasciculus retroflexus controls the integrity of REM sleep by supporting the generation of hippocampal theta rhythm and rapid eye movements in rats. Brain Res Bull 47:171-184
31. Herkenham M (1981) Anaesthetic s and the habenulo-interpeduncular system: Selective sparing of metabolic activity. Brain Res 210:461-466
32. Davis DW, Mans AM, Biebuyck JF et al (1986) Regional brain glucose utilization in rats during etomidate anaesthesia . Anesthesiology 64:751-757
33. Maekawa T, Tommasino C, Shapiro HM et al (1986) Local cerebral blood flow and glucose utilization during isoflurane anaesthesia in the rat. Anesthesiology 65:144-151
34. Duffy TE, Cavazzuti M, Cruz NF et al (1982) Local cerebral glucose metabolism in newborn dogs: effects of hypoxia and halothane anaesthesia . Ann Neurol 11:233-246
35. Savaki HE, Desban M, Glowinski J et al (1983) Local cerebral glucose consumption in the rat. I. Effects of halothane anaesthesia . J Comp Neurol 213:36-45
36. Lenz C, Rebel A, van Ackern K et al (1998) Local cerebral blood flow, local cerebral

glucose utilization, and flow-metabolism coupling during sevoflurane versus isoflurane anaesthesia in rats. Anesthesiology 89:1480-1488
37. Dam M, Ori C, Pizzolato G et al (1990) The effects of propofol anaesthesia on local cerebral glucose utilization in the rat. Anesthesiology 73:499-505
38. Davis DW, Hawkins RA, Mans AM et al (1984) Regional cerebral glucose utilization during Althesin anaesthesia. Anesthesiology 61:362-368
39. Brown DA, Docherty RJ, Halliwell JV (1984) The action of cholinomimetic substances on impulse conduction in the habenulointerpeduncular pathway of the rat in vitro. J Physiol 353:101-109
40. Lena C, Changeux JP, Mulle C (1993) Evidence for "preterminal" nicotinic receptors on GABAergic axons in the rat interpeduncular nucleus. J Neurosci 13:2680-2688
41. Tassonyi E, Charpantier E, Muller D et al (2002) The role of nicotinic acetylcholine receptors in the mechanisms of anaesthesia. Brain Res Bull 57:133-150

Chapter 19

Why and when is inhalation anaesthesia better

I. Salvo, P. Silvani, A. Camporesi

Childhood in itself represents an indication for deep sedation and general anaesthesia in most diagnostic and surgical procedures, and inhalation anaesthetics have been the mainstay of paediatric anaesthesia for over 150 years. Most paediatric surgical procedures are short and therefore well suited to be performed on an outpatient basis. Thus, a restricted number of short-acting drugs, which allow anaesthesia and limit the possibility for unknown and unwanted interactions are needed.

Sevoflurane and propofol appear to be good agents for induction and maintenance of anaesthesia in children, because both allow rapid changes in anaesthetic depth and a favourable emergence profile. It is difficult to assess from the literature alone the frequency of use of total intravenous anaesthesia (TIVA) in paediatric anaesthetic practice, but as a pure technique, it does not appear to be widely applied, even in relation to the need for a venous access before induction and restrictions regarding license for use (Table 1). For these reasons, there has been only limited scientific evidence on the use of propofol in children up to 3 years of age [1].

Table 1. Age restrictions on the use of propofol in different countries (courtesy of Astra Zeneca)

Country	License
USA	>3 years
Great Britain	>1 month (induction), >3 years (maintenance)
France	>1 month
Germany	>1 month
Italy	>3 years
Sweden	>3 years

In the past two decades, local anaesthetics have been widely used in infants and children. Major uses of local anaesthetics for awake infants and children are topical formulations on intact skin for needle procedures, topical formulations on cut skin for suture of lacerations, and infiltration prior to deeper needle procedures or superficial minor surgical procedures.

In the majority of cases, regional anaesthesia for children undergoing surgery is performed in combination with general anaesthesia or deep sedation in order to provide intra-operative and postoperative analgesia.

Regional anaesthesia without general anaesthesia or deep sedation is only indicated for hernia repair in infants at risk of apnoea (see below).

Developmental physiology

Safe anaesthesia in children depends on a clear understanding of the physiologic, pharmacologic and psychological differences between children and adults. The response of neonates, infants and children to medication is modified by many factors: body composition, protein binding, body temperature, distribution of cardiac output, maturation of the blood-brain barrier, the liver and kidneys.

Body compartments (fat, muscle, water) change with age. Total body water is significantly higher in prematures and neonates than in the 2-year-old. Fat and muscle contents increase with age. Therefore, a drug that is water-soluble has a larger volume of distribution and usually requires a larger initial dose to achieve the desired blood level (e.g. most antibiotics, succinylcholine), while a drug that depends on redistribution into fat for its action has a longer clinical effect (e.g. fentanyl). Delayed excretion resulting from the larger volume of distribution, immature hepatic and renal function, and altered drug excretion caused by lower protein binding, are other important factors that must be considered.

Further perturbations in drug pharmacokinetics and pharmacodynamics occur with extreme prematurity and with factors such as sepsis and poor nutritional state [2, 3]. Older children have mature renal and hepatic function, normal adult values for proteins, and fat and muscles content approaching adult values. More of the cardiac output is diverted to the liver and kidneys, which also weigh more in relation to body mass. These factors mean that most medications have a shorter half-life in children older than 2 years than in adults. In general, most medications have a prolonged elimination half-life in premature, neonate and infants, and a shortened half-life in children older than 2 years of age up to the early teen years, and a lengthening of half-life in teenagers approaching adulthood.

Pharmacology of anaesthetics in children

Inhalation agents: sevoflurane

The pharmacokinetics of inhalation anaesthetics in children depends on the same physiological parameters (alveolar ventilation, cardiac output, tissue perfusion and organ capacity) at all ages but, as discussed above, these parameters undergo considerable changes with aging.

The pharmacokinetics of halothane were demonstrated to be more rapid in infants and children than in adults [4]. This difference has been attributed to four factors:

1. Greater alveolar ventilation
2. Greater cardiac output directed to the vessel-rich group
3. Lower tissue solubility
4. Lower blood solubility

The new agents sevoflurane and desflurane are almost insoluble in blood and tissues and thus provide faster changes in the alveolar-to-inspired concentration ratio than older agents, which means they allow more rapid variations in anaesthesia depth. Since changes in alveolar ventilation affect more-soluble anaesthetics to a greater extent than less-soluble ones [5], the pharmacokinetics of sevoflurane and desflurane are as rapid in children as in adults (Fig. 1) [6, 7]. These differences make the two new agents more flexible and can be used more easily by non-paediatric anaesthesiologists occasionally asked to anaesthetize a child.

Anaesthesiologists must be aware that the minimum alveolar concentration (MAC) of desflurane and sevoflurane decreases with age in the same way as it does with the older halothane and isoflurane, but the MAC of sevoflurane does not increase over the first months of life like most other agents do. The MAC of sevoflurane is 3.3% in neonates, 3.2% in infants age 1-6 months, and approximately 2.5% in infants and children aged 6 months to 12 years [6].

Lerman has also demonstrated that the MAC-sparing effect of nitrous oxide is minor with the newer insoluble agents than with the more soluble predecessors [8].

It is important to recognize this diminished effect of nitrous oxide in order to ensure adequate levels of anaesthesia in infants and children when sevoflurane is used. The MAC values of sevoflurane at different ages are shown in Table 2, while the MAC-sparing effect of nitrous oxide is shown in Table 3.

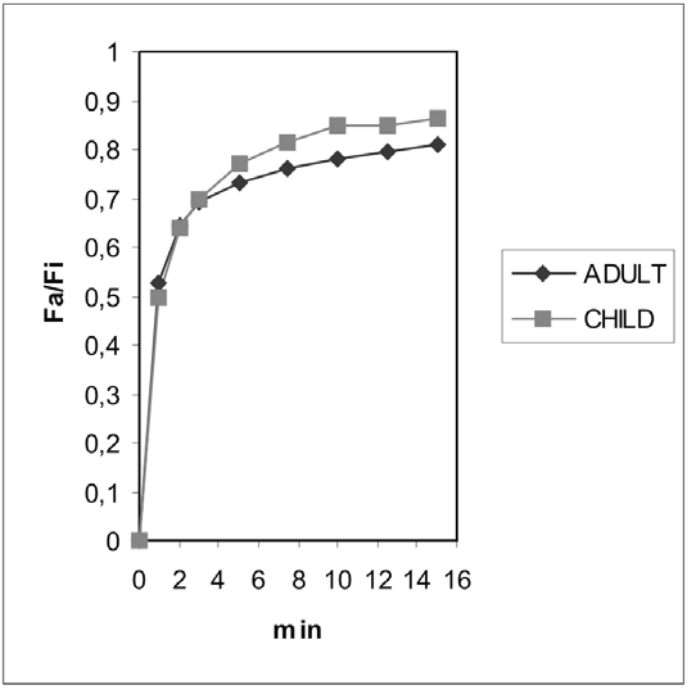

Fig. 1. Adsorbimental kinetics of sevoflurane in children compared to in adults

Table 2. Comparison between MAC values for sevoflurane in different age groups

Age group	MAC (%)
Newborn	3.3
Infant	3.2
Child	2.5
Adult	1.7

Table 3. MAC-sparing effect of nitrous oxide with different volatile agents

Agent	Sparing effect (%)
Halothane + N2O	60 MAC
Isoflurane + N2O	40 MAC
Sevoflurane + N2O	24 MAC
Desflurane + N2O	20 MAC

Intravenous drugs: propofol

The alternative to inhalation anaesthesia is intravenous anaesthesia, with its mainstay being propofol combined with opiates.

The use of propofol requires a deeper knowledge of the child's physiology and its differences with that of the adults', compared to inhalation agents. Children have a large central compartment and a higher clearance than adults. Recommended adult induction does of 2-2.5 $mg \cdot kg^{-1}$ are almost half of those used in small children. Children will need infusion rates 50-100% higher than adults to maintain any desired propofol concentration during the first 30 min [9]. The decreasing exponential dosing in adults, the well-known 10-8-6 rule, becomes in a 2-year-old a 15-13-11-10-9 rule (the numerals represent $mg \cdot kg^{-1}$ at given time intervals) in order to achieve equivalent plasma concentrations. The termination of drug effect with propofol is largely due to redistribution of the drug away from the central compartment rather than elimination of the drug from the body. These larger induction doses and higher infusion rates imply that at the termination of the infusion more drug remains in the body for any given plasma concentration than in adults. This translates into a more prolonged recovery in children. McFarlan demonstrated this phenomenon with accuracy, as shown below [10].

Among the opiates used in adjunct to propofol, special attention should be given to remifentanil, as it introduces a new control of kinetics in anaesthetic pharmacology. Morphine and fentanyl have several side effects in the paediatric population and can cause delayed recovery; their relatively long duration, moreover, makes them unsuitable for an approach whose major advantage should be the possibility of rapid variations in anaesthesia depth.

Remifentanil has specific age-related changes with respect to its kinetics: the volume of distribution is largest in the youngest patients [11] and clearance is also inversely related to age, so that there are no differences in the half-life of the drug in the different age groups. Neonates and infants thus require a faster infusion rate

than older individuals in order to achieve similar target levels, but the half-life is not longer in these categories of patients.

Induction and emergence

The pharmacokinetics of sevoflurane and propofol make these drugs suitable induction agents, allowing rapid changes in anaesthetic depth and a favourable emergence profile. Both can be used as hypnotic agents in combination with central or peripheral regional anaesthesia. Opinions differ as to which is the least traumatic method of anaesthetic induction for paediatric patients. In the USA, inhalation induction is the most common technique because it is believed to be less objectionable to children, who often have an exaggerated fear of needles. However, in many other parts of the world, intravenous induction appears to be used more commonly. It is often claimed that the i.v. technique induces rapid loss of consciousness and it is associated with minimal exposure by operating-theatre personnel.

Aguilera [12] compared peri-operative anxiety and postoperative behavioural changes in children undergoing i.v. induction with thiopental or inhalation induction with sevoflurane. In this study, 54% of children undergoing i.v. induction were calm during the procedure, compared to 90% of the inhalation induction group. The use of EMLA cream in the study did not reduce the number of patients with significant anxiety during i.v. induction compared with an earlier study [13] in which no topical analgesia was used.

This agrees with previous observations suggesting that children fear the "idea" of a needle as much as the pain of its insertion and that inhalation induction is a more pleasant technique from the child's perspective.

Besides allowing smooth inductions and rapid emergence, sevoflurane causes few arrhythmias, minimal cardiovascular depression, minimal hepatic and renal toxicities, qualities that are superior to halothane [8, 14]. The positive qualities of sevoflurane combined with concerns about the risks of halothane-associated immune responses have resulted in halothane almost disappearing from paediatric anaesthetic practices. However, expansion of the use of sevoflurane has been tempered, at least in academic paediatric institutions, by its expense, particularly when compared to halothane.

By contrast, desflurane, a much more stable anaesthetic than other inhalation anaesthetics, has not created a major impact in paediatric aesthesia because it irritates children's airways when administered for induction of anaesthesia [15].

Among inhalation agents used in association with LMA and regional anaesthesia in children undergoing peripheral surgery, it has been shown that isoflurane and sevoflurane can provide similar conditions for optimally managing the airway at induction time, but that isoflurane is significantly associated with higher airway hyperreactivity at the time of LMA removal, especially when carried out in awake patients [16].

Sevoflurane, like halothane, has the advantage that it provides "single agent" anaesthesia. That means that induction and maintenance, and even endotracheal

intubation, can be performed with the use of only one agent. The "single-agent" technique restricts the number of drugs to which the patient is exposed and limits the possibility for unknown and unwanted interactions of multiple drugs.

In adults, sevoflurane inhalation induction has been shown to elicit epileptiform EEG [17]. The EEG features of adults and children, though, differ considerably due to immaturity of the brains of the children. In addition, the results from adult EEG studies cannot be directly adapted to use in children. A recent study [18] has described epileptiform EEG activity, without motor manifestations, in healthy children undergoing sevoflurane inhalation induction of anaesthesia. This report warrants further research as to the suitability of such induction in patients with susceptibility to convulsions or EEG discharges.

Emergence delirium

Sevoflurane, and to a lesser extent desflurane, have been associated with emergence delirium (ED). Other factors associated with this phenomenon include preschool age, a rapid recovery and the presence of pain [19]. Recent evidence suggests that rapid recovery or awakening is not associated with an increased incidence of ED [20]. Pain during the postoperative period has been identified as a confounding factor that is difficult to distinguish from ED. However, in a study of sevoflurane anaesthesia in MRI, a non-painful radiological intervention, the incidence of ED was greater than it was after halothane administration. [21]. Current research is focusing on specific and sensitive tools to assess ED in order to try to better understand this fascinating phenomenon [22].

Awareness

Awareness is a controversial issue in anaesthesia. The availability of new technologies to assess various aspects of the anaesthesia depth (auditory evoked response and especially electroencephalogram) has stimulated new interest in awareness in adults, but applying extrapolations from adult data to children may not be sufficient due to the different pharmacology of anaesthetics and the developmental psychology of children.

The BIS is probably the most widely known and frequently used device in monitoring anaesthesia depth; has been approved for use in adults since 1996 and was recently investigated in infants and children in various settings. Although BIS has yet to be calibrated accurately in children [23], Denman and colleagues [24] found there was an approximately linear relationship between BIS and end-tidal sevoflurane in paediatric patients, indicating clinical usefulness of BIS in this population.

In a prospective, randomized, clinical utility study in children, Bannister et al. [25] demonstrated that BIS monitoring was associated with a significant (25%) reduction in sevoflurane administration and recovery time.

While volatile agents can be monitored through their end-tidal measurement, there is, at the moment, no reliable technique for monitoring the plasma concen-

trations of drugs used in TIVA. Therefore an increased risk of awareness with TIVA, especially with the concurrent use of muscle relaxants, has been cited as a possible drawback to its use. However, two prospective studies conducted on adult populations [26, 27] tend to refute this suggestion. These results, however, still need to be adapted to the paediatric population.

Metabolism and toxicity

Sevoflurane is metabolized 5% in vivo and its use has in early clinical trials raised serious concerns about the risk of fluoride-associated nephrotoxicity. Plasma levels of inorganic fluoride reached levels similar to those reported after methoxyflurane anaesthesia, although no evidence of nephrotoxicity was detected. Kharasch et al. [28] explained the apparent contradiction in renal effects with these two anaesthetics by the fivefold greater affinity of cytochrome P450 IIE1 in the kidney for methoxyflurane than for sevoflurane). The authors postulated that nephrotoxicity after methoxyflurane resulted from local intrarenal production of inorganic fluoride that inhibited tubular reabsorption of water. The limited metabolism of sevoflurane within the kidney failed to produce sufficient fluoride to inhibit tubular reabsorption to any extent. This, together with the more rapid washout of sevoflurane, likely explains the lack of nephrotoxicity after sevoflurane anaesthesia.

Sevoflurane is also degraded in vitro, in the presence of carbon dioxide absorbent. Five degradation compounds result from alkaline hydrolysis of sevoflurane, the most common of which is A [29]. This olefin has been shown to cause nephrotoxicity in rats but not in human beings. In the presence of desiccated soda lime and baralyme, sevoflurane produces very little carbon monoxide, too little to be of concern in clinical practice [30].

Most recently, anaesthesiologists were notified of isolated reports of extreme heat and flammability that occurred in the breathing circuit when sevoflurane was used with desiccated carbon dioxide absorbent [31]. Desiccation of the carbon-dioxide absorbent should therefore always be avoided.

Lack of exposure has also been cited as one of the benefits of TIVA. Halothane was found to be mutagenic in certain in vitro tests. As it is metabolised to reactive intermediates that covalently bind to cellular macromolecules [32] and nitrous oxide, it has been implicated in vitamin B12 metabolism with evidence of genuine risk for health workers [33]. Nitrous oxide is also a potent greenhouse gas and the medical proportion of nitrogen oxide emission is a significant amount of the total global amount [34].

The breakdown of propofol leads to the formation of phenol which can also be a cause of environmental damage.

When is regional anaesthesia better: the ex-premie

A recent review of the American Society of Pediatric Anesthesia has demonstrated that regional anaesthesia is safer than general anaesthesia in children at risk of postoperative apnea [35–38]. This group of patients included children 52-60 weeks post-conceptual age, children on apnoea monitoring or on methylxanthine, and those scheduled for subumbilical surgical procedure. The main advantages for regional anaesthesia are respiratory. Avoidance of instrumentation of an already compromised respiratory tract can help prevent complications such as hypoxemia, laryngospasm, broncospasm, postintubation stridor, and potential for prolonged ventilation. Also, regional anaesthesia decreases the incidence of postoperative apnoea.

These techniques, however, must be performed by skilled anaesthesiologists, fully trained in paediatric regional blocks, and the length of surgery must not exceed 90 min. In addition, some surgeons are uncomfortable without the absolute stillness conferred by intubation and paralysis.

Conclusions

There is a much larger body of literature and wider experience worldwide with inhalation anaesthesia, i.e. with the use of sevoflurane in the last 5 years, in children compared to TIVA. Moreover, propofol is still not licensed for use in small children, with age restrictions varying from country to country, and it is difficult from the literature alone to assess the frequency of use of TIVA in paediatric anaesthetic practice. Non-paediatric anaesthesiologists find inhalation anaesthesia easier to use and therefore safer for patients. TIVA in paediatric anaesthesia could be a valid alternative to inhalation agents, but its administration certainly requires a deeper knowledge of the drug's pharmacokinetic and the physiology of children. Even though the problem of awareness seems to be less relevant than in the past, there is at the moment no reliable technique for monitoring plasma concentration of the drugs used with intravenous anaesthesia, and an increased risk of awareness with TIVA, especially with the concurrent use of muscle relaxants, has been cited as a possible drawback to its use.

References

1. Pessenbacher K, Gutmann A, Eggenreich U et al (2002) Two propofol formulations are equivalent in small children aged 1 month to 3 years. Acta Anaesthesiol Scand 46:257-263
2. Reed MD, Besunder JB (1989) Developmental pharmacology: ontogenic basis of drug disposition. Pediatr Clin North Am 36:1053-1074
3. Morselli Pl, Franco-Morselli R, Bossi L (1980) Clinical pharmacokinetics in newborns and infants:age related differences and therapeutic implications. Clin Pharmacokinet 5:485-527
4. Salanitre E, Rackow H (1969) The pulmonary exchange of nitrous oxide and halothane in infants and children. Anaesthesiology 30:388-394
5. Eger EI II (1974) Anesthetic uptake and action. Baltimore, Williams & Wilkins
6. Lerman J, Sikich N, Kleinman S et al (1994) The pharmacology of sevoflurane in infants and children. Anaesthesiology 80:814-824
7. Roma G, Zoia E, Wolfler A et al (1998) Cinetica di assorbimento del sevofluorane:età pediatrica vs adulto. Atti congressuali SARNePI, Genova 28-30/IX/1998
8. Lerman J, Davis PJ, Welborn LG et al (1996) Induction, recovery and safety characteristics of sevoflurane in children undergoing ambulatory surgery: a comparison with halothane. Anaesthesiology 84:1332-1340
9. Kataria BK, Ved SA, Nicodemus HF et al (1994) The pharmacokinetics of propofol in children using three different data analysis approaches. Anaesthesiology 80:104-122
10. McFarlan CS, Anderson BJ, Short TG (1999) The use of propofol infusions in paediatric anaesthesia:a practical guide. Paediatr Anaesth 9:209-216
11. Ross AK, Davis PJ, Dear G et al (2001) Pharmacokinetics of Remifentanil in Anesthetized Pediatric Patients Undergoing Elective Surgery or Diagnostic Procedures. Anesth Analg 93:1593-1401
12. Aguilera IM, Patel D, Meakin GH et al (2003) Perioperative anxiety and postoperative bahavioural disturbances in children undergoing intravenous or inhalation induction of anaesthesia. Paed Anaesth 13:501-507
13. Kotiniemi LH, Ryhnen PT (1996) Behavioural changes and children's memories after intravenous, inhalation and rectal induction of anaesthesia. Paed Anaesth 6:201-207
14. Sarner J, Levine M, Davis PJ et al (1995) Clinical characteristics of sevoflurane in children:a comparison with halothane. Anaesthesiology 82:38-46
15. Taylor RH, Lerman J (1992) Induction, maintenance and recovery characteristics of desflurane in infants and children. Can J Anaesth 39:6-13
16. Pappas AL, Sukhani R, Lurie J et al (2001) Severity of airway hyperreactivity associated with Laryngeal Mask Airway removal: correlation with volatile anesthetic choice and depth of anesthesia. J Clin Anesth 13:498-503
17. Yli Hankala A, Vakkuri A, Sarkela M et al (1999) Epileptiform electroencephalogram during mask induction of anesthesia with sevoflurane. Anaesthesiology 91:1596-1603
18. Vakkuri A, Yli-Hankala A, Sarkela M et al (2001) Sevoflurane mask induction of anesthesia is associated with epileptiform EEG in children. Acta Anaesthesiol Scand 45:805-811
19. Voepel-Lewis T et al (2003) A prospective cohort study of emergence agitation in the pediatric postanesthesia unit. Anesth Analg 96:1625-1630
20. Cohen IT, Finkel JC, Hannallah RS et al (2003) Rapid emergence does not explain agitation following sevoflurane anaesthesia in infants: a comparison with propofol. Paediatr Anaesth 13:63-67

21. Cravero J et al (2000) Emergence agitation in paediatric patients after sevoflurane anaesthesia and no surgery: a comparison with halothane. Paediatr Anaesth 10:419-424
22. Sikich N, Lerman J (2004) Development and psychometric evaluation of the pediatric anesthesia emergence delirum scale. Anaesthesiology 100 (5):1138-1145
23. Davidsons AJ (2002) Awareness and paediatric anaesthesia. Paediatr Anaesth 12:567-568
24. Denman WT, Swanson EL, Rosow D et al (2000) Pediatric evaluation of the bispectral index (BIS) monitor and correlation of BIS with end-tidal sevofluorane concentration in infants and children. Anesth Analg Apr 90 (4):872-877
25. Bannister CF, Brosius KK, Sigl JC et al (2001) The effect of BIS monitoring on anesthetic use and recovery in children anesthetized with sevofluorane in nitrous oxide. Anesth Analg 11:567-573
26. Sandin RH, Enlund G, Samuelsson P et al (2000) Awareness during anesthesia:a prospective case study. Lancet 355:707-711
27. Nordstrom O (1997) Incidence of awareness in TIVA based on propofol, alfentanil and neuromuscular blockade. Acta Anesthesiol Scand 41:978-984
28. Kharash ED, Hankins DC, Thummel KE (1995) Human kidney methoxyflurane and sevoflurane metabolism. Intrareanal fluoride production as a possible mechanism of methoxyflurane nephrotoxicity. Anaesthesiology 82:689-699
29. Morio M, Fujii K, Satoh N et al (1992) Reaction of sevoflurane and its degradating products with soda lime. Toxicity of the byproducts. Anaesthesiology 77:1155-1164
30. Kharasch ED, Powers KM, Artru AA (2003) Compound A concentration in the circle absorber system during low-flow sevoflurane anesthesia. Comparison of Dragersorb Free, Amsorb, and Sodasorb II. J Clin Anesth 15:33-37
31. (2003) MedWatch Safety Alert letter to practitioners, 17 November 2003
32. Gandolfi AJ et al (1980) Bioactivation and covalent binding of halothane in vitro. J Pharmacol Exp Ther 214:721-725
33. Sharples A (2003) Pollution: just a whiff of gas? Paediatr Anaesth 13:467-472
34. Marx T (1999) Global pollution – the anesthetist's contribution. Anaesthesia 54:301-302
35. Society of Pediatric Anesthesia (2002) Regional Anesthesia for inguinal herniorrhaphy in the ex-premie. www.pedsanesthesia.org/newsletter/2002spring/inguinal.shtml
36. Welborn LG, Rice LJ, Hannallah RS et al (1990) Postoperative apneain former preterm infants: prospective comparison of spinal and general anesthesia. Anesthesiology 72:838-42
37. Somri M, Gaitini L, Vaida S et al (1998) Postoperative outcome in high-risk patients undergoing herniorrhaphy:comparison between spinal and general anesthesia. Anesthesia 53:762-66
38. Furmiento C, Adajian JC, Vane DW (2000) Spinal anesthesia for preterm infants undergoing inguinal hernia repair. Arch Surg 135:445-451

Chapter 20

Analysis and instrumentations for estimating cerebral activity

E. Facco, S. Barbieri, M. Munari

The primary aim of neurointensive care is to prevent secondary brain damage, and the preservation of cerebral perfusion and oxygenation has a key role in this. The mechanisms of secondary damage are complex and may remain undetected by the routine monitoring systemic parameters. Continuous invasive arterial blood pressure monitoring plus pulse oximetry and monitoring of temperature, end-tidal carbon dioxide and urine output should be included as part of standard monitoring of brain-injured patients, while specific techniques are essential (a) to check for secondary neurological deterioration and treat it promptly if it is observed and (b), to monitor therapeutic interventions and provide online feedback.

The assessment of comatose patients is routinely based on clinical data: the Glasgow Coma Scale (GCS) and paediatric scales (such as the Children Coma Score), associated with brain stem reflexes and posture, remain the essential basis of patient evaluation and have a good prognostic value; however, several investigation and monitoring devices now available may significantly improve management (Table 1). The main techniques will be briefly outlined in this paper.

Electroencephalography

Electroencephalography (EEG) records the spontaneous electrical activity of the cerebral cortex and is generated mainly by the summation of excitatory and inhibitory postsynaptic potentials of cortical neurones; it does not, however explore the activity at subcortical levels.

A wide range of EEG signal processing is now available, allowing for quantitative EEG, coherence analysis and topographical mapping. The EEG activity is routinely interpreted in terms of frequency, amplitude, morphology of waves and location (focal or generalised activity); in addition, reactivity to painful stimuli is a factor of paramount importance in comatose patients.

The EEG has shown a proved to have good prognostic value in the acute stage of posttraumatic and ischaemic anoxic coma. It also allows for the diagnosis and treatment of epilepsy: it should be noted that up to 8% of comatose patients may have clinically silent seizures and even a status epilepticus, making EEG an essential tool in diagnosis and neuroprotection for these patients. In fact, it has been proved

Table 1. Main diagnostic and monitoring devices in brain-injured patients

Type of test/measurement	Instrument/parameter
Clinical evaluation	1. Glasgow Coma Scale
	2. Brain stem reflexes and posture
Radiological tests	1. Computed tomography
	2. MRI
Electrophysiological tests	1. EEG
	2. EPS
Blood flow and cerebral metabolism evaluation tests	1. Mean arterial pressure
	2. $SjvO_2$
	3. ICP
	4. Doppler ultrasonography
	5. Near infrared spectroscopy
	6. Brain tissue oximetry
	7. Microdialysis
	8. SPECT
	9. PET

that early detection of subclinical seizures with EEG in the ICU may help reduce mortality and morbidity [3].

Continuous EEG monitoring is also useful in the detection of cerebral ischaemic events, including vasospasm following subarachnoid haemorrhage (SAH) and intracranial hypertension after head injury [4]. In encephalitis, temporal paroxysmal electrical discharges are indicative of herpes encephalitis, whilst paroxysmal bursts of 2–3 Hz may suggest subacute sclerosing panencephalitis. Metabolic suppression brought about by the use of intravenous anaesthetic agents can be monitored by CFM, where burst suppression or isoelectricity is a useful end-point to obtain maximal suppression of cortical electrical activity.

The EEG can provide useful information on patients' outcome, and several grading systems have already been reported in head injury (Table 2); however, the results reported in the literature are rather variable and sometimes conflicting, which is not surprising when the wide variability of grading criteria is considered. Fortunately, a few relevant EEG patterns are common to most grading systems, such as sleep-like activity and reactivity, while the names used for other patterns seem to be synonymous (e.g., changeable and spontaneous arousal activity). In short, there is increasing agreement that reactivity, spontaneous variability (changeable and spontaneous arousal activity seem to be synonymous) and spindles, which are often associated with these, are patterns that have a favourable prognosis. Since patients with the same GCS can show different EEG patterns with different prognostic implications, the combined use of EEG [1] and clinical data may improve the assessment of brain dysfunction and early outcome prediction when correct interpretation of the EEG is ensured by the involvement of a neurophysiologist trained in coma assessment.

Table 2. Main EEG grading criteria in posttraumatic coma. (From [1], modified)

Reference[a]	Criteria	
Bricolo et al. (1979) Acta Neurochir	1. Sleep-like 2. Changeable 3. Border-line (or alpha coma) 4. Slow-wave	
Synek (1988) Clin Electroencephalogr 19: 160–166	1. Predominantly normal alpha, some scattered theta 2. Dominant theta activity 3. Dominant delta activity 4. Burst suppression 5. Flat EEG	
Thatcher et al. (1991) Ann NY Acad Sci 620: 82–101	Prognostic determinants 1. Phase 2. Coherence 3. Amplitude asymmetry 4. Relative power	
Gutling et al. (1995) Neurology 45: 915–918	EEG reactivity 1. Present 2. Doubtful 3. Absent	
Evans and Bartlett (1995) J Neurol Neurosurg Psychiatry 59:17–25	1. Wakeful records 2. Sleep-like records 3. Abnormal spontaneous arousal activity 4. No spontaneous arousal activity	
Rae-Grant et al (1996) J Trauma 40: 401–407	Dichotomous scale (present/absent) 1. Background activity	Normal alpha Widespread anterior unresponsive alpha/alpha coma Beta Theta Theta coma Delta (general/frontal) Delta (focal, nonfrontal) Spindles (symmetrical) Spindles (asymmetrical or abnormal)
	2. Symmetry, reactivity, variability	Asymmetry (not posterior)
	3. Additional patterns	Intermittent rhythmic delta activity Triphasic waves Episodic low amplitude events Epileptiform activity Burst suppression Low-voltage pattern Electrocerebral inactivity
Kane et al. (1998) Electroencephalogr Clin Neurophysiol 106:244-250	Prognostic determinants	
	1. Beta activity power in: 2. Alpha activity power in left centrotemporal regions	A. Left frontocentral regions; B. Left centrotemporal regions

[a] All cited in [1]

Evoked potentials

Evoked potentials (EPs) allow the exploration of specific nervous pathways, and the interest in EPs in posttraumatic coma [2] depends on features that make them more appealing than conventional EEG in a ICU setting, such as:

A. Exploration of well-defined nerve pathways (auditory, somatosensory, etc.).
B. Capability of exploring deep structures (e.g., the brain stem, which often has a key role in prognosis), checking the functional status of known and specific generators.
C. Quantification of damage in the explored structures, in terms of central conduction time (CCT) and wave amplitude, which gives more accurate information than EEG.
D. Exploration of pathways that cannot be checked clinically in comatose patients (e.g., lemniscal pathways).
E. Capability of providing information in sedated patients and even in those in whom barbiturate coma has been induced (when short-latency EPs are concerned).

In the literature there is prevailing agreement on the usefulness of EP in the early prognosis of posttraumatic, postanoxic coma, and of coma following vascular disorders, but the vast amount of published data also harbours contradictions, discrepancies and conflicting results depending on patient selection, test timing, methods used for EP recording and grading criteria.

Short-latency EPs are useful in the assessment of severely head-injured patients; in fact, since they allow deep structures to be investigated they can provide useful information on the level of rostrocaudal dysfunction, which is a prognostic determinant of paramount importance. Auditory brain stem responses (ABRs) yield information from the pontomesencephalic level, while somatosensory EPs (SEPs) allow exploration of the somatosensory and pyramidal pathways in the cervicocortical tract.

A useful and simple grading system for EPs in severe head injury is reported in Table 3.

The relevance and usefulness of the GCS are well known, but its prognostic sensitivity does not seem to be very high. In the acute phase of posttraumatic coma the GCS is beset with a sizeable rate of wrong predictions (most of them falsely optimistic), while EPs have proved to be more accurate than GCS in both head injury and spontaneous cerebral haemorrhage: the best results are achieved by combining GCS and EP data.

Table 3. ABR and SEP grading in severe head injury

ABRs	SEPs
1=Normal	1=Normal
2=CCT4.75 ms and/or amplitude ratio V/I<5	2=N13-N20>8.5 ms bilaterally
3=Absent V	3=Absent N20 bilaterally

In some cases EPs allow detection of a brain stem lesion at a patient's bedside, thus indicating the need for MRI; sometimes (e.g. in the early phase of ischaemic lesions) the MRI is negative while EPs show severe dysfunction, allowing for a proper diagnosis. On the other hand, EPs can occasionally show normal brain stem function in patients who have a poor clinical condition and brain stem lesions seen on CT scan but who ultimately experience a good outcome.

In short, the combined use of EPs, clinical data and radiological investigations may allow a better morphofunctional evaluation of patients' condition and prognosis than the use of CT scan and clinical data only. When properly recorded and interpreted, EPs are the most powerful prognostic indicators and provide an objective, quantifiable measure of the severity of disease and of prognosis, a factor of paramount importance in the ICU, according to the suggestions of the Society of Critical Care Medicine.

Computed tomography scan and magnetic resonance imaging

Computed tomography (CT) is a routine, essential test used to define which side of the brain is affected and the nature of the damage (especially in the case of haemorrhagic lesions). A CT scan can also disclose signs of intracranial hypertension, such as a shift of the midline, ventricular shift and occlusion of cisterns. On the other hand, it may not detect acute ischaemic lesions, posttraumatic oedema or brain stem lesions.

Perfusion CT [5] is a relatively new technique that allows for a rapid qualitative and quantitative evaluation of cerebral perfusion by generating maps of cerebral blood flow (CBF), cerebral perfusion blood volume (CBV), and mean transit time (MTT). The technique is based on the central volume principle (CBF=CBV/MTT), complex deconvolution algorithms being used to produce the perfusion maps. There are still some uncertainties about this technique, including the accuracy of quantitative analysis and the reproducibility of results; nonetheless, perfusion CT has been found to be useful for noninvasive diagnosis of cerebral ischaemia, infarction and vasospasm after subarachnoid haemorrhage.

The main advantages of MRI are its capability of detecting ischaemic areas and brain oedema and of exploring the brain stem. It is not superior to CT scanning in haemorrhagic lesions in the acute stage, but can detect haemosiderin in the subacute and chronic phases, when CT scan has become negative.

Brain perfusion and metabolism

$SjvO_2$

Blood from the venous sinuses of the brain drains into the internal jugular vein; although it was traditionally believed that the majority of venous blood drained into the right internal jugular vein, it seems that supratentorial venous drainage is

less lateralised than previously thought [6]. Although there is no evidence that either side might be better [7], the right internal jugular vein is more commonly preferred. Measurements of $SjvO_2$ can be performed by intermittent sampling or continuous monitoring with a fibreoptic catheter, the former calling for slow, careful aspiration of blood from the jugular bulb, which should ideally be representative of mixed cerebral venous blood.

$SjvO_2$ provides a rough estimate of oxygen extraction from the brain. The normal range for $SjvO_2$ is 60–75%, and desaturations (indicating potential cerebral ischaemia) of less than 50% have been associated with a worse outcome in head injury.

Intermittent sampling allows estimation of the arterovenous oxygen difference and lactate, which will help give an indication of global cerebral oxygenation and metabolism. Increases in arterojugular differences in oxygen content ($AVjDO_2$) to greater than 9 ml/dl also provide a useful marker of inadequate cerebral blood flow (CBF) and may help guide therapy [8]. Continuous $SjvO_2$ monitoring makes it possible to detect episodes of desaturation associated with raised ICP, hyperventilation therapy, hypotension and cerebral vasospasm. However, in up to half of the cases with desaturations below 50% the measurements may be false positives [9].

The major limitation of $SjvO_2$ monitoring is that it is a global, rough measure of cerebral oxygenation. As a result, regional changes may not be detected unless they are so large as to affect global brain saturation: in other words, its sensitivity is very low, which may lead to dangerous underestimation of a patient's conditions. Other inaccuracies can occur if the catheter is not accurately placed or if blood sampling is too rapid. The continuous fibreoptic catheters may give inaccurate readings if they become impacted against the vessel wall or if there is a thrombosis at the catheter tip.

Near infrared spectroscopy

The principle of Near Infrared Spectroscopy (NIRS) is based on the fact that light in the near-infrared red range (700–1000 nm) can pass through skin, bone and other tissues relatively easily. When a beam of light is passed through brain tissue it is both scattered and absorbed.

The absorption of near-infrared light is proportional to the concentration of some chromophores, notably iron in haemoglobin and copper in cytochrome aa3. Oxygenated haemoglobin (HbO_2), deoxygenated haemoglobin (Hb) and cytochrome aa3 have different absorption spectra, depending on the oxygenation status of each. Changes in the concentration of near-infrared light as it passes through these compounds can be quantified using a modification of the Beer-Lambert law, which describes optical attenuation. The main advantage of NIRS is that it is a noninvasive method of estimating regional changes in cortical oxygenation. However, the clinical use of NIRS is limited by its inability to differentiate between intracranial and extracranial changes in blood flow and oxygenation, which adversely affects the reliability of the readings [14]. The validation of this technique in neurointensive care still requires further work.

Brain Tissue Oximetry

The insertion of sensors directly into brain tissue for continuous measurement of brain tissue oxygenation has attracted considerable interest over the last decade. With recent technological advances, two commercially available sensors have been produced. One sensor measures only brain tissue oxygen tension using a polarographic Clarke-type electrode, whilst the other multiparameter sensor measures brain tissue oxygen (PbO_2), carbon dioxide ($PbCO_2$) and pH using fibreoptic technology. Both sensors are approximately 0.5 mm in diameter and can be inserted intraoperatively through a craniotomy or through a specially designed bolt allowing insertion and fixation to the skull in the intensive care unit. They can also measure brain temperature using a thermocouple.

In a recent study comparing the multiparameter sensor and positron electron tomography (PET) there was no correlation between the absolute values of oxygen concentration recorded with the two techniques, but there was between their changes in response to hyperventilation [15]. Furthermore, there is some evidence that brain tissue sensors may detect changes in regional oxygenation that would be missed when $SjvO_2$ was used [16]. This is not surprising, since this technique measures local tissue oxygenation only; on the other hand, it can miss regional ischaemia anywhere in the brain except the tissue around the sensor tip.

Microdialysis

Microdialysis allows for continuous online monitoring of changes in brain tissue chemistry. In common with brain tissue oxygenation monitoring, microdialysis calls for insertion of a catheter (diameter 0.62 mm) into the brain. The catheter is lined with a polyamide dialysis membrane and is perfused with a physiological solution (e.g. Ringer's) at an ultra-low flow rates (0.1–2.0 μl/min) by means of a precision pump, allowing measurement of the concentrations of chemicals in the extracellular space of the brain. Molecules below the cut-off size of the semipermeable membrane (approximately 20,000 Da) diffuse from the extracellular space into the perfusion fluid, which is then collected into vials that are changed every 10–60 min. The collected dialysate is then analysed by sensitive assays.

In theory, any substance that has molecules small enough to diffuse through the dialysis membrane can be measured [17], but the key substances can be categorised as follows:

1. Energy-related metabolites: glucose, lactate, pyruvate, adenosine, xanthine, where the lactate/pyruvate ratio is a better marker of ischaemia than lactate alone [18].
2. Neurotransmitters: glutamate, aspartate, GABA.
3. Markers of tissue damage and inflammation: glycerol, potassium, cytokines.
4. Exogenous substances: administered drugs.

Continuous online measurement of glucose, lactate, pyruvate, glutamate and glycerol can be achieved using a CMA600 microdialysis analyser (CMA Microdialy-

sis, Stockholm, Sweden). A good correlation has been shown between measurements obtained with the CMA600 analyser and by high-performance liquid chromatography (HPLC) [19].

Cerebral microdialysis has been applied to patients with many different clinical conditions, including head injury, subarachnoid haemorrhage, epilepsy, ischaemic stroke and tumours, and during neurosurgery [20]. In patients with severe head injury, disturbances of metabolism have been associated with decreased brain glucose and increased lactate/pyruvate ratios during periods of intracranial hypertension and cerebral ischaemia. Wide variations in the concentration of the excitatory aminoacids glutamate and aspartate have also been detected, with extremely high and toxic levels in secondary ischaemia and contusions. In aneurysm surgery, changes in concentration of glucose, lactate, pyruvate and glutamate have been demonstrated during cerebrospinal fluid drainage, brain retraction and temporary clipping. Epileptic foci in the temporal lobe are associated with elevated glutamate and reduced γ-aminobutyric acid levels prior to seizures and increases in both aminoacids during seizures.

An evolving application of microdialysis is its use for the measurement of drug concentrations in brain parenchyma, with the potential for using this method to administer drugs directly into targeted areas [21].

Transcranial Doppler ultrasonography

Transcranial Doppler ultrasonography (TCD) is a noninvasive technique providing indirect information on CBF in major arteries of the brain. A 2-MHz pulsed ultrasound signal is transmitted through the skull (usually through the temporal bone) and using the Doppler shift principle measures red cell flow velocity (FV). Insonation of one of the arteries produces an arterial waveform giving information on systolic, diastolic and mean blood flow velocity.

The mean FV (FVmean) is a weighted mean velocity that takes into account the different velocities of the formed elements in the blood vessel being insonated (normal mean value = 55±12 cm/s in the MCA). Changes in FV correlate closely with changes in CBF provided the angle of insonation and the diameter of the vessel insonated remain constant [23, 24].

One of the most useful applications of TCD in neurointensive care is in the diagnosis of high-velocity states such as cerebral vasospasm or hyperaemia. The differentiation between the two conditions is important for a proper therapy. Flow velocities of greater than 120 cm/s after sonification of the MCA are considered significantly higher than normal [25]. If the ratio of MCA flow velocity to extracranial internal carotid flow velocity (Lindegaard ratio) is greater than 3, vasospasm is the likely diagnosis[26]; if mean MCA FV is higher than 120 cm/s and the Lindegaard ratio is lower than 3, hyperaemia is diagnosed.

In traumatic brain injury, TCD monitoring can be used to observe changes in FV and waveform pulsatility and for testing cerebral vascular reserve. Currently, the application of TCD as a noninvasive means of estimating ICP or CPP is under

investigation [27].

Single photon emission computed tomography

Since CBF [30, 31] and $CMRO_2$ are important targets in neuroprotection, the lack of data on single photon emission computed tomography (SPECT) in coma is surprising: so far, out of 3,722 papers found in PubMed when the MESH terms 'SPECT' and 'brain' were entered, only 34 deal with coma and brain death; only 10 of these deal with posttraumatic coma (including case reports and editorials) and 1, with coma following cardiac arrest. Most of the papers on neurocritical patients deal with the chronic phase of the clinical course and outcome evaluation. There are probably two aspects of this lack of interest: (1) logistical problems, since nuclear medicine departments are often a long way away from the NICU and patient transport is required; (2) a cultural problem, leading intensive care specialists to focus on the monitoring techniques mentioned and underestimate the potential effectiveness of SPECT in the assessment of comatose patients.

Regional perfusion can be assessed using the ^{133}Xe-clearance method, ^{133}Xe-dynamic SPECT, ^{99m}Tc-HMPAO (or ^{99m}Tc-ECD) static SPECT and PET. PET is the most sophisticated method, giving the unique possibility of measuring regional CBF, blood volume and metabolism, but it is very expensive and available only in a few centres. SPECT is much cheaper and more widely available than PET, while the ^{133}Xe-clearance method is now obsolete.

As far as radiopharmaceuticals are concerned, ^{99m}Tc-HMPAO and ^{99m}Tc-ECD are routinely used for brain SPECT, but allow for a qualitative or semiquantitative analysis of perfusion only; on the contrary, ^{133}Xe dynamic SPECT provides a quantification of regional CBF (rCBF) in absolute values, although with a marked decrease of spatial resolution in comparison to ^{99m}Tc-HMPAO and ^{99m}Tc-ECD. Even if ^{133}Xe, ^{99m}TcHMPAO and ^{99m}Tc-ECD distribution in the brain look to be linearly related, regional high-flow states with CBF80 ml 100 g^{-1} min^{-1} (as measured by ^{133}Xe SPECT) tend to be underestimated by ^{99m}Tc tracers in routine semiquantitative analysis [1], limiting the evaluation of brain swelling in comatose patients.

The assessment of brain perfusion during the acute phase of coma makes it possible to check focal or diffuse abnormalities that cannot be checked by any other means, improving the management of neurocritical patients: both excessive perfusion and lingering blood flow (close to the ischaemic threshold) can be easily detected, as can the response of each to treatment. These opposing changes can occur in different regions of the brain at the same time in the same patient, and/or shift from low to high flow and vice versa during the acute phase; furthermore, both ischaemia and hyperaemia can lead to neurological deterioration (the latter through intracranial hypertension), but require opposite therapeutic efforts. As already mentioned, $SjvO_2$ monitoring may detect global changes in oxygen extraction, but may underestimate regional abnormalities. On the other hand, a semiquantitative analysis of regional perfusion may be misleading, since it is essential

to know whether: (a) oligaemic areas are above or below ischaemic threshold and (b) well-perfused areas are above or within the normal values. When these opposing changes coexist a bias is introduced in the analysis of asymmetries, calling for the measurement of absolute rCBF values: in this regard ^{133}Xe dynamic SPECT, despite its lower spatial resolution may be superior to ^{99m}TC-HMPAO-SPECT in many instances.

In the acute phase of coma, up to 50% of patients show relevant regional perfusion abnormalities that are not related to any detectable structural lesions on CT scan; conversely, some lesion on CT may not be detected by SPECT. This lack of correlation between SPECT and neuroradiological investigations reflects their different targets and shows that their combined use can improve the assessment of neurocritical comatose patients. When SPECT is added to CT, MRI, clinical data and monitoring techniques a noninvasive insight into the pathophysiology of any damage can be obtained in real time.

References

1. Facco E (1999) The role of EEG in brain injury. Intensive Care Med 25:827-877
2. Facco E, Munari M (2000) The role of evoked potentials in severe head injury. Intensive Care Med 26:998-1005
3. Young GB, Jordan KG, Doig GS (1996) An assessment o nonconvulsive seizures in the intensive care unit using continuous EEG monitoring: an investigation of variables associated with mortality. Neurology 47:83-89
4. Jordan KG (1996) Continuous EEG monitoring in the neurosciences intensive care unit and emergency department. J Clin Neurophysiol 16:14-39
5. Hoeffner EG, Case I, Jain R et al (2004) Cerebral perfusion CT: technique and clinical applications. Radiology 231:632-644
6. Metz C, Holzschuh M, Bein T et al (1998) Monitoring of cerebral oxygen metabolism in the jugular bulb: reliability of unilateral measurements in severe head injury. J Cereb Blood Flow Metab 18:332-343
7. Stocchetti N, Paparella A, Bridelli F et al (1994) Cerebral venous oxygen saturation studied with bilateral samples in the internal jugular veins. Neurosurgery 34:38-44
8. Sheinberg M, Kanter MJ, Robertson CS et al (1992) Continuous monitoring of jugular venous oxygen saturation in head injured patients. J Neurosurg 76:212-271
9. Cruz J (1998) The first decade of continuous monitoring of jugular bulb oxyhemoglobin saturation: management strategies and clinical outcome. Crit Care Med 26:344-351
10. Czosnyka M, Guazzo E, Whitehouse H et al (1996) Significance of intracranial pressure waveform analysis after head injury. Acta Neurochir (Wien) 138:531-542
11. Czosnyka M, Smielewski P, Kirkpatrick P et al (1997) Continuous assessment of the cerebral vasomotor reactivity in head injury. Neurosurgery 41:11-19
12. Rosner MJ, Daughton S (1990) Cerebral perfusion pressure management in head injury. J Trauma 30:933-941
13. Czosnyka M, Czosnyka Z, Pickard JD (1996) Laboratory testing of three intracranial pressure microtransducers (technical report) Neurosurgery 38:219-224
14. Owen-Reece H, Smith M, Elwell CE, Goldstone JC (1999) Near infrared spectroscopy. Br J Anaesth 82:418-426

15. Gupta AK, Hutchinson PJ, Fryer T et al (2002) Measurement of brain tissue oxygenation performed using positron emission tomography scanning to validate a novel monitoring method. J Neurosurg 96:263-268
16. Gupta AK, Hutchinson PJ, Al-Rawi P et al (1999) Measurement of brain tissue oxygenation compared with jugular venous oxygen saturation for monitoring cerebral oxygenation after traumatic brain injury. Anesth Analg 88:549-553
17. Johnston AJ, Gupta AK (2004) Advanced monitoring in neuro-ICU: microdialysis. Curr Opin Crit Care Med (in press)
18. Persson L, Valtysson J, Enblad P et al (1996) Neurochemical monitoring using intracerebral microdialysis in patients with subarachnoid hemorrhage. J Neurosurg 84:606-616
19. Hutchinson PJ, O'Connell MT, Al-Rawi PG et al (2000) Clinical cerebral microdialysis: a methodological study. J Neurosurg 93:37-43
20. Peerdeman SM, Girbes AR, Vandertop WP (2000) Cerebral microdialysis as a new tool for neurometabolic monitoring. Intensive Care Med 26:662-669
21. Muller M (2002) Science, medicine and the future: microdialysis. BMJ 324:588-591
22. Balestra L, Bertino C, Lattuada M et al (1999) Intracranial pressure and cerebral microdialysis. Riv Med 5(1-2)
23. Bishop CCR, Powell S, Rutt D et al (1986) Transcranial Doppler measurement of the middle cerebral blood flow velocity: a validation study. Stroke 17:913-915
24. Dahl A, Russell D, Nyberg-Hansen R et al (1992) A comparison o regional cerebral blood flow and middle cerebral artery blood flow velocities: simultaneous measurements in healthy subjects. J Cereb Blood Flow Metab 12:1049-1054
25. Aaslid R, Huber P, Nornes H (1984) Evaluation of cerebrovascular spasm with transcranial Doppler ultrasound. J Neurosurg 60:37-41
26. Lindegaard KF, Nornes H, Bakke SJ et al (1988) Cerebral vasospasm after subarachnoid haemorrhage investigated by means of transcranial Doppler ultrasound. Acta Neurochir (Wien) 42:81-84
27. Schmidt EA, Czosnyka M, Gooskens I et al (2001) Preliminary experience of the estimation of cerebral perfusion pressure using transcranial Doppler ultrasonography. J Neurol Neurosurg Psychiatry 70:198-204
28. Kirkpatrick PJ, Czosnyka M, Pickard JD (1996) Multimodal monitoring in neurointensive care. J Neurol Neurosurg Psychiatry 60:131-139
29. Czosnyka M, Kirkpatrick PJ, Pickard JD (1996) Multimodal monitoring and assessment of cerebral haemodynamic reserve after severe head injury. Cerebrovasc Brain Metab Rev 8:273-295
30. Facco E, Zucchetta P, Munari M et al (1998) ^{99m}Tc- HMPAO SPECT in the diagnosis of brain death. Intensive Care Med 24:911-917
31. Facco E, Munari M, Baratto F et al (1993) rCBF in severe head injury by Xe-133 clearance. Minerva Anestesiol 59:797-807

Chapter 21

Neuroimaging pharmacology of attention and memory

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Arousal, attention and memory are the focus of different research fields. Although a generally accepted definition is not available, arousal and attention are operatively indicated as the capacity to react and to orient mental processes to relevant stimuli. Memory is described as the capacity to record, retain and retrieve information [1]. In cognitive neuropsychology, arousal, attention and memory are subdivided into processes such as low- and high-level arousal, selective and sustained attention and implicit and explicit memory [1]. In neuropsychiatry, arousal, attention and memory are studied because they are often impaired in different disease conditions, especially in neurodegenerative pathologies such as Alzheimer's disease, Parkinson's disease, post-traumatic brain disorders and depression [1]. In addition, cognitive enhancing therapies are actively pursued. In anaesthesiology, by contrast, anaesthetic agents are required to depress central nervous system functions, including consciousness and memory, in a complete, safe and reversible fashion.

Arousal, attention and memory are often regarded as separate, hierarchically ordered neurological functions [1]. This view is challenged by the fact that arousal and memory both can be altered by the same pharmacological treatments (see below) or the same stimulation/lesion of discrete brain regions. Thalamic nuclei [2, 3] and aminergic nuclei (e.g. nucleus basalis of Meynert, locus coeruleus) [4, 5] give rise to widespread efferent projections to cortical and subcortical regions and are critical in modulating cortical electrical activity and levels of arousal and attention [2, 3]. Both types of nuclei belong to neural circuitries that are involved in maintaining arousal and attention and in facilitating memory functions.

Functional neuroimaging techniques are advancing our knowledge of the neurobiological substrata of arousal, attention and memory [6, 7]. Since under normal conditions neuronal functional activity is tightly coupled with neuronal metabolic activity, techniques that provide brain maps of regional cerebral metabolic rates for glucose (rCMRglc) [7] have been developed. rCMRglc has been measured in rodents with [^{14}C]2-deoxyglucose autoradiography and in humans with [^{18}F]2-deoxyglucose positron emission tomography (PET). Furthermore, since rCMRglc is, in turn, coupled with regional cerebral blood flow (rCBF), techniques have been developed to measure rCBF. rCBF is determined in humans with [^{15}O]H_2O PET and in animals and in humans with magnetic resonance imaging (MRI) of the blood-oxygen-level-dependent signal [7], so called functional MRI. Brain maps of rCMRglc and rCBF can be obtained during different pharmacological treatments

that affect arousal and memory. Spatial normalisation using the Talairach atlas and subtraction paradigms have improved and facilitated the identification of anatomical patterns of rCBF activation/deactivation during mental performance and pharmacological treatment [6, 7]. The widespread use of MRI scanners and the possibility to carry out a large number of repeated, non-invasive sessions employing MRI techniques is spurring a rapidly growing number of studies.

This presentation will summarise functional neuroimaging studies on non-anaesthetic drugs that affect arousal and memory and that may be pertinent to the understanding of neural correlates of the anaesthetic state.

Aminergic agents

Cholinergic agonists and antagonists are of particular interest because of their reciprocal, opposite effects on arousal and memory: cholinergic agonists enhance and cholinergic antagonists impair arousal and memory [6]. Cholinergic agonists act by a direct stimulation of nicotinic receptors (e.g. nicotine) and/or of muscarinic receptors (e.g. arecoline). Cholinergic agonists may also act indirectly by supplementing acethylcholine precursors (e.g. L-a-glyceryl-phosphoryl-ethanolamine) or by preventing acetylcholine break-down (e.g. physostigmine) thereby increasing synaptic acetylcholine concentrations. Cholinergic antagonists work by direct receptor blocking of nicotinic (e.g. mecamylamine) or muscarinic (e.g. scopolamine, atropine) receptors.

Cholinergic antagonists alter different aspects of cognition and cause mental confusion [6]. They also prolong and deepen anaesthesia induced by general anaesthetics [8] and, at high doses and as part of the anticholinergic syndrome, induce loss of consciousness themselves [9]. Cholinergic agonists, by contrast, improve performance in tests of different cognitive functions, including attention, memory and visuospatial abilities, and global cognitive functioning [6]. Furthermore, cholinergic agonists improve cognition in several neuropsychiatric pathologies, including Alzheimer's disease, Alzheimer's disease with vascular risk factors, attention-deficit hyperactivity disorder, dementia with Lewy bodies, Korsakoff syndrome and multiple sclerosis [6]. Cholinergic agonists reverse or shorten unconsciousness from general anaesthesia. Physostigmine, the prototypical acetylcholinesterase inhibitor, increases the dose of propofol that is required to induce unconsciousness [10]. Physostigmine antagonises anaesthesia induced by halothane, sevofluorane, ketamine and propofol [11–13], shortens post-anaesthetic sedation by midazolam and halothane and speeds up recovery from cognitive impairment induced by combined treatment with meperidine, propiomazione and scopolamine [14–18]. Interestingly, physostigmine counteracts depressant effects of propofol on two physiological indexes of anaesthesia depth, the auditory steady-state response and the bispectral index [12]. Finally, physostigmine's restoring effects on consciousness and physiological measurements were blocked by pretreatment with the muscarinic antagonist scopolamine [12]. The findings suggest that cholinergic receptor systems appear to mediate or potently interact with the

neuronal structures and circuitries that generate and maintain arousal and the anaesthetic state.

Possible neuronal targets of cholinergic drugs have been investigated with different functional neuroimaging techniques. Early studies focused, almost exclusively, on rCBF and rCMRglc changes induced by cholinergic agonists in patients with Alzheimer's disease. Phosphatidylserine, a precursor of acetylcholine, increased rCMRglc at rest and during visual stimulation in those patients [6]. In addition, L-a-glyceryl-phosphoryl-ethanolamine, a second acetylcholine precursor, increased rCBF in occipital lobe regions and decreased rCBF in limbic areas [6]. Physostigmine acutely induced both rCMRglc increases and decreases in healthy subjects and in those with Alzheimer's disease. Long-term treatment with the acetylcholinesterase inhibitor tetrahydroaminoacridine increased rCMRglc in temporal and frontal cortices and in subcortical areas, whereas long-term administration of rivastigmine prevented cognitive deterioration and increased rCMRglc in cortical regions and in the hippocampus. In functional MRI studies, physostigmine had no effect on rCBF in normal subjects at rest [6].

Nicotine is a potent agonist of cholinergic nicotinic receptors and has both addictive and cognitive enhancing properties [22]. In healthy nonsmoking subjects, intravenous nicotine reduced rCMRglc in most brain regions [23] but increased rCBF at rest in the parahippocampal gyrus, cerebellum, and medial occipital lobe [22]. In healthy subjects performing a working-memory task, nicotine enhanced rCBF activation in the anterior cingulate, superior frontal and superior parietal cortices and in the midbrain tectum [24]. In abstinent smokers, nicotine increased rCBF in subcortical areas (e.g. thalamus, pons and cerebellum) and in visual cortex, and decreased rCBF in hippocampal and parahippocampal areas [25]. Performance of a rapid visual-information-processing task correlated with rCBF activation in the fronto-parietal-thalamic region of smoking and nonsmoking subjects [26], and to a lesser extent in the parietal cortex and caudate of abstinent smokers [26]. Transdermal nicotine improved task performance in smokers and increased task-induced rCBF activation in the parietal cortex, thalamus, and caudate [26]. In active smoking subjects, intravenous nicotine induce behavioural effects of "rush" and "high" and rCBF increases in the nucleus accumbens, amygdala, cingulate, and frontal lobes. In schizophrenic subjects, nicotine improved performance during an attention and working-memory task and enhanced task-induced rCBF activation in the anterior cingulate cortex and thalamus [27]. Nicotine's activating properties have been interpreted by investigators as consistent with nicotine's behaviour-arousing and -reinforcing properties [22, 23].

In a PET study, physostigmine improved performance in a working-memory task for faces and reduced task-associated rCBF activation in the right inferior temporal and right prefrontal cortices of healthy subjects [6]. The findings of cognitive enhancement and rCBF reduction were interpreted as a result of a lessened effect by physostigmine. In a second functional MRI experiment during the same working-memory task for faces, physostigmine increased rCBF activation in extrastriate regions and infraparietal sulcus, suggesting that physostigmine may facilitate stimulus processing in perceptual brain regions and, this way, reduce

mental effort [6]. In tasks of visual stimulation, spatial working memory and spatial attention, physostigmine speeded all behavioural responses but enhanced accuracy only in the attention task [28]. Physostigmine increased rCBF activation in extrastriate occipital cortex only during attention and working memory performances [28]. In a study on flashing-light visual stimulation, physostigmine determined rCBF changes that were preferentially muscarinic in occipital cortex and preferentially nicotinic in the thalamus and parietal areas [29]. These findings suggest that muscarinic receptors modulate visual processing, and nicotinic receptors modulate arousal and attention.

Donepezil and rivastigmine are acetylcholinesterase inhibitors approved in Europe and in the United States for the treatment of Alzheimer's disease. In patients with mild cognitive impairment, a clinical condition indicating a high risk of developing Alzheimer's disease, a short course of donepezil enhanced frontal rCBF activation during a working-memory task [30]. In patients with schizoaffective disorder, donepezil increased basal ganglia and frontal activation during a word-generation task [31]. In Alzheimer's disease patients, a single dose of rivastigmine increased rCBF activation in the fusiform gyrus during face encoding, and enhanced rCBF activation in the prefrontal cortex in a simple working-memory task [32].

Scopolamine is a typical muscarinic antagonist that has been employed to study the effects of cholinergic derangement on attention and memory in health and disease. In healthy subjects, scopolamine decreased rCBF in frontal regions and the effect was reversed by physostigmine [33]. In older healthy subjects, scopolamine decreased rCMRglc in prefrontal and occipital regions and increased rCMRglc in parietal-occipital and temporal cortices [6]. During a verbal working-memory task, scopolamine impaired performance and reduced task-associated rCBF increases in prefrontal and anterior cingulate cortices; furthermore, at rest scopolamine increased rCBF in occipital and orbitofrontal regions [35]. In an object-recognition task, scopolamine delayed recognition and impaired rCBF activation in the fusiform gyrus. Administered during encoding, scopolamine impaired the subsequent retrieval and rCBF activation in fusiform cortex and increased thalamic rCBF [36]. In a word-stem-completion task, scopolamine impaired repetition suppression and the associated rCBF decreases in left parietal, left extrastriate and left frontal cortices [37]. In a face-recognition task, scopolamine impaired priming suppression and rCBF repetition suppression in the fusiform gyrus [38]. During auditory discrimination, scopolamine reduced rCMRglc in thalamus, cingulate cortex and basal ganglia [37]. Mecamylamine is a nicotinic antagonist that has been investigated poorly; in a study with [^{133}Xe] inhalation method mecamylamine decreased rCBF in parieto-temporal cortices [39]. The findings indicate that central muscarinic and nicotinic blockade impair performances and rCBF activations that depend on attention and memory.

Animal autoradiography studies can be carried out at high spatial resolution and thus provide useful information on cholinergic effects on small brain regions. In rats, acetylcholine precursors and agonists and acetylcholinesterase inhibitors caused dose-dependent increases in rCMRglc. At low doses, the acetylcholine precursor acetyl-L-carnitine increased rCMRglc exclusively in cholinergic and

aminergic nuclei, nicotine in habenular, thalamic and visual accessory system nuclei and the muscarinic agonists arecoline and oxotremorine in median raphe nucleus, basal ganglia, and in thalamic and limbic areas that constitute the Papez circuit (e.g. anterior thalamus, hippocampus and cingulate cortex) [6]. In a recent study, the nicotinic antagonist mecamylamine determined marked rCBF increase in the nucleus accumbens and cortical regions of nicotine-dependent rats [40]. Acetylcholinesterase inhibitors (e.g. eptastigmine, physostigmine and tetrahydroaminoacridine) increased rCMRglc in thalamic and visual accessory system nuclei and limbic areas [6]. At higher doses, all cholinergics further increased rCMRglc but the effect was substantially larger for muscarinic agonists [6]. rCMRglc increases by cholinergics do not depend on cholinergic system integrity, suggesting possible pleiotropic effects of this class of drugs. The muscarinic antagonists scopolamine and atropine reversed rCMRglc increases by acetylcholinesterase inhibitors [6] and independently decreased rCMRglc in limbic, thalamic [6] and cortical areas [6]. Mecamylamine prevented rCMRglc increases by nicotine [6].

Taken together, the animal data suggest that cholinergic agonists increase and cholinergic antagonists decrease rCMRglc preferentially in subcortical regions, such as thalamus, hippocampus and visual processing regions, that may be responsible for the cholinergic effects on arousal and memory.

Adrenergic drugs affect cognition but in a fashion less clear than cholinergics. In a target detection task, the noradrenergic alpha2-agonist dexmedotomidine impaired performance [41]. Dexmedotomidine-induced impairment was attenuated by the presentation of white noise and was accompanied by a selective rCBF increase in the left medial pulvinar nucleus of the thalamus [41]. Clonidine, another noradrenergic alpha2-agonist, impaired behavioural measures of arousal and attenuated rCBF activity in the left temporo-parietal junction [42].

GABAergic drugs

GABAergic antagonists and agonists have prominent effects on arousal. Flumazenil is a benzodiazepine antagonist with few intrinsic features but with the ability to reverse benzodiazepine-induced states. Flumazenil caused a slight decline in cognitive performance in healthy volunteers [43] and in patients with Alzheimer's disease [44]. It reverses psychomotor slowing in hepatic encephalopathy [45], alcohol intoxication [45] and coma from different causes [45, 46]. Flumazenil is capable of shortening and reversing cognitive and psychomotor impairment by the benzodiazepines diazepam, lorazepam and midazolam and by the opioid fentanil [47–49]. It also improves recovery of cognitive and motor functions following halothane, enflurane and isoflurane anaesthesia, reduces shivering and improves the overall quality of emergence, including patients' subjective feelings [50]. Finally, flumazenil reverses rCMRglc decreases induced in the thalamus and occipital cortex by lorazepam [34].

Flumazenil had no effect on rCMRglc in drug-naive rats. In diazepam-dependent rats, however, flumazenil precipitated diazepam withdrawal and produced a

marked increase in glucose use in structures of the Papez circuit (mammillary body, anterior thalamus, cingulate cortex) and in the septal nucleus, basolateral amygdala and nucleus accumbens [51].

Lorazepam is a benzodiazepine that is largely used as an anxyolitic and as an anti-epileptic. In healthy humans, lorazepam caused marked decreases in rCMRglc in the thalamus and occipital cortex that were significantly correlated with lorazepam-induced sleepiness [34, 52]. Flumazenil reversed both behavioural and metabolic effects of lorazepam, and there was a trend of an association between the reversal by flumazenil of lorazepam-induced change in thalamus and sleepiness [52]. In a recent study, a positive correlation was found between alpha power and metabolism of the bilateral thalamus and the occipital and adjacent parietal cortex during placebo [53]. Under lorazepam, the thalamic and parietal correlations were maintained, whereas the occipital correlation was no longer detectable [53]. The correlation analysis of the difference lorazepam-placebo showed alpha power exclusively correlated with the thalamic activity [53]. Recently, a lorazepam derivative [3-(4-acetamido)-butyryl lorazepam (DDS2700)] decreased alertness and rCMRglc at rest in the thalamus, cerebellum and caudate nucleus. During auditory attentive tasks, DDS2700 abolished rCBF activations in frontal and temporal regions and increased rCBF in cingulate cortex, occipitoparietal regions, pons and cerebellum [54].

Midazolam is a benzodiazepine routinely for sedative/anaesthetic purposes. It produces widespread rCBF decreases in the prefrontal cortex, superior frontal gyrus, anterior cingulate gyrus, parietal and temporal association areas, insular cortex and thalamus. Several of these regions belong to neural circuitries that are implicated in attention and memory functions. In a study by Veselis, midazolam induced unconsciousness and, similar to lorazepam, large rCBF decreases in thalamus [55].

Conclusions

Pharmacology neuroimaging studies suggest that certain class of drugs, such as cholinergics and GABAergics have specific, receptor-mediated actions on arousal and cognition. In human studies, cholinergics and GABAergics altered arousal and cognition by affecting sensory and association cortical areas. In animals, high-resolution studies showed that cholinergic and GABAergic agents seem to affect the subcortical nuclei and reticular formation in the midbrain and thalamus. Hence, similar neuronal networks seems to underlie the effects of structurally different drugs on arousal and memory.

References

1. Lezak MD (1995) Neuropsychological assessment, 3rd edn. Oxford University Press, New York
2. Steriade M (1996) Arousal: revisiting the reticular activating system. Science 272: 225-226
3. Steriade M, Amzica F, Contreras D (1996) Synchronization of fast (30-40 Hz) spontaneous cortical rhytms during brain activation. J Neurosci 52: 460-476
4. Mesulam M (1995) Structures and functions of cholinergic pathways in the cerebral cortex, limbic system, basal ganglia, and thalamus of the human brain. In Bloom FE, Kupfer DJ (Eds) Psychopharmacology. The fourth generation of progress. Raven, New York, pp 135-146
5. Foote SL, Aston-Jones GS (1995) Pharmacology and physiology of central noradrenergic system. In Psychopharmacology In Bloom FE, Kupfer DJ (Eds) Psychopharmacology. The fourth generation of progress. Raven, New York, pp 335-346
6. Freo U, Pizzolato G, Dam M et al (2002) A short review of cognitive and functional neuroimaging studies of cholinergic drugs: implications for therapeutic potentials. J Neural Transm 109:857-870
7. Kessler RM (2003) Imaging methods for evaluating brain function in man. Neurobiol Aging 24:S21-S35
8. Zucker J (1991) Central cholinergic depression reduces MAC for isoflurane in rats. Anesth Analg 72:790-795
9. Rumack BH (1973) Anticholinergic poisoning: treatment with physostigmine. Pediatrics 52:449-452
10. Fassoulaki A, Sarantopoulos C, Derveniotis C (1997) Physostigmine increases the dose of propofol required to induce anaesthesia. Can J Anaesth 44:1148-1151
11. Toro-Matos A, Rendon-Platas AM, Avila-Valdez et al (1980) Physostigmine antagonizes ketamine. Anesth Analg 59:764-767
12. Meuret P, Backman S, Bonhomme V et al (2000) Physostigmine reverses propofol-induced unconsciousness and attenuation of the auditory steady state response and bispectral index in human volunteers. Anesthesiology 93:708-713
13. Artru AA, Hui GS (1986) Physostigmine reversal of general anesthesia for intraoperative neurological testing: associated EEG changes. Anesth Analg 65:1059-1062
14. Smith DB, Clark RB, Stephens SR et al (1976) Physostigmine reversal of sedation in parturients. Anesth Analg 55:478-480
15. Hill GE, Stanley TH, Sentker CR (1977) Physostigmine reversal of postoperative somnolence. Can Anaesth Soc J 24:707-711
16. Caldwell CB, Gross JB (1982) Physostigmine reversal of midazolam-induced sedation. Anesthesiology 57:125-127
17. Hamilton-Davies C, Bailie R et al (1995) Physostigmine in recovery from anaesthesia. Anaesthesia 50:456-458
18. Kesecioglu J, Rupreht J, Telci L et al (1991) Effect of aminophylline or physostigmine on recovery from nitrous oxide-enflurane anaesthesia. Acta Anaesthesiol Scand 35:616-620
19. Ho ST, Wong CS, Hu OY et al (1991) Effect of physostigmine on the loss of consciousness induced by midazolam, etomidate and althesin. Ma Zui Xue Za Zhi 29:643-647
20. Mimura M, Namiki A, Kishi R et al (1992) Central cholinergic action produces antagonism to ketamine anesthesia. Acta Anaesthesiol Scand 36:460-462
21. Sarlis NJ, Kaniaris PK (1991) Physostigmine is equipotent to flumazenil only in excessive

doses, while naloxone is ineffective in reversing midazolam anesthesia. Middle East J Anesthesiol 11:271-288
22. Kumari V, Gray JA, Ffytche DH et al (2003) Cognitive effects of nicotine in humans: an fMRI study. Neuroimage 19:1002-1013
23. Stapleton JM, Gilson SF, Wong DF (2003) Intravenous nicotine reduces cerebral glucose metabolism: a preliminary study. Neuropsychopharmacology 28:765-772
24. Domino EF, Minoshima S, Guthrie S (2000) Nicotine effects on regional cerebral blood flow in awake, resting tobacco smokers. Synapse 38:313-321
25. Lawrence NS, Ross TJ, Stein EA (2002) Cognitive mechanisms of nicotine on visual attention. Neuron 36:539-548
26. Stein EA, Pankiewicz J, Harsch HH et al (1998) Nicotine-induced limbic cortical activation in the human brain: a functional MRI study. Am J Psychiatry 155:1009-1015
27. Jacobsen LK, D'Souza DC, Mencl WE et al (2004) Nicotine effects on brain function and functional connectivity in schizophrenia. Biol Psychiatry 55:850-858
28. Bentley P, Husain M, Dolan RJ (2004) Effects of cholinergic enhancement on visual stimulation, spatial attention, and spatial working memory. Neuron 41:969-982
29. Mentis MJ, Sunderland T, Lai J et al (2001) Muscarinic versus nicotinic modulation of a visual task. a pet study using drug probes. Neuropsychopharmacology 25:555-564
30. Rombouts SA, Barkhof F, Van Meel CS et al (2002) Alterations in brain activation during cholinergic enhancement with rivastigmine in Alzheimer's disease. J Neurol Neurosurg Psychiatry 73:665-671
31. Risch SC, McGurk S, Horner MD et al (2001) A double-blind placebo-controlled case study of the use of donepezil to improve cognition in a schizoaffective disorder patient: functional MRI correlates. Neurocase 7:105-110
32. Saykin AJ, Wishart HA, Rabin LA et al (2004) Cholinergic enhancement of frontal lobe activity in mild cognitive impairment. Brain 127:1574-1583
33. Prohovnik I, Arnold SE, Smith G (1997) Physostigmine reversal of scopolamine-induced hypofrontality. J Cereb Blood Flow Metab 17:220-228
34. Molchan SE, Matochik JA, Zametkin AJ et al (1994) A double FDG/PET study of the effects of scopolamine in older adults. Neuropsychopharmacology 10:191-198
35. Grasby PM, Frith CD, Paulesu et al The effect of the muscarinic antagonist scopolamine on regional cerebral blood flow during the performance of a memory task. Exp Brain Res 104:337-348
36. Rosier AM, Cornette L, Dupont P et al (1999) Regional brain activity during shape recognition impaired by a scopolamine challenge to encoding. Eur J Neurosci 11:3701-3714
37. Thiel CM () Cholinergic modulation of learning and memory in the human brain as detected with functional neuroimaging. Neurobiol Learn Mem 80:234-244
38. Speling R, Greve D, Dale et al (2002) Functional MRI detection of pharmacologically induced memory impairment. Proc Natl Acad Sci U S A 99:455-460
39. Gitelman DR, Prohovnik I (1992).Muscarinic and nicotinic contributions to cognitive function and cortical blood flow. Neurobiol Aging 13:313-318
40. Shoaib M, Lowe AS, Williams SC (2004) Imaging localised dynamic changes in the nucleus accumbens following nicotine withdrawal in rats. Neuroimage 22:847-854
41. Coull JT, Jones ME, Egan TD et al (2004) Attentional effects of noradrenaline vary with arousal level: selective activation of thalamic pulvinar in humans. Neuroimage 22:315-322
42. Coull JT, Nobre AC, Frith CD (2001) The noradrenergic alpha2 agonist clonidine modulates behavioural and neuroanatomical correlates of human attentional orienting and alerting. Cereb Cortex 11:73-84

43. Neave N, Reid C, Scholey AB et al (2000) Dose-dependent effects of flumazenil on cognition, mood, and cardio-respiratory physiology in healthy volunteers. Br Dent J 189:668-674
44. Ott BR, Thompson JA, Whelihan WM (1996) Cognitive effects of flumazenil in patients with Alzheimer's disease. J Clin Psychopharmacol 16:400-402
45. Whitwam JG, Amrein R (1995) Pharmacology of flumazenil. Acta Anaesthesiol Scand Suppl 108:3-14
46. Lassaletta A, Martino R, Gonzalez-Santiago P et al (2004) Reversal of an antihistamine-induced coma with flumazenil. Pediatr Emerg Care 20:319-320
47. Girdler NM, Lyne JP, Wallace R et al (2002) A randomised, controlled trial of cognitive and psychomotor recovery from midazolam sedation following reversal with oral flumazenil. Anaesthesia 57:868-876
48. Ghouri AF, Ruiz MA, White PF (1994) Effect of flumazenil on recovery after midazolam and propofol sedation. Anesthesiology 81:333-339
49. Finder RL, Moore PA, Close JM (1995) Flumazenil reversal of conscious sedation induced with intravenous fentanyl and diazepam. Anesth Prog 42: 11-16
50. Weinbroum AA, Geller E (2001) Flumazenil improves cognitive and neuromotor emergence and attenuates shivering after halothane-, enflurane- and isoflurane-based anesthesia. Can J Anaesth 48:963-972
51. Laurie DJ, Pratt JA (1993) Flumazenil induces localised increases in glucose utilization during diazepam withdrawal in rats. Brain Res 631:277-286
52. Volkow ND, Wang GJ, Hitzemann R (1995) Depression of thalamic metabolism by lorazepam is associated with sleepiness. Neuropsychopharmacology 12:123-132
53. Schreckenberger M, Lange-Asschenfeld C, Lochmann M (2004) The thalamus as the generator and modulator of EEG alpha rhythm: a combined PET/EEG study with lorazepam challenge in humans. Neuroimage 22:637-644
54. Moresco RM, Tettamanti M, Gobbo C et al (2001) Acute effect of 3-(4-acetamido)-butyrril-lorazepam (DDS2700) on brain function assessed by PET at rest and during attentive tasks. Nucl Med Commun 22:399-404
55. Veselis RA, Reinsel RA, Beattie BJ (1997) Midazolam changes cerebral blood flow in discrete brain regions: an H2(15)O positron emission tomography study. Anesthesiology 87:1106-1117

Chapter 22

Intracranial pressure monitoring

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Brain injury is the result of both primary and secondary damage, yielded by a complex range of factors including ischemia, biochemical changes and inflammatory cascade. Secondary brain injury may be caused by systemic or intracranial mechanisms including oligaemia due to low cerebral perfusion pressure (CPP) or increased cerebral vascular resistance (vascular distortion or cerebro-vascular narrowing), hypoxemia (airway obstruction, pulmonary pathology or anaemia), intracranial hypertension and changes of brain metabolic rate. Furthermore, secondary insults cause tissue damage according to their nature, severity and duration, making their early detection and correction an essential step of management.

Several neuroprotective agents have been introduced in the past two decades, but, despite their potential effectiveness, the results have been disappointing; therefore, the current basis for prevention of secondary brain damage remains prevention and correction of secondary insults. While nowadays several techniques are available for monitoring severely head-injured patients, monitoring intracranial pressure (ICP) still plays a key role, providing essential information for further decision making.

Methods of ICP monitoring

When ICP monitoring is indicated, the first decision regards the type of device to be used. The optimal ICP monitoring device should provide accurate measurement and constant values over time, cause minimal patient morbidity and be cost-effective. As far as accuracy and safety are concerned, the Association for the Advancement of Medical Instrumentation has published the American National Standard for Intracranial Pressure Monitoring Devices [1]. According to this standard, an ICP device should have the following features: (a) pressure range: 0-100 mmHg; (b) accuracy: ± 2 mmHg over a range of 0-20 mmHg; (c) maximum error: 10% over a range of 20-100 mmHg.

A ventricular catheter connected to an external strain gauge is still considered to be the "golden standard", against which all new methods must be compared for reference, since it is the most accurate, low-cost and reliable method of monitoring ICP. It also allows for therapeutic cerebrospinal fluid (CSF) drainage and recalibration of external strain gauge transducers; however, obstruction of the fluid couple can cause inaccuracy. Furthermore, the pressure wave conduction from the ven-

tricles to the external transducer can be changed by air bubbles, blood clots and brain or other debris, resulting in incorrect ICP readings. In addition, the external transducer must be maintained at a fixed reference point relative to the patient's head to avoid measurement errors. Draining CSF and measuring ICP at the same time is difficult, since the latter becomes inaccurately low. In patients with advanced brain swelling, compression or shift of the ventricles, inserting the ventricular catheter may be difficult or impossible. In such cases, the ICP waveform may be dampened and the values recorded may be lower than real ones.

The potential risks of catheter displacement, such as infection, haemorrhage and obstruction, have led to alternative modalities and intracranial sites for ICP monitoring. Current ICP monitors allow for pressure transduction by catheter-tip strain gauge and catheter-tip fibre-optic technology. A pressure transduction device for ICP monitoring can be placed in the epidural, subdural, subarachnoid, parenchymal or ventricular location, but with newer devices ICP is typically measured in the parenchyma. The fibre-optic device is a thin cable with a pressure transducer at the tip, requiring a dedicated microprocessor to read the signal; this system is expensive, and the cable, being nonflexible, is subject to breakage when bent excessively. The wire system consists of a microtransducer at the tip of a flexible wire; it is made of plastic and copper wire with a silicon catheter-tip strain gauge transducer mounted in a titanium housing. This system is interfaced to be used with standard bedside monitors.

These devices are calibrated before intracranial insertion and cannot be recalibrated once inserted, thus implying a potential for inaccurate measurement, especially during prolonged ICP monitoring. The data obtained by independent testing of microtransducers generally meet the performance data supplied by the manufacturers. The major advantages include the accuracy of pressure recording, the minimisation of drift over prolonged use and stable linearity. The pressure-sensitive element is placed inside the head so that the risk of infection is minimised compared to prolonged ICP monitoring using a fluid-filled catheter and external transducer [2, 3]. Parenchymal or sudbural monitoring locations were reported to have accurate monitoring features [4, 5]; however, other studies found that their pressure values did not always correlate well with ventricular ICP. Although the fibre-optic method showed a close correlation with the ventricular method, its pressure values were always 3±2 mmHg lower than those obtained with the conventional pressure transducer system, especially in critically ill patients [6].

On the other hand, the most common intraparenchymal probes measure a local tissue pressure, which may be compartmentalised and not necessarily representative of real ICP (namely, ventricular CSF pressure). A uniformly distributed ICP can probably be measured only when CSF freely circulates between all its natural pools, while the assumption of one, uniform value of ICP is debatable when CSF volume is reduced or left due to brain swelling, [7]. Therefore, one must consider that ICP values may reflect different conditions in different patients, or even in the same patient at different times, while clinical conclusions and decision making depend on the ability to understand what is really measured and what is relevant for the individual patient.

In addition, ICP monitoring should be possible during patient transport, an essential aspect of patient management during diagnostic procedures, e.g. computed tomography (CT) and magnetic resonance (MR). MR has become a standard technique for imaging the central nervous system and is increasingly being used to assess acute brain injury. The use of MR to evaluate critically ill patients has led to the development of a wide range of monitoring devices compatible with the MR environment. The packaging label "MR safe" indicates that the device is not dangerous to the patient during MR recording, while the label "MR compatible" indicates that a "MR safe" device does not significantly affect the diagnostic quality of the imaging procedure . So far, only the Codman-Microtransducer system has been tested to be MR safe at field strengths up to 0.5 Tesla [8] (even for intraparenchymal monitoring), and it may be tunnelled beneath the scalp in order to minimise MRI artefacts. The system remains accurate during most MRI functions, apart from diffusion-weighted imaging, whereas the ICP monitor yields a decreased signal-to-noise ratio during T2-weighted imaging and proton spectroscopic imaging, with acceptable quality of the obtained images for clinical purposes [9]. Other commonly used ICP monitors may be unsafe in a MR scanner, due to possible movements of the intracranial part when subjected to the magnetic field.

Current practice

ICP monitoring has been used in clinical practice for more than four decades, but evidence from randomised controlled trials in support of this intervention is still lacking. A recent study reported the association of ICP monitoring with a statistically significant decrease in the death rate among patients with severe brain injury [10]. Also, ICP measurement disclosed a high rate of intracranial hypertension that was not suspected in patients evaluated on a clinical basis alone [11]. ICP monitoring has become an integral part of the management of severe head injury and it is recommended in various guidelines for surgical and medical treatment [12-14]. In patients at high risk for ICP elevation, ICP monitoring is appropriate. According to national and international guidelines, it should be initiated as soon as possible in the majority of patients with:

(a) Glasgow Coma Scale (GCS) scores of 8 or less and abnormal CT scan on admission.
(b) GCS≤8 and a normal CT scan, but with two or more of the following conditions on admission: age over 40 years; unilateral or bilateral motor posturing; one or more episodes of hypotension with systolic blood pressure less than 90 mmHg.

In fact, 53-63% of comatose patients with an abnormal CT scan undergo intracranial hypertension during the clinical course, while in patients with a normal CT scan the risk of intracranial hypertension is relatively low [15]. In patients with mild or moderate head injury, the risk for intracranial hypertension is relatively low as well: less than 3% of patients with mild head injury and 10-20% of patients with moderate head injury undergo neurological deterioration and become comatose

[12]. The data from the Traumatic Coma Data Bank show that pre-hospital hypotension and/or hypoxia occur in one-third of severely head-injured patients and are among the five most powerful predictors of outcome. Even a single episode of hypotension is related to increased morbidity and a doubling of mortality [16]. It is difficult to establish a "normal value" for ICP as it depends on age, body posture and clinical conditions; the definition of raised ICP depends on the specific pathology as well. Following head injury, ICP values above 20 mmHg are abnormal, and aggressive treatment usually starts above 25 mmHg. A few ICP patterns can be defined:

(a) Low and stable ICP.
(b) Low and stable ICP in the early stage, followed by raised ICP related to the development of secondary damage (e.g. brain oedema or swelling).
(c) Stable and elevated ICP.

ICP dynamics may become unstable in patients with elevated CSF outflow resistance and decreased intracranial compliance, giving rise to plateau waves. When compensatory mechanisms are poor, even modest hypotension may induce a large transient increase in ICP and a significant transient reduction in cerebral blood flow (CBF), with risk of secondary brain damage. High waves of ICP may be caused also by a sudden increases in arterial blood pressure (ABP) or by hyperaemia. Refractory intracranial hypertension is another typical pattern: it is characterised by an increase of the ICP within a few hours to above 100 mmHg, usually leading to death unless aggressive treatment is administered.

The ICP waveform provides much more information than the time-averaged ICP mean value alone. The intracranial volume may be subdivided into three compartments (brain tissue, CSF and blood) and is connected to the ICP via a pressure-volume relationship. While the volume of CSF and tissue may be viewed as constant over a short time range, changes in intracranial blood volume account for the faster periodic changes in the ICP. The latter may be caused by an increased arterial inflow of blood, changes in the vasomotor tension or a decreased venous outflow. Lundberg [17] classified the resulting pressure waves according to their shape and frequency, as follows:

(a) A-waves or plateau waves are related to strongly elevated ICP and reflect a severe decrease of intracranial compliance, calling for immediate treatment. They are characterised by a rise of ICP above 50 mmHg, duration up to 20 min and a prompt decline to near the initial value.
(b) P-waves are caused by the pulsating inflow of arterial blood and are thus linked to heart rate. These waves more frequently reflect a condition with impaired compliance; however, this pattern may occasionally be seen in patients with normal compliance and normal ICP value and may fail to appear in those with severe intracranial hypertension. Nevertheless, the appearance of P-waves discloses an increased risk of developing intracranial hypertension and harmful impairment of intracranial compliance.
(c) B-waves have frequencies in the range of 0.5-2 per min. Their shape is variable (e.g. sinusoidal or sawtooth), while their amplitude depends on changes in the pressure/volume relationship.

Although "slow waves" were not as well defined by Lundberg, waveform analysis has provided further information allowing improved patient management. All components with a spectrum within frequency limits of 0.05-0.0055 Hz can be classified as slow waves. In patients with intracranial hypertension following head injury, the presence of slow waves reported to be predictive of outcome, with a low content of slow waves was associated with a fatal outcome [18]. Furthermore, ICP waveform provides valuable information on cerebrovascular pathophysiology, since autoregulation of CBF and compliance of the cerebrospinal system are both reflected in the ICP.

Nowadays, ICP, ABP and CPP measurements are readily and routinely available at the patient's bedside. However, in current clinical practice only a simple tracking of data values is usually displayed, thereby losing both all information that could be drawn from trends and the ability to integrate the data into a complete, meaningful picture. Thus, the best clinical approach implies more than simple data tracking. With respect to the ICP, the ICP waveform probably contains much more information than pressure alone. It includes three components that overlap in the time domain but which can be separated in the frequency domain. The increase of ICP is paralleled by an increase and merging of the first two peaks (of arterial origin) and the disappearance of the third peak (assumed to be of venous origin). These changes may be explained by vasodilatation of cerebral blood vessels as a compensatory mechanism, thus yielding an "arterialised" shape of the waveform.

Since a decrease of intracranial compliance may predict an increase of the ICP, indices drawn from ICP waveform analysis can be helpful in the management of severely head-injured patients. Here, it is worth considering the pressure-volume index (PVI) in order to better understand the relationship between ICP and cerebral compliance. Marmarou [20] described the craniospinal volume-pressure correlation and the slope of this relationship was termed the PVI, which is the volume required to raise ICP tenfold. The PVI is calculated from the pressure change resulting from a rapid injection or withdrawal of fluid from the CSF space. It is obtained by repeated withdrawal and injection of 2 ml of CSF and calculation of the average value. PVI changes precede and are inverse with respect to ICP changes [19]. A decrease of PVI below the normal value is predictive of reduced compliance and eventually leads to increased ICP. Through measurement of the PVI and CSF outflow resistance, the percentage contribution of CSF and vascular factors to the elevation of ICP may be calculated [20]. In severely head-injured patients, the CSF contribution to ICP is around 30% of the ICP rise, while vascular mechanisms play a major role [20]. Nevertheless, PVI is not routinely calculated in clinical practice due to its limits, such as the variability of the tests (due to manual injection) and the risk of infections.

Complications

The use of ICP monitoring has been limited in the past by the concern regarding complications, such as infection, haemorrhage, probe damage and/or dislocation.

In general, the rate of complications of ICP devices is low and is affected by several factors. e.g. age, patient condition, prolonged monitoring and prolonged hospitalisation.

The incidence of infection depends on the ICP device and time, since colonisation increases significantly 5 days after insertion. The reported rate of ventricular catheter infections is 10-17% [21], and since irrigation of fluid-coupled ICP devices significantly increases bacterial colonisation; the incidence of ventriculitis is 10.4%. The replacement of catheters at 5-day intervals does not seem to decrease the incidence of infections [22]. However, when the fluid-couple devices are excluded, the average rate of bacterial colonisation is 5% for ventricular and subarachnoid and 14% for parenchymally placed catheter-tip strain gauge or fibre-optic devices [23-24]. Even though data from these studies indicate an increase of bacterial colonisation, the rate of clinically significant intracranial infections is low.

Bleeding with all ICP devices has been reported in some 1.4% of patients. The incidence of significant haematomas requiring surgical evacuation is 0.5% [25]. However the average rate of haemorrhage depends on the sensor type, likewise the incidence of infection. A rate of haemorrhage of 3.28% and infection of 7.29% has been associated with the use of ventricular catheters, while haemorrhage related to the use of fibre-optic devices occurs in 0.87% of patients, with no infections [26]. A rate of 0.7% infection and 5.1% intraparenchymal haematoma has been reported with Camino devices; but the complication rate was reported to be as high as 23.5% due to technical complications [27], including measuring errors, probe dislocation and probe damaging following cable rupture or kinking of the sensor (mainly due to nursing manoeuvres and patient transport).

Technical complications have been reported with other devices as well. Malfunction or obstruction, especially with ICP levels higher than 50 mmHg, were observed in fluid-coupled ventricular catheters, subarachnoid bolts and subdural catheters with a rate of 6.3%, 16% and 10.5%, respectively [28].

Raised ICP and outcome

The role of ICP monitoring in patients with severe head injury has been extensively analysed. It is well recognised that persistently raised ICP correlates with a higher risk of mortality. Despite the lack of randomised studies demonstrating an influence of ICP monitoring on overall outcome, a recent study has shown almost twofold lower mortality in patients at neurosurgical centres, where ICP is usually monitored, versus those on general intensive care units, where ICP monitoring is not included in clinical management. An "aggressive" management strategy, defined as ICP monitoring in more than 50% of patients meeting Brain Trauma Foundation criteria, is associated with a significant reduction of mortality in head injury, without a statistically significant difference in the quality of survival [29].

A management regimen including immediate CT scan, surgical decompression of significant mass lesions, artificial ventilation and ICP monitoring is the policy

in many neurosurgical centres, but even with aggressive treatment, the outcome of severe head injury is often suboptimal.

Evidence is still missing as to whether CPP is more predictive than ICP; however, both ICP- and CPP-targeted therapies need monitoring ICP. The analysis of ICP waveform may improve the diagnostic and prognostic value of this measurement. Indeed, several studies have shown that outcome prediction is improved by combining ICP monitoring with an assessment of the usual clinical signs (such as age, papillary response, motor activity) [29-33].

Conclusion

ICP monitoring is an essential tool in neuro-intensive care, allowing for a timely treatment of intracranial hypertension. Furthermore, it also allows for an estimation of intracranial compliance. Proper patient management must take into account both the ICP trend and the information drawn from its waveform.

Severely head injured patients have a high mortality (39-51%) and a high risk of intracranial hypertension in the acute phase; this situation calls for ICP monitoring. Despite the availability of guidelines for the management of head-injured patients, there is still considerable variability in patient management among centres, with indications for ICP monitoring remaining one of the most controversial topics. Although there is not yet evidence that lowering ICP may directly affect outcome, several studies have shown an improved outcome with aggressive ICP management.

References

1. Brown E (1988) Intracranial pressure monitoring devices. Association for the Advancement of Medical Instrumentation, Arlington, Virginia
2. Czosnyka M, Czosnyka Z, Pickard JD (1996) Laboratory testing of three intracranial pressure microtransducers: technical report. Neurosurgery 38:219-224
3. Zhong J, Dujovny M, Park HK et al (2003) Advances in ICP monitoring Neurol Res 25:339-350
4. Cooper PR, Golfinos JG (2000) Head injury, 4th edn. McGraw-Hill, New York
5. Yau YH, Piper IR, Clutton RE et al (2000) Experimental evaluation of the Spiegelberg intracranial pressure and intracranial compliance monitor. Technical note. J Neurosurg 93:1072-1077
6. Gambardella G, Zaccone D, Cardia E et al (1993) Intracranial pressure monitoring in children: comparison of external device with the fibreoptic system. Child Nerv Syst 9:470-473
7. Wolfla CE, Luerssen TG, Bowman RM (1996) Brain tissue pressure gradients created by expanding frontal epidural mass lesion. J Neurosurg 84:642-647
8. Williams EJ, Bunch CS, Carpenter TA et al (1999) Magnetic resonance imaging compatibility testing of intracranial pressure probes. J Neurosurg 91:706-709
9. Macmillan C, Wild JM, Andrews P et al (1999) Accuracy of a miniature intracranial

pressure monitor, its function during magnetic resonance scanning, and assessment of image artifact generation. Neurosurgery 45:188-195
10. Lane PL, Skoretz GT, Doig G et al (2000) Intracranial pressure monitoring and outcome after traumatic brain injury. Can J Surg 43:442-448
11. Stocchetti N, Penny KL, Dearden M et al (2001) Intensive care management of head injured patients in Europe: A survey from the European Brain Injury Consortium. Intensive Care Med 27:400-406
12. Bullock R, Chesnut RM, Clifton G et al (2000) Guidelines for the management of severe traumatic brain injury. J Neurotrauma 17:451-553
13. Procaccio F, Stocchetti N, Citerio G et al (2000) Guidelines for the treatment of adults with severe head trauma (Part II). J Neurosurg Sci 44:11-18
14. D'Avella D, Brambilla GL, Delfini R et al (2000) Guidelines for the treatment of adults with severe head trauma (Part III). J Neurosurg Sci 44:19-24
15. Narayan RK, Kishore PR, Beker DP et al (1982) Intracranial pressure: to monitor or not to monitor? A review of our experience with severe head injury. J Neurosurg 56:650-659
16. Chesnut RM, Marshall LF, Klauber MR et al (1993) The role of secondary brain injury in determining outcome from severe head injury. J Trauma 34:216-222
17. Lundberg N (1960) Continuous recording and control of ventricular fluid pressure in neurosurgical practice. Acta Psychiatr Neurol Scand 36 [Suppl]: 149
18. Lemaire JJ, Khali T, Cervenansky F et al (2002) Slow pressure waves in the cranial enclosure. Acta Neurochir 144:243-254
19. Maset AL (1987) Pressure-volume index in head injury. J Neurosurg 67:832-840
20. Marmarou A, Maset AL, Ward JD et al (1987) Contribution of CSF and vascular factors to elevation of ICP in severely head-injured patients. J Neurosurg 66:883-890
21. Vinas FC (2001) Bedside invasive monitoring techniques in severe brain injured patients. Neurol Res 23:157-166
22. Holloway KL, Barnes T, Sung C et al (1996) Ventriculostomy infections: the effect of monitoring duration and catheter exchange in 584 patients. J Neurosurg 85:419-424
23. Winfield JA, Rosenthal P, Kanter RK et al (1993) Duration of intracranial pressure monitoring does not predict daily risk of infection complications. Neurosurgery 33:424-430
24. Artru F, Terrier A, Gibert I et al (1992) Monitoring of intracranial pressure with parenchymal fiberoptic transducer. Technical aspects and clinical reliability. Ann Fr Anesth Reanim 11:424-429
25. Paramore CG, Turner DA (1994) Relative risks of ventriculostomy infection and morbidity. Acta Neurochir (Wien) 127:79-84
26. Guyot L, Diaz FG, Dowling C et al (1998) Cerebral monitoring devices: analysis of complications. Acta Neurochirurgica 71:47-49
27. Munch E, Weigel R, Schmiedek P et al (1998) The CAMINO intracranial pressure device in clinical practice: reliability, handling characteristics and complications. Acta Neurochir 140:1113-1120
28. Piek J, Bock WJ (1990) Continuous monitoring of cerebral tissue pressure in neurosurgical practice. Experience with 100 patients. Intensive Care Med 16:184-188
29. Bulger EM, Nathens AB, Rivara FP et al (2002) Management of severe head injury: institutional variations in care and effect on outcome. Crit Care Med 30:1870-1876
30. Narayan RK, Kishore PRS, Becker DP et al (1982) Intracranial pressure: to monitor or not to monitor: a review of our experience with severe head injury. J Neurosurg 56:650-659
31. Marmarou A, Anderson RL, Ward JD et al (1991) Impact of ICP instability on outcome in patients with severe head trauma. J Neurosurg 75:s59-s66

32. Lane PL, Skoretz TG, Doig G et al (2000) Intracranial pressure monitoring and outcomes after traumatic brain injury. Can J Surg 43:442-228
33. Juul N, Morris GF, Marshall SB et al (2000) Intracranial hypertension and cerebral perfusion pressure: influence on neurological deterioration and outcome in severe head injury. The Executive Committee of the International Selfotel Trial. J Neurosurg 92:1-6

Chapter 23

Improving quality of recovery

M. Klimek

Attempts of a definition

The difficulties in defining 'quality of recovery' start with the definition of recovery: Does 'recovery' mean the complete restoration of the milieu interne and the restart of all activities of daily living, or does it mean the period in the recovery room until a certain Aldrete score is reached and the patient is discharged to the general ward?

Postoperative recovery is closely linked to restitution of cerebral function after a surgical procedure and anaesthesia. Besides the anaesthetic regimen many other factors contribute to cerebral recovery: type of procedure, hypothermia, hypoglycaemia, hypoxia, age, pre-existing disease and medication are some of these. Therefore, it is difficult to quantify the importance of one specific (anaesthetic) drug for the quality of recovery.

One thing is certain: postoperative recovery is part of the overall process of perioperative care and cannot be considered separately. A good recovery begins with a good preoperative assessment (e.g. identifying risk factors for postoperative nausea and vomiting) and is highly influenced by the anaesthetic technique selected intraoperatively. However, what is a good recovery? Is it a product or a process we want to improve?

In September 2002 a working party of the Association of Anaesthetists of Great Britain and Ireland published recommendations on "immediate postanaesthetic recovery" [1]. They gave 13 key recommendations, including the following:

- The anaesthetist must formally hand over care of a patient to a recovery room nurse or other appropriately trained member of staff.
- Agreed criteria for discharge of patients from the recovery room to the ward should be in place in all units.
- No fewer than two staff should be present when there is a patient in the recovery room who does not fulfil the criteria for discharge to the ward.
- All patients must be observed on a one-to-one basis by an anaesthetist, recovery nurse or other appropriately trained member of staff until they have regained airway control and cardiovascular stability and are able to communicate.
- Patient dignity and privacy should be considered at all times.
- Audit and critical incident systems should be in place in all recovery rooms.

These points – like the whole paper – sound absolutely reasonable, and their realisation one by one in every hospital mean a great improvement in the quality of postoperative recovery.

I am afraid that daily practice in the most European hospitals is far from following these recommendations. Much worse, when thoughts go to improving the quality of recovery, they go in completely different directions: less nausea and vomiting, less shivering, fast track, better pain control, higher alertness, higher patient satisfaction, short stay – to name but a few. This contrast leads us to ask what it is that we want when we try to improve the quality of recovery. Of course it is easier to inject a certain drug that provides a particular desired effect than to develop internal protocols, transfer every patient with supplemental oxygen to the recovery room, train recovery staff in ACLS, equip the recovery room adequately in all areas where anaesthesia is administered and ask recovery staff to maintain careful documentation. Dazzled by the promotion of modern drugs that might have an impact on the fine-tuning of the quality of recovery, nobody is making the effort to establish the minimum standard of quality in the recovery room suggested in the AAGBI Recommendations.

There is another point to think about: it is broadly agreed among anaesthesiologists that these recommendations describe a high quality of recovery. However, there is much less agreement about whether a very rapid, perhaps agitated recovery is of a higher quality than a delayed recovery. Of course, a faster turnover with the same resources means an improvement from the economic point of view, but what about patient comfort? What about the nurses' perspective? Whose definition of quality counts? What is quality and what can be considered as an improvement? What price are we willing to pay for a virtual improvement? The following paragraphs may give some inspiration.

Preoperative assessment

There is no doubt that efficient preoperative assessment and management optimise postoperative outcomes. Careful and adequate preoperative evaluation and optimisation of the patient can make it possible to provide safer and more efficient care even for high-risk patients without exhausting precious intensive care resources. However, this is beyond the scope of this article, and a reference to the excellent recent review written on this topic by Halaszynski et al. will be the final inspiration relating to this point [2].

Outpatient surgery

The recovery room is an expensive facility within the hospital. If the newer anaesthetics were also effective from the economic viewpoint, it should be possible to bypass the recovery room and allow the patients treated with them to recover in a sitting position in a wheelchair in a kind of waiting area with fewer staff and less equipment. Apfelbaum et al. found in a prospective trial (according to defined criteria) that 59% of more than 2,300 patients who had undergone outpatient procedures might be suitable for such a 'light' recovery before being discharged

home [3]. They had no safety problems, and it might be expected that in a setting where all out-patient procedures of a hospital with high turnover are performed in a single unit this kind of recovery facility might lead to economic advantages. However, we should be aware that the overall incidence of postdischarge symptoms in out-patients is reported to be approximately 45% for pain, 42% for drowsiness, 21% for fatigue, 18% for dizziness, 17% for nausea, and 8% for vomiting; 62% of such patients require 3.2 postoperative days to resume activities of daily living because the symptoms persist so long [4]. I wonder (a) whether we would accept such an incidence in a modern hospital in-patient-setting and (b) whether the patients' family members, neighbours and/or friends are actually able to manage these symptoms in a safe and comfortable way? Do the possible advantages of not being in hospital outweigh the obvious stress and discomfort a freshly operated outpatient might suffer?

In-patient problems

In a recently published study Tarnow shows that about 20% of the time a patient spends in the recovery unit is occupied with waiting for the nurses from the general ward to fetch them once they have been classified as dischargeable [5]. Engaged telephone lines, blocked elevators, nurses too busy to leave the ward – daily practice knows millions of these examples. On the other hand, one might seriously discuss whether short-acting agents have enough advantages to justify the higher costs when they are used for longer lasting surgical procedures: Dexter and Tinker have shown that 95% of the costs of postoperative recovery are due to the staffing and are heavily dependent on two factors: the number of beds and the distribution of patient flow over the day [6]. What, then, is the quality of recovery if after a 5-hour operation a patient is alert again 10 min earlier but spends this time continuously calling to the nurses in efforts to get any kind of care, moaning in pain, wanting to urinate, and asking four times about the result of the procedure?

Evidence-based interventions

In a review published in 2001, Myles attempts to evaluate some anaesthesiological measures that can or should be taken to optimise patients' outcome and their quality of recovery in a strictly evidence-based manner [7]:

1. Use of beta-blockers in patients at risk of myocardial ischaemia.
2. Prophylactic treatment of PONV with dexamethasone, a 5-HT3-antagonist, propofol-based anaesthesia, maintenance of patient's hydration status and acupressure at the P6 point.
3. Use of chlorhexidine for skin preparation before intravascular cannulation.
4. Avoidance of intraoperative hypothermia.
5. Supplemental oxygen (80%) to reduce wound infection (including avoidance of nitrous oxide).

Whilst the evidence on the points 1–3 is still accumulating, some comments must be made on the last two points:

1. Hypothermia is still under discussion for improvement of the neurological and/or cardiac outcome of selected patients, e.g. after circulatory arrest, cerebral hypoperfusion and traumatic brain injury [8]. However, application of warm air and use of warm infusions should be standard parts of the perioperative management of every standard surgical patient.
2. The use of perioperative hyperoxia to prevent surgical site infections has come in for severe criticism – the authors, who are anaesthesiologists, conclude: "The routine use of high perioperative FiO_2 in a general surgical population does not reduce the overall incidence of surgical site infections and may have predominantly deleterious effects. General surgical patients should receive oxygen with cardiorespiratory physiology as the principal determinant" [9].

In their review on challenges in postoperative recovery, Kehlet and Dahl outline some other important issues, and specifically address the concept of fast-track surgery [10]: in addition to the points already mentioned, such as careful preoperative assessment and psychological preparation of the patient, the use of propofol, avoidance of nitrous oxide to prevent PONV and avoidance of hypothermia, they suggest the following measures for improvement of postoperative recovery:

- Prevention of surgical stress and postoperative dysfunction by afferent neuronal blockade and minimally invasive surgery.
- A multimodal pain regimen, including COX-2 inhibitors and NMDA-receptor antagonists.
- Pharmacological interventions such as administration of anti-inflammatory drugs, antiemetics, beta blockers and anabolic agents and optimised preoperative carbohydrate nutrition.
- Careful perioperative fluid management.
- Restrictive use of nasogastric tube, drains and urinary catheters.

Their review also underlines the need for new outcome measures when attempts are made to quantify a possible improvement in quality of recovery [10]. As well as anaesthesia-related complications and postoperative morbidity, such matters as patients' expectations, patient satisfaction, fatigue and mobilisation, to name but a few, must also be considered.

Some recent trials of interest

Larijani et al. have published a study showing significant benefit of a single oral dose of modafinil (200 mg) in postoperative cognitive recovery [11]. This drug, which promotes wakefulness through an unknown mechanism is usually prescribed to treat narcolepsy. Patients treated with modafinil in this prospective, randomised, double-blind setting experienced significantly less postoperative fatigue and less exhaustion. Because no serious side effects were seen, these data can encourage further research with this drug with a view to its use in patients who wish to regain maximum alertness and energy as soon as possible after general anaesthesia.

In a prospective, randomised, controlled multi centre trial Hofer et al. give impressive insights into factors affecting patients' wellbeing after general anaesthesia [12]. They emphasise the importance of avoiding PONV and conclude that total i.v. anaesthesia with propofol is followed by better early postoperative patient wellbeing than inhalational anaesthesia with sevoflurane, and also involves a lower incidence of PONV (OR 7.8, CI 3.48-13.51 for the use of sevoflurane as a risk factor for PONV). However, patient satisfaction 24 h after anaesthesia was similar in both groups.

A Swedish group has demonstrated a significant short-term effect of relaxing music played intra- and/or postoperatively on the consumption of analgesics during the first postoperative hours [13]. They discuss whether music played postoperatively might work by distraction, in a similar way to a short-acting analgesic, which reduces pain perception. Why music played intraoperatively also has a pain-reducing effect remains unclear. However, these authors suggest music therapy as an additional component in multimodal acute pain treatment. These findings are supported by the results of Tsuchiya et al., who played relaxing natural sounds to their patients during surgery and noted fewer and less pronounced haemodynamic changes and higher acceptability of the experience of anaesthesia [14].

Some publications deal with the patients' point of view: Eberhart et al. performed a so-called conjoint analysis of patients' preferences for postoperative recovery and found that PONV was the most important topic (49%), followed by pain (27%), alertness (13%) and costs (11%) [15]. In summary, the average patient has no problems with some sleepiness and accepts a certain amount of pain after a surgical procedure, as long as the anaesthesiologist does his or her best to avoid PONV, which is something the patient is willing to pay extra money for.

The future

The role of the anaesthesiologist as the manager of perioperative care will develop further. In a multidisciplinary context, together with surgeons and physiotherapist, the anaesthesiologist should "take the lead in studying the impact of post-discharge symptoms and advocating for our patients' best care, even if it involves care beyond our traditional period of involvement" [16]. The directions we have to take are clear: in addition to implementing the guidelines that are already published and evidence-based medical principles and procedure-specific management protocols, we have to improve preoperative information, risk assessment and optimisation. We should aim for minimally invasive anaesthesia and should make every effort to reduce surgical stress by pharmacological means, provide opioid-sparing multimodal analgesia, assess the economic implications of postdischarge symptoms and optimise logistics, planning and coordination in perioperative medicine [10].

References

1. The Association of Anaesthetists of Great Britain and Ireland (2000) Immediate postanaesthetic recovery. AAGBI, London
2. Halaszynski TM, Juda R, Silverman DG (2004) Crit Care Med 32:S76-S86
3. Apfelbaum JL, Walawander CA, Grasela TH et al (2002) Eliminating intensive postoperative care in same-day surgery patients using short-acting anesthetics. Anesthesiology 97:66-74
4. Wu CL, Berenholtz SM, Pronovost PJ et al (2002) Systematic review and analysis of postdischarge symptoms after outpatient surgery. Anesthesiology 96:994-1003
5. Tarnow J (2004) "Fast track"-Anästhesie: Der grosse Fortschritt? In: Deutsche Akademie für Anästhesiologische Fortbildung. (Refresher Course, vol 30) Diomed, Ebelsbach, Germany, pp 211-217
6. Dexter F, Tinker JH (1995) Analysis of strategies to decrease postanesthesia care unit costs. Anesthesiology 82:94-101
7. Myles PS (2001) Improving quality of recovery: what anaesthetic techniques make a difference? Best Pract Res Clin Anaesthesiol 15:621-631
8. Kabon B, Bacher A, Spiss CK (2003) Therapeutic hypothermia. Best Pract Res Clin Anaesthesiol 17:551-568
9. Pryor KO, Fahey TJ 3rd, Lien CA et al (2004) Surgical site infection and the routine use of perioperative hyperoxia in a general surgical population: a randomized controlled trial. JAMA 291:79-87
10. Kehlet H, Dahl JB (2003) Anaesthesia, surgery, and challenges in postoperative recovery. Lancet 362:1921-1928
11. Larijani GE, Goldberg ME, Hojat M et al (2004) Modafinil improves recovery after general anesthesia. Anesth Analg 98:976-981
12. Hofer CK, Zollinger A, Büchi S et al (2003) Patient well being after general anaesthesia: a prospective, randomized, controlled multi-centre trial comparing intravenous and inhalation anaesthesia. Br J Anaesth 91:631-637
13. Nilsson U, Rawal N, Unosson M (2003) A comparison of intra-operative or postoperative exposure to music – a controlled trial of the effects on postoperative pain. Anaesthesia 58:699-703
14. Tsuchiya M, Asada A, Ryo K et al (2003) Relaxing intraoperative natural sound blunts haemodynamic change at the emergence from propofol general anaesthesia and increases the acceptability of anaesthesia to the patient. Acta Anaesthesiol Scand 47:939-943
15. Eberhart LHJ, Morin AM, Wulf H et al (2002) Patient preferences for immediate postoperative recovery. Br J Anaesth 89:760-761
16. Miller RD (2002) The place of research and the role of academic anaesthetists in academic departments. Best Pract Res Clin Anaesthesiol 16:353-370

LUNG AND ARTIFICIAL VENTILATION

Chapter 24

Molecular biology and lung disease
What is the impact?

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Many centuries passed without too much thought about why children resembled their parents. People were able to cross animals or plants with the purpose of generating more resistant or stronger offsprings, without knowing how the information was able to pass from one generation to the next. Even after Gregor Mendel revealed the concept of phenotype inheritance [1], it took almost 100 years to convince the scientific community that the deoxyribonucleic acid (DNA) was the molecule responsible for carrying heredity information [2], and to unravel its double-helix structure [3, 4]. Now, 51 years after Watson and Crick's findings, the study of the molecular basis of life is progressing much faster, and it can change the outcomes of science. This development leads to a wider understanding of how organisms function as scientists progressively reveal the roles of genes roles and evolution.

Although molecular genetics technology has burgeoned in the last 20 years, making it possible for researchers to discover many gene disorders and characterise other diseases at the molecular level, it has still had no evident impact on medicine. However, scientists predict that molecular biology will dominate clinical studies and revolutionise present-day medical concepts and treatments.

Molecular biology is based on the concept that all living creatures depend on the production of proteins codified by genes inside the DNA. In a more detailed approach, the information contained in the nuclear DNA is transcribed into messenger ribonucleic acid (mRNA) by a RNA polymerase that binds to DNA in a nucleotide sequence called a promoter directly before the gene, which can be regulated in order to allow or inhibit gene expression. This mRNA can be processed inside the nucleus, after which it is exported to the cytoplasm, where a complex involving ribosomes, transporter RNA and free aminoacids will give origin to a new protein.

The 'central dogma' of molecular biology emerges from the sum of this information: DNA is transcribed into mRNA, which is later translated into protein. Knowledge of this chain of events makes careful study of these molecules and of the chain's variance among different conditions and species possible. Each of the molecules involved in this process can be studied, and the insights so gained offer some new perspective on old issues that are not yet completely understood.

This paper gives an overview of the importance of each of these molecules and the most common methods used in studies of respiratory physiology and treatment of lung disease.

Deoxyribonucleic acid

Deoxyribonucleic acid (DNA) is located in the cell nucleus and is the molecule that is responsible for carrying the genetic information. It is composed of subunits, which scientists have called nucleotides, and each nucleotide is made up of a sugar, a phosphate and a nitrogen-containing base. There are four different bases in a DNA molecule: (a) two purines (adenine and guanine) and (b) two pyrimidines (cytosine and thymine). It is well known that the number of purine bases is equal to the number of pyrimidine bases [5]. DNA structure has two helical chains, each coiled round the same axis, and these two chains run in opposite directions, with bases on the inside of the helix and the phosphates on the outside [3].

DNA sequencing

The molecular biology technique of DNA sequencing was responsible for the first step taken by the scientific community in the direction of revealing the genome code. The complete genomes of many species are now totally mapped; these include the human genome. DNA sequencing is a simple reaction based on the addition of either radiolabelled or fluorescence-labelled dideoxynucleotides [6] (adenosine, guanine, cytosine and thymine), also called terminators, to a single-stranded DNA replication reaction. These dideoxynucleotides are modified nucleotides that prevent the addition of any new nucleotide to the DNA strand by a DNA polymerase also present in the reaction, generating fragments of different sizes which are separated by gel electrophoresis to reveal the DNA sequence. DNA automatic sequencing is already available nowadays: a fluorescence reader gives the results of these reactions very rapidly and dynamically.

DNA sequencing made it possible to discover many hitherto unknown genetic disorders by determining mutations or nucleotide deletions in certain genes. For example, cystic fibrosis (CF) is the most common lethal disease in Caucasians and is caused by failure of the CFTR (cystic fibrosis transmembrane conductance regulator) chloride channel function properly, causing exocrine pancreatic dysfunction, gastrointestinal disorders and infertility, and specifically in the lungs, reduced fluid secretion, which leads to the accumulation of thick, dehydrated mucus in the airways with resultant high susceptibility to repetitive bacterial lung infection, mainly by *Pseudomonas aeruginosa* and *Staphylococcus aureus* [7], which in turn causes pulmonary fibrosis. The protein defect is a result of CFTR gene autosomic disorder, and in 70% of cases the cause is a deletion of three nucleotides from the CFTR sequence that codes for the phenylalanine at position 508 (ΔF508). This information was not revealed until such techniques as DNA sequencing were applied in different CF patients. The ΔF508 mutation leads to misprocessing and subsequent degradation of the mutant protein in the endoplasmatic reticulum, preventing CFTR protein from arriving in the cellular membrane [8–11].

Knockout animal models

The second step in decoding the genome is to find out the exact function of genes after the whole genome is sequenced. To this end, molecular biology uses an important counting tool called the knockout technique, which allows genotype manipulation of an animal model in the form of removal of a gene so that further study of this gene function is possible, or of mutation of target genes to simulate common diseases and study the physiological function of the genes removed. A phenomenon called homologous recombination allows scientists to trade a whole gene in its locus for an engineered construct, which can even be the same gene with mutations (gene targeting). By mechanisms that are poorly understood but are similar to those occurring during meiosis and mitosis, when homologous chromosomes become aligned along the metaphase plane, the engineered construct, which includes some flanking DNA that is identical in sequence to the targeted locus, finds the targeted gene and recombination takes place within the homologous sequence. This procedure is the basis of the knockout technique. Embryonic stem cells that have been subjected to ablation or targeting mutation of the gene of interest are selected and injected into blastocysts, producing chimeras. Chimeras are crossed with each other until knockout or targeted homozygous offsprings appear. The absence or mutation of a gene makes it possible to understand its functions inside the organism or produces a study model for mutations that happen frequently in human beings.

In a very recent study conducted by Durie et al. in a CFTR knockout model in long-lived mice, the animals had symptoms similar to those found in the human form of cystic fibrosis, such as lung interstitial thickening and fibrosis, liver disease with hepatosteatosis, pancreas acinar atrophy and adherent fibrillar material in the ileal lumen and crypts, and these animals could be used as a model for testing drugs and therapies [12]. Another example, in lung, is the study that highlighted the importance of surfactant protein-D (SP-D) in an SP-D knockout mice model: delayed clearance of *Pneumocystis carinii* infection, increased lung inflammation and nitric oxide-altered metabolism were observed [13]. These are some examples of how powerful knowledge of molecular biology can be and how much it can add to the understanding of lung physiology and the origin of diseases affecting other organs.

Gene transfection

Another instrument commonly used to study gene function is the cloning technique, which allows expression of a gene product outside the genome. Cloning begins with the insertion of a gene into small circular molecules of DNA called plasmids, which are found in bacteria separate from the bacterial chromosome. They usually carry only one or several genes, have a single origin of replication and are used as vectors to deliver the gene under scrutiny. There are other vectors, such as cosmids or retroviruses, that are also used for the same purpose. Plasmids are a very interesting instrument, because they can also be overexpressed in bacteria and can be

transfected into cells lines in vitro or into organisms in vivo, permitting the expression of foreign genes. Transfection of wild-type CFTR and other commonly mutations to CF patients (ΔF508, G551D, R334W, R347P, A455E) to IB3 cells (a human bronchial epithelial cell line derived from a CF patient) and to *Xenopus* oocytes allowed comparison of the characteristics and functions of these mutated chloride channels and those of wild-type CFTR by electrophysiological methods [14, 15].

Polymerase chain reaction

Polymerase chain reaction (PCR) was the technique that revolutionised molecular biology and made the study of DNA easier. A pair of oligonucleotides, each complementary to one strand of DNA, called primers, containing a known portion of DNA, is incubated with DNA samples, free nucleotides and a DNA polymerase in a thermal cycler. Repeated cycles of 1 min or less at 94°C for denaturing DNA strands and a specific temperature for primer annealing usually with a range of 50–60°C, and 72°C for extension of the newly formed strands by DNA polymerase, lead to exponential amplification of the known portion of the DNA. This technique made it possible to amplify genes specifically and to use the amplified samples for sequencing and for the possible discovery of genetic disorders. The amplified PCR products can also be inserted in vectors, in the same way as plasmids, for cloning, sequencing or gene targeting. PCR can be very helpful in the detection of some mutations and infectious agents in different diseases, such as human cytomegalovirus (HCMV), which have been identified in small amounts in idiopathic interstitial pneumonia observed after allogeneic bone marrow transplantation [16].

Current research advances have brought about real-time PCR, with fluorescence-labelled primers or nucleotides that, once incorporated by the new strand, release their fluorescence and allow the amplification to be followed cycle by cycle, so that this is a more accurate technique. The use of this technique for diagnosis leads to rapid identification of organisms of clinical and epidemiological importance. *Streptococcus pneumoniae*, the leading cause of community-acquired pneumonia, is one of the lung infectious agents that can be specifically and rapidly identified using real-time fluorescence PCR [17].

Ribonucleic acid

Other molecules than DNA can be studied with the aim of understanding more of the molecular basis of life. Messenger RNA is a valuable tool, since it reflects the cell gene expression pattern, and it differs from DNA mainly in its structure and composition: (a) a single-stranded chain of RNAs, instead of deoxyribonucleic acids; (b) a uracil base instead of thymine. By measuring the mRNA quantities of a certain gene, we are able to analyse different expression characteristics of a cell, tissue or organism in different conditions, giving an insight into what happens at the molecular level to generate the known phenotypes.

Reverse transcription followed by PCR

Reverse transcription followed by polymerase chain reaction (RT-PCR) is the tool most frequently used for the study of mRNA expression. Basically, in order to have a PCR reaction, mRNA needs to be turned into a DNA strand. Reverse transcriptase, a DNA polymerase capable of using RNA moulds obtained from retroviruses, is used to transform mRNA, usually primed with oligonucleotide dTs (oligo-dT) that bind to the poly-A tail (only present in mRNAs), into complementary single-stranded DNA (cDNA). This cDNA is used in PCR reactions with primers specific to the gene under scrutiny to amplify the quantities of mRNA of that gene found in the cell.

Indirectly, RT-PCR can in fact identify the expression of specific genes, as seen when placental growth factor (PGF) expression was verified in small-cell lung cancers (SCLC) and non-small-cell lung cancers (NSCLC). PGF gene expression was identified in these cell lines and also showed a greater expression pattern in SCLC cell lines than in NSCLC cell lines [18], which conferred on this gene a medical importance as a tumour marker.

Other molecules can also indicate lung disease. In CF patients' airways epithelia an increased IL-8 mRNA expression was observed early in the disease by means of real-time RT-PCR, which shows the importance of this method as a diagnostic instrument [19].

RNase Protection Assay

Another important technique for the quantification of RNA is the RNase Protection Assay (RPA). This assay consists of an in vitro transcription of a (usually) radiolabelled antisense RNA probe that is complementary to the mRNA that is to be studied. This happens with the addition of free nucleotides, including labelled UTP or CTP, to a reaction with an RNA polymerase and a plasmid carrying the mould DNA fragment to synthesise the RNA probe. After the purification of these antisense RNA probes, RNA samples are incubated with it for 12–16 hours, after which complementary RNA anneals to the probe. After incubation, samples are digested with RNase, an enzyme responsible for cleavage of single-stranded molecules, and target mRNA will be protected from degradation by probe annealing. Samples are separated by denaturating urea gel electrophoresis and exposed to autoradiographic films, where the quantity of labelled probe will be relative to the quantities of target mRNA. This technique helped Murray et al. to elucidate the role of the CLC-2 chloride channel in lung embryology, showing that it is highly expressed in fetal lung and down-regulated after birth [20].

RNA interference

The newest technique involving RNA is RNA interference (RNAi), which is a major tool for use in silencing genes. The mechanisms of RNAi are based on the cellular delivery of long double-stranded RNAs (dsRNAs ~200 nt) that are processed into

small 20 - to 25 - nucleotide interfering RNAs (siRNAs) by an enzyme called DICER (RNase III-like enzyme). These siRNAs are assembled into complexes called RNA-induced silencing complexes (RISCs), which are responsible for the cleavage of cell target complementary mRNA molecules. The cellular delivery of long dsRNA initiates a potent antiviral response; in order to bypass this response, which can generate the inhibition of protein synthesis and RNA degradation, scientists started to introduce siRNAs into cells. Antisense oligonucleotides are commonly used to anneal to their complementary mRNAs that are to be degraded, and they cause silencing of the target gene. This technique can be adjusted to gene therapy in the lungs. It has already been shown that ZEB1 (a transcription repressor) suppression by RNAi leads to E-cadherin induction in different lung cancer cell lines. E-Cadherin loss is associated with cancer de-differentiation, invasion and metastasis [21].

DNA arrays

Most experiments in molecular biology work with analysis of one gene per experiment. A recent technique called DNA array uses chips to screen a biological sample for the presence of a large number of genetic sequences at once, showing interactions among thousands of genes simultaneously; the principle of this tool is simple base pairing or hybridisation. Arrays allow researchers to identify sequences (e.g. genes) or determine the expression levels of genes.

DNA arrays consist, first, of immobilisation of known DNA in a solid surface such as glass or nylon substrates using robot spotting. Arrays are used to detect the presence of any mRNAs that may have been transcribed from different genes. The cDNA labelled with fluorescent tags will pair to the spot at which the complementary DNAs are affixed. The spot will then be visualised, indicating that cells in the sample had recently transcribed a gene that contained the probed sequence. The intensity of the glow depends on how many copies of a particular mRNA were present and thus roughly indicates the expression level of that gene. Arrays indicate which genes in the genome are active in a particular cell type under a particular condition. Two cDNA samples tagged with different fluorochromes can reveal which genes have been transcribed in two different situations.

DNA arrays have been very important in the detection of different expression patterns in many situations, and also in the identification of mutations, such as those described by Sougakoff et al., in which various different rpoB (gene associated with antibiotic resistance) mutations are detected in clinical isolates of *Mycobacterium tuberculosis*, conferring rifampicim resistance [22]. Another great importance of DNA array is its capability of wide gene expression screening, as observed for gene expression in CF mouse small intestine, which revealed up-regulation of innate immune response genes and down-regulation of transport and lipid metabolism genes [23].

Protein

The mRNA is not always a reflex of the translation pattern of a cell. Processing of mRNA can lead to a minor quantity of translated protein, even with high levels of mRNA. This is why it is necessary to also study the protein product of genes.

Western blot

Many techniques have been developed to study protein expression. The most common tool is called western blot, an adaptation of one of the first experiments developed to study DNA and RNA: Southern and Northern blot, respectively. Western blot involves separation of sample proteins by size in a polyacrylamide gel electrophoresis and posterior transference of those proteins to a nitrocellulose membrane, which is incubated with primary antibody against target protein and secondary antibody that recognises the primary antibody conjugated to a detection molecule, e.g. alkaline phosphatase or peroxidase. This technique allows researchers to detect specific protein levels in different tissues or cells and/or evaluate different protein expression in different situations.

Western blot has proved a useful tool in establishing or excluding the diagnosis of bacterial or fungal pneumonia, as the presence of soluble TREM-1 protein (triggering receptor expressed in myeloid cells) in bronchoalveolar-lavage fluid from patients receiving mechanical ventilation may indicate pneumonia. The diagnosis and treatment of bacterial pneumonia in patients who are receiving mechanical ventilation is a difficult challenge, and these findings are very important as TREM-1 expression on phagocytes is up-regulated specifically by microbial products [24].

Immunolocalisation

Fixation of tissues or cells monolayers made it possible to localise proteins with antibody in situ, with an approach to what is happening inside the cell, the localisation of functional proteins and their traffic in the cytoplasm or inside organelles that is far closer to reality. Those of these techniques that are used in tissues are called immunohistochemical methods, or immunohistochemistry, and those used in cells are immunocytochemical techniques, or immunocytochemistry; their basic principle is incubation of cryostat or paraffin sections of tissue or cells with primary antibodies raised against the target proteins and then with a second antibody conjugated to fluorophores or enzymes, such as peroxidase or alkaline phosphatase. The primary antibody can also be conjugated to the detection molecules.

Diagnosis can be facilitated by immunohistochemistry, since it shows protein markers in their exact location throughout the tissue, as seen when mesothelioma is differentiated from renal cell carcinoma by means of a few markers [25]. Studies using these techniques have also helped a great deal in expanding out under-

standing of the physiology of lung disease. Lauredo et al. found that monocytes, neutrophils and alveolar macrophages might contribute to increased lung tissue kallikrein (TK) activity, a serine protease that is important in the pathophysiology of asthma and responsible for the generation of kallidin and bradykinin, mediators that contribute to airway hyperresponsiveness. Knowing the type of cells responsible for the production of TK in the airways could be important in understanding the mechanisms of inflammation that contribute to the pathophysiology of asthma and may help in the development of new therapies to control the disease [26].

Protein array

The newest technique in protein detection is the protein array, which establishes a means of detecting target proteins, monitoring their expression levels and investigating interactions and functions. Like the DNA array, it allows efficient, sensitive and high throughput protein analysis, carrying large numbers of determinations in parallel by the use of automated means. Protein array is poised to be the central proteomics technology, since the human proteome is much more complex than the genome, as reflected in the facts that many proteins can be derived from the same gene by alternative gene splicing and that proteins can even suffer post-translational modifications.

Protein arrays consist of binding assay systems using immobilised proteins on such surfaces as glass and membranes. Ligand-binding reagents, which can be antibodies, proteins or nucleic acids, are incubated with chips to reveal affinity spots. Proteins other than specific ligand binders can be used for in vitro functional interaction screenings between two proteins, between protein and DNA, between protein and drugs, etc. Software for data analysis can be easily adapted from that used for DNA arrays, as can the corresponding hardware and detection systems.

Many diagnoses are made in blood or urine samples by means of immunoassays such as ELISA (enzyme-linked immunosorbent assay), which is capable of identifying proteins in complex protein samples, using antibodies specific to the target protein. This kind of diagnosis can be used, for example, to detect HIV, pregnancy (chorionic gonadotrophin), or even pulmonary tuberculosis [27]. Microarray ELISA-style assays will accelerate immunodiagnostics significantly.

With regard to lung physiology, very few applications have been developed, since this technique is so new, but Chen et al. performed the identification of proteins associated with patient survival in lung adenocarcinoma. Morphologic assessment of lung tumours is informative, but not sufficiently so to provide adequate predictions of patient outcome. These studies identify new prognostic biomarkers and indicate that protein expression profiles can predict the outcome of patients with early-stage lung cancer [28].

Gene therapy

The most promising application of molecular biology is gene therapy, which is a technique for correcting defective genes responsible for disease development. The most common approach is the insertion of a normal gene into a nonspecific location within the genome to replace a nonfunctional gene, but there are others, such as exchanging the abnormal gene for a normal one by homologous recombination, repairing the abnormal gene by selective reverse mutation, or even altering the regulation (degree of transcription) of certain genes. The vectors used in gene therapy to deliver the gene to be inserted into the patient's target cells also vary. The most commonly used vectors are viruses, which have developed a way of encapsulating and delivering their genes to human cells in a pathogenic manner. By manipulating the virus genome, scientists can remove genes that cause disease and insert therapeutic genes. Many strands of viruses can be used in gene therapy: (a) retroviruses, a class of viruses that can create double-stranded DNA copies of their RNA genomes, which can then be integrated into the chromosomes of host cells (e.g. human immunodeficiency virus [HIV]) [29]; (b) adenoviruses, a class of viruses with double-stranded DNA genomes [30] that cause respiratory, intestinal, and eye infections in humans; (c) adeno-associated viruses, which are small, single-stranded DNA viruses that can insert their genetic material at a specific site on chromosome 19 [31]; (d) herpes simplex viruses, a class of double-stranded DNA viruses that infect mainly a particular cell type: neurons [32]. The major problem in using viruses is that they present various potential problems for the patient, such as toxicity and immune and inflammatory responses [33]. In addition, there is always the fear that the viral vector, once inside the patient, may recover its ability to cause disease. Besides virus-mediated gene-delivery systems, there are several nonviral vectors for gene delivery. The simplest methods are direct introduction of therapeutic DNA into target cells [34] and insertion of oligonucleotides complexes capable of correcting the abnormal gene into cells containing deletion mutations, restoring them to the normal cell genotype [35]; or the creation of an artificial lipid sphere with an aqueous core [36], which carries the therapeutic DNA (liposome/DNA complex) and is capable of passing the DNA through the target cell membrane. Despite being less immunogenic than vectors, liposome/DNA complexes have a low-level correction component and are extremely transient.

Besides the immune system barrier, there are also physical barriers that influence the effectiveness of gene therapy. For instance, the normal human airway surface reduces liposomal/DNA complex-mediated gene delivery by more than 75% [37], while thick inflammation from CF patients blocks and/or inactivates recombinant adenoviruses (rAV), liposome/DNA complex [37–39] and recombinant adeno-associated virus (rAAV) transduction in cells *in vitro* [40]. In addition to physical barriers, gene therapy has such shortcomings as (a) a short-lived nature because integrating therapeutic DNA into the genome and the rapidly dividing nature of many cells prevent gene therapy from achieving any long-term benefits; (b) multigene disorders, since some of the most commonly occurring disorders, such as heart disease, high blood pressure, Alzheimer's disease, arthritis and diabetes, are

caused by the combined effects of variations in many genes, which are especially difficult to treat effectively with gene therapy.

Among the genetic disorders affecting the lungs, cystic fibrosis is one of those that have been most extensively studied with reference to gene therapy. Clinical trials started in 1993, in CF patients in whom rAV was delivered to their nasal epithelium and corrected partial transient chloride transport defects [41], but other authors found that delivery of CFTR mediated by rAV to the nasal epithelium of CF patients failed to reproduce functional correction [42]. Adenovirally mediated delivery to the airways seems to result in low gene transfer (<1%), and at high doses it is associated with inflammatory responses to rAV [33, 43, 44]. Liposome/DNA complex vectors have also been tested in CF patients, and the first clinical trial demonstrated 20% restoration of transepithelial PD [45]. However, four of eight patients developed such reactions as fever, myalgias and anthralgia, associated with increased IL-6 expression [46].

Trials with rAAV type 2 delivered by aerosol administration demonstrated an absence of toxicity and vector genomes when quantified at 0.6 and 1 copy per cell at 14 and 30 days, respectively. Despite these promising results, no vector-derived mRNA was detected at any time [47], results already seen in vitro studies of human airway epithelia [48]. More recent clinical trials revealed advances in the tolerance to rAAV-2-containing CFTR gene therapy and some improvement in the pulmonary function of patients with CF [49].

Conclusions

As shown in this paper, molecular biology already has a major role in several fields of medicine, such as disease characterisation, identification and diagnosis. The advances in gene therapy suggest that molecular knowledge can change radically the concepts of medical treatments, since a large number of human disease are caused by genetic disorders. The improvements that the studies of molecular basis of life can bring to medical science are enormous, which justifies efforts to see that these two areas of science progress close together so as to develop better quality of life.

References

1. Peter JA (1959) Mendel's experiments in plant hybridizations. (Classic papers in genetics. Prentice-Hall, New Jersey
2. Hershey AD, Chase M (1952) Independent functions of viral protein and nucleic acid in growth of bacteriophage. J Gen Physiol 36:39-56
3. Watson JD, Crick FHC (1953) Molecular structure of nucleic acids: a structure for deoxyribonucleic acid. Nature 171:737-738
4. Watson JD, Crick FHC (1953) Genetical implications of the structure of deoxyribonucleic acid. Nature 171:964-967

5. Chargaff E (1951) Structure and function of nucleic acids as cell constituents. Fed Proc 10:654-659
6. Sanger F, Nicklen S, Coulson AR (1977) DNA sequencing with chain termination inhibitors. Proc Natl Acad Sci USA 74:5463–5468
7. Morales MM, Capella MA, Lopes AG (1999) Structure and function of the cystic fibrosis transmembrane conductance regulator (review). Braz J Med Biol Res 32:1021-1028
8. Dalemans W, Barbry P, Champigny G et al (1991) Altered chloride ion channel kinetics associated with the delta F508 cystic fibrosis mutation. Nature 354:526-528
9. Cheng SH, Gregory RJ, Marshall J et al (1990) Defective intracellular transport and processing of CFTR is the molecular basis of most cystic fibrosis. Cell 63:827-834
10. Kartner N, Augustinas O, Jensen TJ, Naismith AL, Riordan JR (1992) Mislocalization of delta F508 CFTR in cystic fibrosis sweat gland. Nat Genet 1:321-327
11. Kopito RR (1999) Biosynthesis and degradation of CFTR. Physiol Rev 79: s167-s173
12. Durie PR, Kent G, Phillips MJ, Ackerley CA (2004) Characteristic multiorgan pathology of cystic fibrosis in a long-living cystic fibrosis transmembrane regulator knockout murine model. Am J Pathol 164:1481-1493
13. Atochina EN, Gow AJ, Beck JM et al (2004) Delayed clearance of *Pneumocystis carinii* infection, increased inflammation, and altered nitric oxide metabolism in lungs of surfactant protein-D knockout mice. J Infect Dis 189:1528-1539
14. Schwiebert EM, Morales MM, Devidas S et al (1998) Chloride channel and chloride conductance regulator domains of CFTR, the cystic fibrosis transmembrane conductance regulator. Proc Natl Acad Sci USA 95:2674
15. Fulmer SB, Schwiebert EM, Morales MM et al (1995) Two cystic fibrosis transmembrane conductance regulator mutations have different effects on both pulmonary phenotype and regulation of outwardly rectified chloride currents. Proc Natl Acad Sci USA 92:6832-6836
16. Jiwa M, Steenbergen RD, Zwaan FE et al (1990) Three sensitive methods for the detection of cytomegalovirus in lung tissue of patients with interstitial pneumonitis. Am J Clin Pathol 93:491-494
17. McAvin JC, Reilly PA, Roudabush RM et al (2001) Sensitive and specific method for rapid identification of *Streptococcus pneumoniae* using real-time fluorescence PCR. J Clin Microbiol 39:3446-3451
18. Woo IS, Park MJ, Byun JH et al (2004) Expression of placental growth factor gene in lung cancer. Tumour Biol 25:1-6
19. Muhlebach MS, Reed W, Moah TL (2004) Quantitative cytokine gene expression in CF airway. Pediatr Pulmonol 37:393-399
20. Murray CB, Morales MM, Flotte TR et al (1995) CIC-2: a developmentally dependent chloride channel expressed in the fetal lung and downregulated after birth. Am J Respir Cell Mol Biol 12:597-604
21. Ohira T, Gemmill RM, Ferguson K et al (2003) WNT7a induces E-cadherin in lung cancer cells. Proc Natl Acad Sci USA 100:10429-10434
22. Sougakoff W, Rodrigue M, Truffot-Pernot C et al (2004) Use of a high-density DNA probe array for detecting mutations involved in rifampicin resistance in *Mycobacterium* tuberculosis. Clin Microbiol Infect 10:289-294
23. Norkina O, Kaur S, Ziemer D et al (2004) Inflammation of the cystic fibrosis mouse small intestine. Am J Physiol Gastrointest Liver Physiol 286:G1032-1041
24. Gibot S, Cravoisy A, Levy B et al (2004) Soluble triggering receptor expressed on myeloid cells and the diagnosis of pneumonia. N Engl J Med 350:451-458
25. Ordonez NG (2004) The diagnostic utility of immunohistochemistry in distinguishing

between mesothelioma and renal cell carcinoma: a comparative study. Hum Pathol 35:697-710
26. Lauredo IT, Forteza RM, Botvinnikova Y et al (2004) Leukocytic cell sources of airway tissue kallikrein. Am J Physiol Lung Cell Mol Physiol 286:L734-L740
27. Meyer G, Roy PM, Sors H, Sanchez O (2003) Laboratory tests in the diagnosis of pulmonary embolism (review). Respiration 70:125-132
28. Chen G, Gharib TG, Wang H et al (2003) Protein profiles associated with survival in lung adenocarcinoma. Proc Natl Acad Sci USA 100:13537-13542
29. Kobinger GP, Weiner DJ, Yu QC et al (2001) Filovirus-pseudotyped lentiviral vector can efficiently and stably transduce airway epithelia in vivo. Nat Biotechnol 19:225-230
30. Song JS, Kim HP (2004) Adenovirus-mediated HSV-TK gene therapy using the human telomerase promoter induced apoptosis of small cell lung cancer cell line. Oncol Rep 12:443-447
31. Auricchio A, O'Connor E, Weiner D et al (2002) Noninvasive gene transfer to the lung for systemic delivery of therapeutic proteins. J Clin Invest 110:499-504
32. Natsume A, Wolfe D, Hu J et al (2003) Enhanced functional recovery after proximal nerve root injury by vector-mediated gene transfer. Exp Neurol 184:878-886
33. Joseph PM, O'Sullivan BP, Lapey A et al (2001) Aerosol and lobar administration of a recombinant adenovirus to individuals with cystic fibrosis. I. Methods, safety, and clinical implications. Hum Gene Ther 12:1369-1382
34. Yoshida M, Iwasaki Y, Asai M et al (2004) Gene therapy for central diabetes insipidus: effective antidiuresis by muscle-targeted gene transfer. Endocrinology 145:261-268
35. Zamecnik PC, Raychowdhury MK, Tabatadze DR et al (2004) Reversal of cystic fibrosis phenotype in a cultured Delta508 cystic fibrosis transmembrane conductance regulator cell line by oligonucleotide insertion. Proc Natl Acad Sci USA 101:8150-8155
36. Li HY, Neill H, Innocent R et al (2003) Enhanced dispersibility and deposition of spray-dried powders for pulmonary gene therapy. J Drug Target 11:425-432
37. Kitson C, Angel B, Judd D et al (1999) The extra- and intracellular barriers to lipid and adenovirus-mediated pulmonary gene transfer in native sheep airway epithelium. Gene Ther 6:534-546
38. Stern M, Caplen NJ, Browning JE et al (1998) The effect of mucolytic agents on gene transfer across a CF sputum barrier in vitro. Gene Ther 5:91-98
39. Perricone MA, Rees DD, Sacks CR et al (2000) Inhibitory effect of cystic fibrosis sputum on adenovirus-mediated gene transfer in cultured epithelial cells. Hum Gene Ther 11:1997-2008
40. Virella-Lowell I, Poirier A, Chesnut KA, Brantly M, Flotte TR (2000) Inhibition of recombinant adeno-associated virus (rAAV) transduction by bronchial secretions from cystic fibrosis patients. Gene Ther 7:1783-1789
41. Zabner J, Couture LA, Gregory RJ et al (1993) Adenovirus-mediated gene transfer transiently corrects the chloride transport defect in nasal epithelia of patients with cystic fibrosis. Cell 75:207-216
42. Knowles MR, Hohneker KW, Zhou Z et al (1995) A controlled study of adenoviral-vector-mediated gene transfer in the nasal epithelium of patients with cystic fibrosis. N Engl J Med 333:823-831
43. Zuckerman JB, Robinson CB, McCoy KS et al (1999) A phase I study of adenovirus-mediated transfer of the human cystic fibrosis transmembrane conductance regulator gene to a lung segment of individuals with cystic fibrosis. Hum Gene Ther 10:2973-2985
44. Bellon G, Michel-Calemard L, Thouvenot D et al (1997) Aerosol administration of a recombinant adenovirus expressing CFTR to cystic fibrosis patients: a phase I clinical trial. Hum Gene Ther 8:15-25

45. Caplen NJ, Alton EW, Middleton PG et al (1995) Liposome-mediated CFTR gene transfer to the nasal epithelium of patients with cystic fibrosis. Nat Med 1:39-46
46. Ruiz FE, Clancy JP, Perricone MA et al (2001) A clinical inflammatory syndrome attributable to aerosolized lipid-DNA administration in cystic fibrosis. Hum Gene Ther 12:751-761
47. Aitken ML, Moss RB, Waltz DA et al (2001) A phase I study of aerosolized administration of tgAAVCF to cystic fibrosis subjects with mild lung disease. Hum Gene Ther 12:1907-1916
48. Duan D, Yue Y, Yan Z et al (2000) Endosomal processing limits gene transfer to polarized airway epithelia by adeno-associated virus. J Clin Invest 105: 1573-1587
49. Moss RB, Rodman D, Spencer LT et al (2004) Repeated adeno-associated virus serotype 2 aerosol-mediated cystic fibrosis transmembrane regulator gene transfer to the lungs of patients with cystic fibrosis: a multicenter, double-blind, placebo-controlled trial. Chest 125:509-521

Chapter 25

Surfactant metabolism: factors affecting lipid uptake in vivo and in vitro

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Kurt von Neergaard [1] was the first to draw attention to the role of surface tension within the lung. In 1929, he demonstrated that the pressure needed to inflate a fluid-filled lung with fluid was less than approximately one third to one quarter of the pressure necessary to inflate an air-filled lung with the same volume of air (Fig. 1 [1]). From these experiments he concluded that about two thirds of the retractive forces were due to surface tension phenomena acting at the air–liquid interface within the lung; this implies that this surface tension at the alveolar level is reduced by the presence of a surface-active agent with a low surface tension to allow normal breathing.

Unfortunately, these findings were published only in German, and for approximately 25 years they remained practically unnoticed by other scientists in the

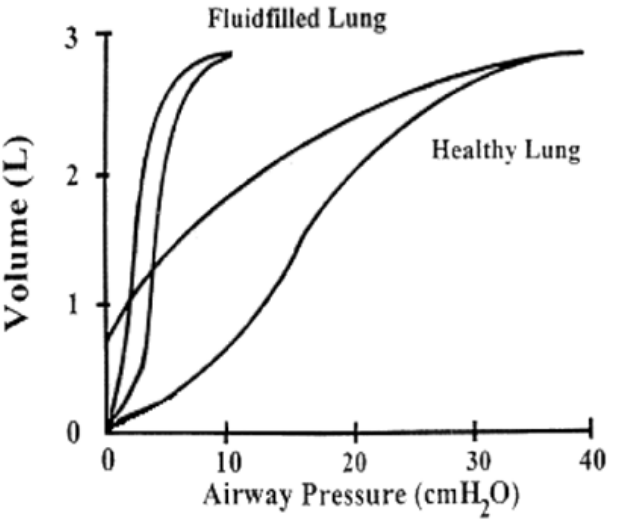

Fig. 1. Pressure volume diagram of a healthy air-filled lung and a lung affected by ARDS. In ARDS higher pressures are required to expand the lung than when the lung is healthy, because of the high surface tension at the air–liquid interface in the alveoli, which is caused by surfactant inactivity. (Adapted from [1])

field. The next description of the presence of a surface active agent within the lung was in 1954 by Macklin, who described a thin aqueous mucoid film that was formed by granular pneumocytes on the alveolar wall and which moved constantly towards bronchioles and phagocytic pneumocytes [2]. The following year, it was noted by Pattle et al. that the foam and bubbles from lung oedema and healthy lung cuts had a remarkable stability; they concluded that these bubbles consisted of a surface-active agent that was able to lower surface tension towards zero [3].

In 1957, Clements used the Wilhelmy balance to demonstrate that the surface tension derived from the alveolar lining fluid of the lung was not a constant value; with a large surface the surface tension was high, but when the surface area was decreased surface tension fell to values near zero [4].

Avery and Mead made the first steps towards extensive research on this surface-active agent, called pulmonary surfactant, by demonstrating higher surface tension in very small premature infants and infants who died of respiratory failure due to hyaline membrane disease [5]. Even today, almost half a century later, small steps are still being made towards better understanding of this surface-active agent.

Pulmonary surfactant

This pulmonary surfactant, lining the alveolar surface, is a complex of lipids and proteins produced in the alveolar type II cells and secreted into the alveolar space.

Lipids

The lipid composition is generally the same in both compartments [6, 7]. Most of the lipids are phospholipids (80–90%), and in decreasing order of content are cholesterol, triacylglycerol and free fatty acids [7] (Fig. 2). Phosphatidylcholine (PC) compromises most of the phospholidids (70–80%), and approximately 50% of it is disaturated (DPPC) [6, 8].

This subgroup of PC is an unusual species, with palmatic acid at both the 1- and the 2-position rather than a saturated fatty acid at the 1-position and an unsaturated fatty acid at the 2-position of the diacylglycerolphospholipid found in most mammalian tissues; although not specific for surfactant (because it is also found in other tissues) it compromises a very high percentage of the surfactant phospholipids.

Even in early fetal gestation, about 20% of the total amount of PC retrieved from the lung is DPPC [9]. This DPPC is the main surface tension-lowering phospholipid in the lung. Although only a small fraction of the extracellular DPPC is necessary to cover the alveolar wall throughout the lung with a monolayer (as calculated by Wright and Clements [10]), its pool size is tightly regulated. For example, short-term decreases in the amount of DPPC due to an abnormal nutritional state, such as fasting [11], fatty acid deficiency [12] or choline deficiency [13], are replenished rapidly by adaptation mechanisms [14].

Next, all mammalian pulmonary surfactants have been shown to contain significant amounts of phosphatidylglycerol (PG) (7–18%) and phosphatidylinositol

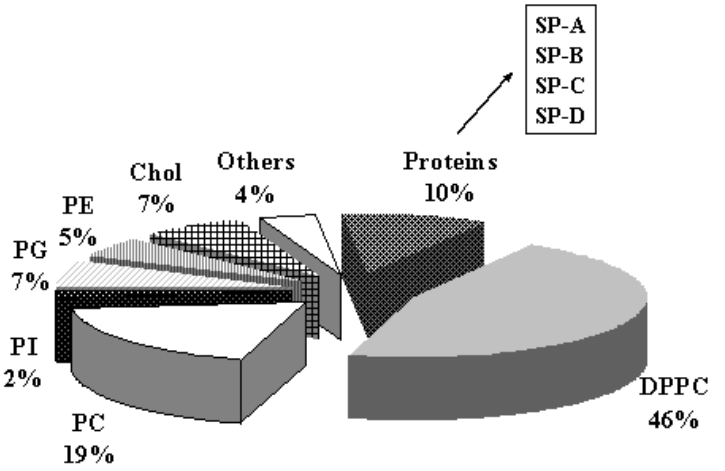

Fig. 2. Schematic overview of surfactant composition. *PC* phosphatidylcholine, *DPPC* dipalmitoylphosphatidylcholine, *PI* phosphatidylinositol, PG phosphatidylglycerol, *PE* phosphatidylethanolamine, *Chol* cholesterol

(PI) (2–4%) [15], suggesting a specific role of these acidic phospholipids. In adult mammalians, PG is the second major lipid component after PC, comprising approximately 5–10% of total surfactant phospholipids in humans [7, 16-18] and rats [6, 19]. However, in preterm fetal lungs the PG component of surfactant is extremely small, although its relative absence is compensated by an increased amount of PI in the surfactant compartments [8, 20–22].

When DPPC is mixed with PG or PI, adsorption of the lipids in the monolayer is enhanced, indicating that these negatively charged lipids may play an important role in the surface tension-lowering activity of surfactant. For PG, this enhanced adsorption may be caused by a specific interaction between PG and SP-B [23, 24].

Finally, the remaining phospholipids consist mainly of phosphatidyl-ethanolamine (PE) (2–3%) and some other minor phospholipids, whereas the total surfactant is completed by cholesterol [15].

Proteins

Pulmonary surfactant contains at least four surfactant proteins (SP), SP-A, SP-B, SP-C and SP-D. Of these proteins, SP-A and SP-D are hydrophilic proteins and SP-B and SP-C are hydrophobic.

SP-A has been studied extensively, and although its role is not yet completely clear it is suggested that it has an important role in regulating surfactant function

via binding to phospholipids [25, 26], modifying phospholipid structure to tubular myelin [27, 28], maintaining the surface properties of surfactant [29], regulating secretion and clearance of surfactant [30-37] and regulating alveolar macrophage function [38], as well having a possible role in the immunological properties of surfactant [38, 39].

SP-B and SP-C are two hydrophobic proteins that are known to play an important part in the formation of a stable lipid monolayer. Especially SP-B has been shown to be essential for normal surfactant function, lowering surface tension [40, 41]; absence of SP-B at birth leads to death caused by respiratory insufficiency [42, 43], and conditional knockout of SP-B in adult animals leads to respiratory failure [44]. In addition, it has been suggested that SP-B has a role in protection of the surfactant system against endotoxin-induced lung inflammation by enhancing surfactant function, resulting in reduced lung injury, decreased influx of inflammatory cells and lower cytokine levels [45].

SP-C also enhances the surface-active properties of surfactant [40, 41, 46-48]. Although (unlike SP-B) its absence at birth is not lethal, it does result in decreased stability of surfactant at low volumes even though surfactant pool sizes and lung morphology are similar in wild-type and SP-C knockout mice [49]. Another function of SP-C is to increase the resistance of surfactant against inactivation by plasma proteins [50]. On the other hand, elevated expression of SP-C is thought to be related to cytotoxicity and, ultimately, altered lung development [51]. Though it is thought that SP-D might be the fourth surfactant protein, it is not found only within the lung but also in other organ systems, and its specific contribution with regard to surfactant is not completely clear; however, several studies have suggested that, together with SP-A, it has an immunomodulatory role in the lung [39, 52-55].

Metabolism

The presence of surfactant within the alveolus is the result of a complex system of production, secretion, insertion into the lipid monolayer and turnover, uptake and recycling (Fig. 3).

Production and secretion

Surfactant phospholipids are produced by alveolar type II cells which comprise only 15% of the total number of cells in the lung [56-58]. The de novo synthesis of surfactant is thought to be relatively slow, especially in newborn animals [59, 60] and also in humans, as demonstrated by Bunt et al. using stable isotopes [61]. Bunt et al. also demonstrated that the use of prenatal corticosteroids increased surfactant synthesis in the preterm infant [62] and in very premature baboons [63]. Therefore, most surface-active surfactant is produced by recycling. Martini et al. have demonstrated that approximately 50–90% of the PC in surfactant is recycled, depending on age and species, the contribution of recycling decreasin with increasing age [64]. The surfactant lipids are synthesised in the endoplasmatic reticulum and then stored

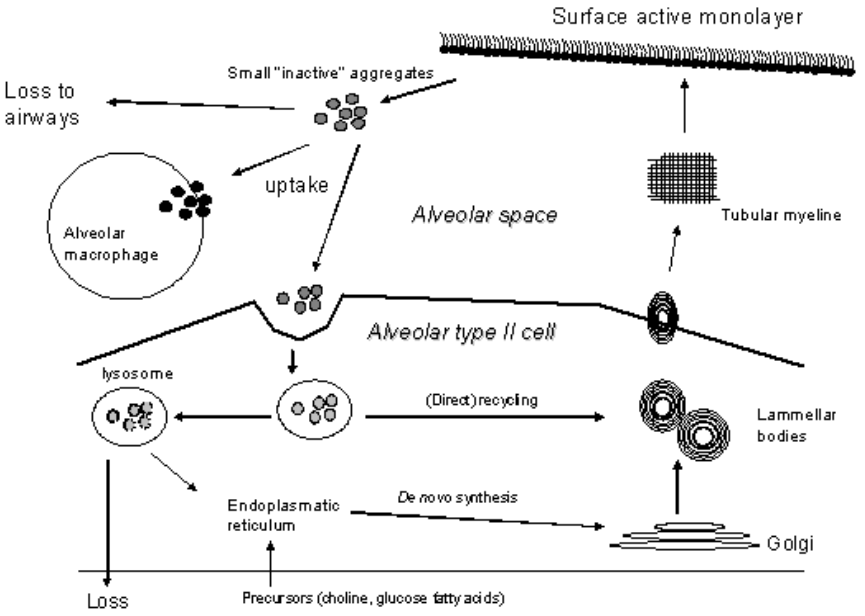

Fig. 3. Diagram showing surfactant metabolism

in lamellar bodies [65, 66]. In these lamellar bodies surfactant-specific proteins A, B and C are already present [67]; however, the content of SP-A is extremely low (1%), suggesting that the SP-A present in the alveolar space might be derived from parts other than lamellar bodies. When the alveolar type II cell is stimulated, intracellular effectors diffuse and activate the movement of the lamellar bodies to the apical plasma membrane of the alveolar type II cells and the content of the lamellar bodies is secreted into the alveolar space by a process of regulated exocytosis [58, 68, 69]. (For more details on the regulation of secretion see [56, 70, 71].)

After excretion into the alveolar space the lamellar bodies unravel and form tubular myelin after association with SP-A [28, 72]. Subsequently, the material of the lamellar bodies is absorbed/inserted into the lipid monolayer. This tubular myelin is most probably the immediate precursor for lipids inserted into the monolayer; however, it should be noted that SP-A knockout mice do not produce normal tubular myelin and the structure and in vitro properties of surfactant have changed. However, the in vivo function of surfactant in SP-A knockout mice has not changed, and thus tubular myelin is not essential for normal lung function [74].

Conversion of surfactant

During respiration the surfactant in the lipid monolayer is converted from large surface-active aggregates into small inactive surfactant aggregates [74–76]. However, little is known about the exact mechanism of this conversion. These small aggregates are not surface active and are removed from the alveolar space to be reutilised or recycled to ensure the presence of surface active aggregates in the lipid monolayer.

Uptake/removal of small aggregates

The converted, inactivated surfactant is cleared from the alveolar space mainly by way of uptake by alveolar type II cells and alveolar macrophages. However, their relative contribution to the uptake of surfactant lipids remains obscure and is dependent on several factors. In vitro studies suggest a major role for alveolar macrophages [77], whereas in vivo experiments suggest an equal contribution or even a major role for alveolar type II cells in the clearance of surfactant [78–80].

Because of the need for recycling, as suggested previously, re-uptake of surfactant by alveolar type II cells is essential, and this is possibly a crucial factor in the surfactant metabolism. Unfortunately, little is known about the regulation and mechanisms of removal of surfactant from the alveolar space by alveolar type II cells and alveolar macrophages.

This uptake of surfactant lipids is thought to take place (at least in part) via a coated-pit pathway [81–83]. More recently, it was demonstrated that all surfactant phospholipids are internalised via the same pathway by alveolar macrophages and alveolar type II cells, though alveolar cells have a higher affinity for negatively charged phospholipids [84]. In addition, the surfactant proteins are known to affect the uptake, especially SP-A [34, 36, 80, 85, 86].

Measuring uptake

Most studies on surfactant metabolism, especially those focused on the uptake of surfactant lipids by alveolar type II cells and alveolar macrophages, have used radioactive labeled DPPC to measure the uptake. In addition, most studies have been performed in an in vitro setting, whereas in vivo studies have focused mainly on alveolar macrophages. Unfortunately, the use of radioactivity does not discriminate between uptake or intracellular presence of the label and association with the outer cell membrane or adherence. In addition, it is not possible to specify precisely which cells are involved in the 'uptake', as whole-lung tissue is tested for radioactivity.

Recently, we described a method using fluorescence-labeled liposomes to study the uptake of surfactant-like liposomes both in vivo and in vitro and in both alveolar type II cells and alveolar macrophages [87]. Our method mimics the small aggregates of surfactant, as these are the surfactant aggregates generally thought to

be removed from the alveolar space. In addition, confocal laser microscopy can be used to demonstrate that the fluorescence-labeled liposomes are indeed intracellularly located rather than adherent to the outer cell membrane.

More interestingly, when our method is used it is not DPPC that is labeled but PE, a minor component of surfactant, as a part of liposomes consisting of the main lipid components of surfactant, providing the opportunity to study the role of the main lipid components in regulation of the uptake of surfactant.

One of the advantages of the use of fluorescence-labeled liposomes is the possibility of focusing on one particular cell type; with the use of specific fluorescence-labeled antibodies it is possible to discriminate between different cell types and study their relative contributions or roles in the removal of surfactant lipids and possible mutual regulation of the uptake; even more specifically, it is possible to determine whether all cells or just a subpopulation of cells are involved in the uptake. Another important advantage of the method described by our group is that it allows the measurement of uptake by alveolar type II cells and alveolar macrophages both in vivo and in vitro. We believe we were the first to demonstrate that in vivo a significantly smaller percentage of the alveolar type II cells is involved in the uptake than in vitro; this indicates the need to study uptake both in vitro and in vivo (Fig. 4).

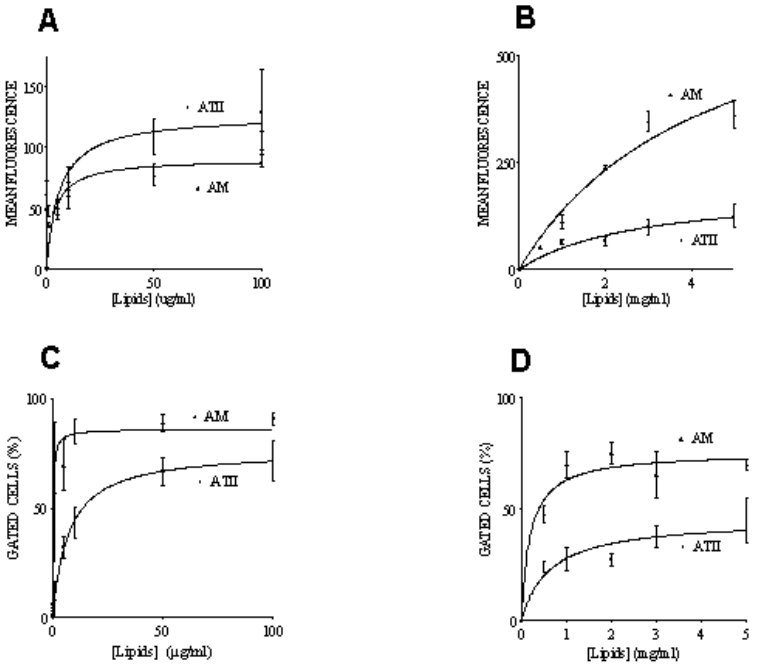

Fig. 4A–D. Differences in uptake in vivo and in vitro. Cell-associated fluorescence as a measure of the uptake of surfactant-like liposomes was determined for different concentrations of labeled liposomes both in vitro (**A**, **C**) and in vivo (**B**, **D**). In addition, the percentage of cells involved in the uptake was determined. (Data derived from [94]). *ATII* alveolar type II cells, *AM* alveolar macrophages

Effect of lipid composition on uptake

The composition of surfactant is largely similar across different species, including humans [88, 89]; however, small differences in the relative concentrations of the individual lipids are observed, which are also related to age. For example, fetal or neonatal surfactant contains a larger percentage of phosphatidylinositol and less phosphatidylglycerol, whereas adult surfactant contains more phosphatidylglycerol than phosphatidylinositol [15]. In addition, neonates have been shown to rely more on recycling, and thus uptake, than do adults [59, 64], which suggests a possible effect/role of the lipid composition on the uptake. Moreover, severe lung injury (initiated by a wide variety of causes) is known to be related to alterations in the lipid composition of surfactant [90, 91], which could also contribute to a decreased surfactant function, implying an effect of the different surfactant lipids on the uptake. However, it is still not known how these alterations in composition are related to the disease.

Bates et al. [92] and Chander et al. [93] were the first to report on the influence of the individual surfactant lipids on uptake, demonstrating that radiolabeled PG was cleared more rapidly by alveolar type II cells in vitro. This higher uptake of PG than of DPPC in vitro was also demonstrated for alveolar macrophages [94].

More recently, we have demonstrated a common pathway for the uptake of surfactant lipids by both cell types in vitro [84]. A significantly lower percentage of alveolar type II cells than of alveolar macrophages is involved in the uptake of DPPC (29% vs 72%, respectively), whereas the number of cells involved in the uptake of PG is approximately the same. The presence of a possible phospholipid receptor would simplify the explanation of these results. A different distribution of this phospholipid receptor to alveolar macrophages and type II cells might be the reason for the difference in the percentages of these cells involved in the uptake. The uptake of DPPC requires more receptors than the uptake of, for instance, PG; or, more generally, more negatively charged than neutrally charged phospholipids are taken up, and the negatively charged phospholipids are taken up more easily. A higher receptor density on alveolar macrophages than on alveolar type II cells, and the presence of several subpopulations of type II cells with different receptor densities could explain the lower percentage of alveolar type II cells than of alveolar macrophages.

These results relating to the role of individual surfactant lipids indicate that, besides surfactant proteins, the phospholipid composition of the small aggregates affects the surfactant metabolism. However, the relevant studies were performed in vitro, whereas significant differences have been demonstrated in the uptake of surfactant-like liposomes by alveolar cells in in vivo and in vitro experiments, and extrapolation of these results to the in vivo situation should be done with caution [87].

The effects of lipid composition in vivo was studied by increasing the amount of PG, the second major phospholipid, present in the small aggregates. The incorporation of PG influences the uptake of surfactant-like liposomes by alveolar cells, though the effects on the two cell types differ. The uptake of surfactant-like liposomes by alveolar type II cells is hardly affected by different concentrations of

PG. More interestingly, however, the influence of the intratracheal instillation of PG-containing liposomes on alveolar macrophages is dramatic; in particular, the number of alveolar macrophages obtained in the lung lavage is influenced by the amount of PG. In addition, not only does an increase in the amount of PG reduce the number of alveolar macrophages, but this decrease in the number of cells is accompanied by a deterioration in arterial oxygenation. Although PG does not interfere with the function of endogenous surfactant in vitro, as was tested, its increase does lead to reduced surface activity in vivo. Moreover, these adverse affects of PG on endogenous surfactant function can be avoided by adding so-called co-factors, such as calcium or magnesium.

The 'fatal' effect of PG on alveolar macrophages, as suggested by our group, is absent in vitro, because in that setting the aforementioned co-factors are already present during incubation. However, the effects of PG on the uptake of surfactant-like liposomes by alveolar type II cells in vivo are completely different from those derived from the in vitro experiments, even when co-factors are present. In vitro, increased concentrations of PG result in an increased uptake of these liposomes by alveolar type II cells, whereas the uptake of these liposomes by alveolar type II cells in vivo is hardly affected by the concentration of PG within the liposomes, irrespective of the presence of the suggested co-factors. These results underline the presence of 'environmental' factors that influence the uptake in vivo and thus emphasise the need to study the uptake of lipids and/or surfactant by alveolar type II cells and alveolar macrophages both in vivo and in vitro.

Effect of surfactant proteins

As previously mentioned, surfactant contains four proteins: SP-A, SP-B, SP-C and SP-D. The first, SP-A, has been extensively studied and is thought to fulfil several roles within surfactant homeostasis, especially in regulation of the clearance of surfactant from the alveolar space [85].

Next, both SP-B and SP-C are known to be important for the surface-active surfactant monolayer [40–44, 95, 96]. On the other hand, as far as the effects on the uptake of surfactant by alveolar cells are concerned, SP-B is capable of increasing the uptake of lipids by alveolar cells [36, 97] (Poelma et al., submitted for publication); however, high concentrations of SP-B are required to induce this increase, which raises the question of the physiological contribution of SP-B to regulation of the uptake of surfactant lipids by alveolar cells. On the other hand, SP-C has a similar function to SP-B with regard to enhancing surface-active properties of surfactant [40, 41, 46–48], but it should be noted that SP-C increases the uptake of surfactant-like liposomes at lower concentrations than SP-B. This effect of SP-C is concentration dependent, with a maximum at 2% SP-C. In addition, the presence of co-factors (such as calcium) within the liposomes decreasing the possibility of dilution of the endogenous pool has been shown to further increase the effect of SP-C. When 1% SP-C is incorporated the uptake is already increased, but the maximum increase is at 2% (Poelma et al., submitted for publication). However, the effects of SP-C on the uptake of surfactant-like liposomes are suggested to be

suppressed in vivo, since in vitro experiments have shown a much larger effect, more specifically a nonsaturable effect, on uptake [36, 97]. Furthermore, SP-C is known to combine very rapidly with lung tissue and alveolar macrophages [98, 99]. This increased association, coming about even more rapidly than an association with DPPC, might be an explanation for the increased uptake of liposomes containing SP-C. Nonetheless, other factors, such as the conformational changes observed in liposomes after the incorporation of SP-C, may also affect the binding and uptake of these liposomes by alveolar cells, as suggested by Rice et al. [100]. Finally, the presence of a putative SP-C receptor could also induce increased uptake. However, because its presence has not yet been demonstrated, further studies are needed on this point.

Effect of surfactant therapy

Currently, exogenous surfactant is increasingly used in the clinical setting, mostly in neonates but its use in adults is now under consideration [101]. However, the administration of exogenous surfactant is known to influence the endogenous surfactant. Most studies have focused on the effects of exogenous surfactant on the production and/or secretion of DPPC, and they have yielded conflicting results [33, 102–105]. In premature infants with respiratory distress syndrome, treatment with exogenous surfactant stimulates the synthesis of endogenous surfactant [106]. Little is known about the clearance or uptake of surfactant. Exogenous surfactant is taken up by alveolar type II cells and alveolar macrophages [107–10]; however, the specific effects of exogenous surfactant, i.e. surface-active surfactant, on the clearance of non-surface-active surfactant, whether endogenous or exogenous, is unknown. Our group has demonstrated significant effects of exogenous surfactant on the clearance of surfactant-like liposomes (unpublished data). Nevertheless, the effect of exogenous surfactant on uptake differs significantly between in vivo and in vitro conditions.

Effect of surfactant protein analogues

As previously mentioned, SP-B is essential for the biophysical properties of pulmonary surfactant, and its presence is thus the most highly appreciated in exogenous surfactant.

The high cost of naturally derived exogenous surfactant increases the demand for a synthetically produced surfactant. Therefore, synthetic analogues of SP-B based on the known human amino-acid sequence have been tested and closely mimic the function of natural surfactant proteins [111]. In addition, these SP-B analogues might be optimised: only essential parts of SP-B are reproduced and further developed, to increase the efficiency of SP-B within the exogenous surfactant preparation. SP-B analogues are based on the 1-25 sequence of the N-terminal site of human SP-B with a modification at position 11: cysteine is replaced by alanine (Cys-11>Ala-11) [112, 113]. A mutant SP-B (serine SP-B-1-25) was synthesised with site-specific substitu-

tion of serine for arginine in positions 12 and 17 and for lysine in positions 16 and 24 of the N-terminal (Fig. 5). A disulfide-linked homodimer of these SP-B analogues was formed by oxidising the monomeric SP-1-25 peptide [112, 113].

The serine-SP-B-1-25 analogues have been shown to be less surface active than the SP-B-1–25 variants. We have shown that the less surface-active SP-B analogues, the SP-B serine variations, reduce the uptake of surfactant-like liposomes by alveolar type II cells when incorporated into the liposomes; on the other hand, the SP-B-1-25 analogues mimic the effect of native SP-B and do not induce any changes in the uptake of liposomes by alveolar type II cells (unpublished data). With regard to the uptake of these liposomes with SP-B analogues incorporated by alveolar macrophages, our group has demonstrated that the surface-active SP-B analogues influence the uptake by alveolar macrophages (unpublished data).

SP-C has also been shown to enhance the surface-tension-lowering properties of surfactant; therefore, surfactant preparations intended for clinical use will most probably contain not only SP-B but also SP-C. The use of recombinant SP-C (rSP-C) in surfactant preparations is under investigation, to establish the efficiency of this SP-C in enhancing the surface-tension-lowering activities of surfactant [111, 114–116]. In terms of surface-tension-lowering activity, rSP-C surfactant (Altana, Konstanz, Germany) has similar results to natural surfactant [117, 118]. This rSP-C surfactant contains an SP-C that is an analogue of human SP-C; it contains pheny-

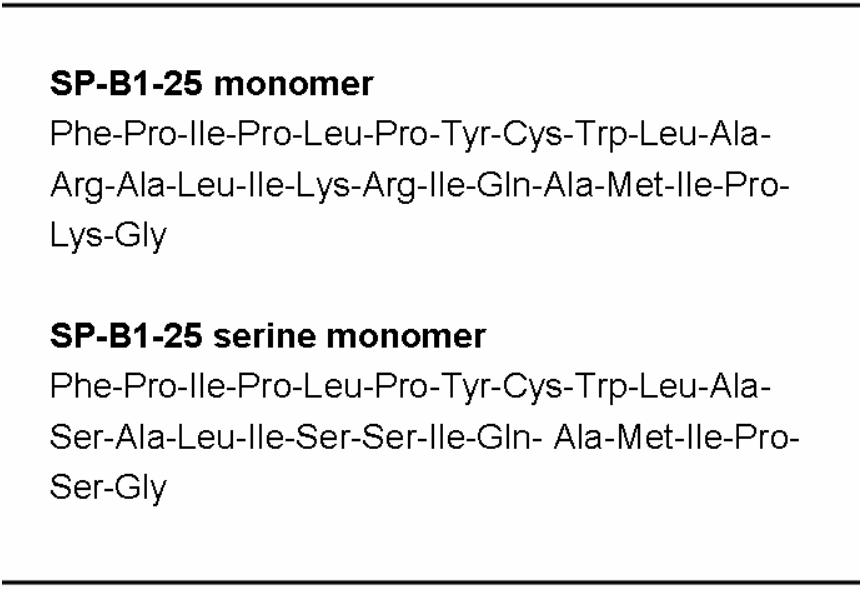

Fig. 5. Peptide sequences of the SP-B analogues and their serine mutants. The SP-B1-25 homodimer consists of two SP-B1-25 monomers disulfide-linked at Cys8 (not shown). The fluorescent label was inserted in all peptides at the N-terminus, shown at the left side of the sequence

lalanine instead of two cysteines in positions 4 and 5 of the human SP-C sequence, and isoleucine instead of methionine in position 32. However, the effects of these SP-C-analogues on the uptake, or more generally on the metabolism of surfactant, are not known. Our group has shown that the uptake of surfactant lipids by alveolar type II cells and alveolar macrophages is regulated by SP-C (Poelma et al., submitted for publication), and the influence of recombinant SP-C on surfactant metabolism therefore needs to be clarified.

Additional factors influencing surfactant uptake

Finally, besides factors related directly to surfactant, our group has shown that multiple 'environmental' factors influence and affect the surfactant metabolism. Some of these factors have been described previously; for example, calcium has been shown to influence the metabolism, insofar as its presence PG promotes the association of SP-A and DPPC [119, 120], and to affect the function of SP-B [29, 121]. The effects or influences of these alveolar factors (e.g. divalent cations, as suggested by the study of our group with regard to the effects of SP-B and SP-C) are also underlined by the fact that in vivo and in vitro results differ significantly, even when the absence or dilution of known co-factors such as calcium are compensated for. It should be emphasised that in our opinion in vitro experiments are indeed useful, although caution must be exercised in extrapolation of their results to the in vivo situation. Use of a similar technique for both in vivo and in vitro studies enables the researcher to compare the results and might help to clarify the complex mechanism of the regulation of uptake of surfactant lipids by alveolar cells in vivo.

In addition, although most studies on the uptake of surfactant have focused on healthy animals, many different diseases can disturb the surfactant system, and the presence of cytokines and other inflammatory parameters are known to affect the presence of surface-active surfactant in the lung. For example, tumor necrosis factor (TNF)-α, interleukin (IL) -1 and interferon (IFN)-γ are known to influence the production of SP-A, SP-B and SP-C, which regulates the uptake of surfactant by alveolar cells and thus affects the total metabolism [122–126]. In addition, prenatal steroids have been shown to increase surfactant synthesis [62].

Future studies

Because the uptake of surfactant in healthy adult animals has been clarified to some extent, future research could focus on the uptake of surfactant-like liposomes, with different models used for diseased animals. Possible irregularities in uptake and thus in endogenous surfactant metabolism might be elucidated. The known regulatory factors, at least those clarified hitherto, will then provide options for restoration of normal metabolism by influencing the uptake. For example, if uptake of surfactant is reduced in a certain disease state, it might be beneficial to increase the concentration of PG within the surfactant preparation used for therapy. In other words, clarifying regulating factors in the surfactant uptake and uncovering irregularities in the meta-

bolism, or more specifically in the uptake of surfactant, will allow the development of an exogenous surfactant preparation that is disease specific, by modifying the composition depending on the underlying deviation from normal.

References

1. Von Neergaard K (1929) Neue Auffassungen über einen Grundbegriff der Atemmechanik; Die Retraktionskraft der Lunge, abhängig von deer Oberflächenspannung in den Alveolen. Z Ges Exp Med 66:373-394
2. Macklin CC (1954) The pulmonary alveolar mucoid film and pneumocytes. Lancet II:1099-1104
3. Pattle RE (1955) Properties, function, and origin of the alveolar lining layer. Nature 175:1125-1126
4. Clements JA (1957) Surface tension of lung extracts. Proc Soc Exp Biol Med 95:170-172
5. Avery ME, Mead J (1959) Surface properties in relation to atelectasis and hyaline membrane disease. Am J Dis Child 97:517-523
6. Adachi H, Hayashi H, Sato H et al (1989) Characterization of phospholipids accumulated in pulmonary-surfactant compartments of rats intratracheally exposed to silica. Biochem J 262:781-786
7. King RJ (1984) Isolation and chemical composition of pulmonary surfactant. In: Robertson B, Van Golde LM, Batenburg JJ (eds) Pulmonary surfactant: from molecular biology to clinical practice. Elsevier Science, Amsterdam, pp 1-15
8. Hayashi H, Adachi H, Kataoka K et al (1990) Molecular species profiles of acidic phospholipids in lung fractions of adult and perinatal rabbits. Biochim Biophys Acta 1042:126-131
9. Okano G, Akino T (1978) Changes in the structural and metabolic heterogeneity of phosphatidylcholines in the developing rat lung. Biochim Biophys Acta 528:373-384
10. Wright JR, Clements JA (1987) Metabolism and turnover of lung surfactant. Am Rev Respir Dis 136:426-444
11. Gail DB, Massaro GD, Massaro D (1977) Influence of fasting on the lung. J Appl Physiol 42:88-92
12. Nakamura M, Kawamoto T, Akino T (1980) Dietary regulation of dipalmitoyl phosphatidylcholine in the lung. Effects of essential fatty acid deficiency. Biochim Biophys Acta 620:24-36
13. McMahon KE, Farrell PM (1986) Effect of choline deficiency on lung phospholipid concentrations in the rat. J Nutr 116:936-943
14. Brown LA, Bliss AS, Longmore WJ (1984) Effect of nutritional status on the lung surfactant system: food deprivation and caloric restriction. Exp Lung Res 6:133-147
15. Veldhuizen R, Nag K, Orgeig S et al (1998) The role of lipids in pulmonary surfactant. Biochim Biophys Acta 1408:90-108
16. Honda Y, Tsunematsu K, Suzuki A et al (1988) Changes in phospholipids in bronchoalveolar lavage fluid of patients with interstitial lung diseases. Lung 166:293-301
17. Hallman M, Spragg R, Harrell JH et al (1982) Evidence of lung surfactant abnormality in respiratory failure. Study of bronchoalveolar lavage phospholipids, surface activity, phospholipase activity, and plasma myoinositol. J Clin Invest 70:673-683
18. Robinson PC, Watters LC, King TE et al (1988) Idiopathic pulmonary fibrosis. Abnormalities in bronchoalveolar lavage fluid phospholipids. Am Rev Respir Dis 137:585-591

19. Hallman M, Gluck L (1975) Phosphatidylglycerol in lung surfactant. II. Subcellular distribution and mechanism of biosynthesis in vitro. Biochim Biophys Acta 409:172-191
20. Hallman M, Gluck L (1980) Formation of acidic phospholipids in rabbit lung during perinatal development. Pediatr Res 14:1250-1259
21. Benson BJ, Kitterman JA, Clements JA et al (1983) Changes in phospholipid composition of lung surfactant during development in the fetal lamb. Biochim Biophys Acta 753:83-88
22. Hallman M, Feldman BH, Kirkpatrick E et al (1977) Absence of phosphatidylglycerol (PG) in respiratory distress syndrome in the newborn. Study of the minor surfactant phospholipids in newborns. Pediatr Res 11:714-720
23. Baatz JE, Elledge B, Whitsett JA (1990) Surfactant protein SP-B induces ordering at the surface of model membrane bilayers. Biochemistry 29:6714-6720
24. Yu SH, Possmayer F (1990) Role of bovine pulmonary surfactant-associated proteins in the surface-active property of phospholipid mixtures. Biochim Biophys Acta 1046:233-241
25. King RJ, Phillips MC, Horowitz PM et al (1986) Interaction between the 35 kDa apolipoprotein of pulmonary surfactant and saturated phosphatidylcholines. Effects of temperature. Biochim Biophys Acta 879:1-13
26. Kuroki Y, Akino T (1991) Pulmonary surfactant protein A (SP-A) specifically binds dipalmitoylphosphatidylcholine. J Biol Chem 266:3068-3073
27. Williams MC, Hawgood S, Hamilton RL (1991) Changes in lipid structure produced by surfactant proteins SP-A, SP-B, and SP-C. Am J Respir Cell Mol Biol 5:41-50
28. Suzuki Y, Fujita Y and Kogishi K (1989) Reconstitution of tubular myelin from synthetic lipids and proteins associated with pig pulmonary surfactant. Am Rev Respir Dis 140:75-81
29. Hawgood S, Benson BJ, Schilling J et al (1987) Nucleotide and amino acid sequences of pulmonary surfactant protein SP 18 and evidence for cooperation between SP 18 and SP 28-36 in surfactant lipid adsorption. Proc Natl Acad Sci USA 84:66-70
30. Wirtz HR, Dobbs LG (1990) Calcium mobilization and exocytosis after one mechanical stretch of lung epithelial cells. Science 250:1266-1269
31. Rice WR, Ross GF, Singleton FM et al (1987) Surfactant-associated protein inhibits phospholipid secretion from type II cells. J Appl Physiol 63:692-698
32. Kuroki Y, Mason RJ, Voelker DR (1988) Pulmonary surfactant apoprotein A structure and modulation of surfactant secretion by rat alveolar type II cells. J Biol Chem 263:3388-3394
33. Dobbs LG, Wright JR, Hawgood S et al (1987) Pulmonary surfactant and its components inhibit secretion of phosphatidylcholine from cultured rat alveolar type II cells. Proc Natl Acad Sci USA 84:1010-1014
34. Bates SR, Dodia C, Fisher AB (1994) Surfactant protein A regulates uptake of pulmonary surfactant by lung type II cells on microporous membranes. Am J Physiol 267:L753-L760
35. Horowitz AD, Kurak K, Moussavian B et al (1997) Preferential uptake of small-aggregate fraction of pulmonary surfactant in vitro. Am J Physiol 273:L468-L477
36. Horowitz AD, Moussavian B, Whitsett JA (1996) Roles of SP-A, SP-B, and SP-C in modulation of lipid uptake by pulmonary epithelial cells in vitro. Am J Physiol 270:L69-L79
37. Tsuzuki A, Kuroki Y, Akino T (1993) Pulmonary surfactant protein A-mediated uptake of phosphatidylcholine by alveolar type II cells. Am J Physiol 265:L193-L199
38. van Iwaarden JF (1992) Surfactant and the pulmonary defense system. In: Robertson B, van Golde LMG, Batenburg JJ (eds) Pulmonary surfactant: from molecular biology to clinical pratice. Elsevier, Amsterdam, pp 215-228
39. Kramer BW, Speer CP (2003) [Surfactant proteins A and D: major factors of the immune response of the lung]. Z Geburtshilfe Neonatol 207:41-47

40. Curstedt T, Jornvall H, Robertson B et al (1987) Two hydrophobic low-molecular-mass protein fractions of pulmonary surfactant. Characterization and biophysical activity. Eur J Biochem 168:255-262
41. Revak SD, Merritt TA, Degryse E et al (1988) Use of human surfactant low molecular weight apoproteins in the reconstitution of surfactant biologic activity. J Clin Invest 81:826-833
42. Stahlman MT, Gray MP, Falconieri MW et al (2000) Lamellar body formation in normal and surfactant protein B-deficient fetal mice. Lab Invest 80:395-403
43. Tokieda K, Whitsett JA, Clark JC et al (1997) Pulmonary dysfunction in neonatal SP-B-deficient mice. Am J Physiol 273:L875-882
44. Melton KR, Nesslein LL, Ikegami M et al (2003) SP-B deficiency causes respiratory failure in adult mice. Am J Physiol Lung Cell Mol Physiol 285:L543-L549
45. Epaud R, Ikegami M, Whitsett JA et al (2003) Surfactant protein B inhibits endotoxin-induced lung inflammation. Am J Respir Cell Mol Biol 28:373-378
46. Notter RH, Shapiro DL, Ohning B et al (1987) Biophysical activity of synthetic phospholipids combined with purified lung surfactant 6000 dalton apoprotein. Chem Phys Lipids 44:1-17
47. Warr RG, Hawgood S, Buckley DI et al (1987) Low molecular weight human pulmonary surfactant protein (SP5): isolation, characterization, and cDNA and amino acid sequences. Proc Natl Acad Sci USA 84:7915-7919
48. Takahashi A, Fujiwara T (1986) Proteolipid in bovine lung surfactant: its role in surfactant function. Biochem Biophys Res Commun 135:527-532
49. Glasser SW, Burhans MS, Korfhagen TR et al (2001) Altered stability of pulmonary surfactant in SP-C-deficient mice. Proc Natl Acad Sci U S A 98:6366-6371
50. Venkitaraman AR, Hall SB, Whitsett JA et al (1990) Enhancement of biophysical activity of lung surfactant extracts and phospholipid-apoprotein mixtures by surfactant protein A. Chem Phys Lipids 56:185-194
51. Conkright JJ, Na CL, Weaver TE (2002) Overexpression of surfactant protein-C mature peptide causes neonatal lethality in transgenic mice. Am J Respir Cell Mol Biol 26:85-90
52. Kishor U, Madan T, Sarma PU et al (2002) Protective roles of pulmonary surfactant proteins, SP-A and SP-D, against lung allergy and infection caused by Aspergillus fumigatus. Immunobiology 205:610-618
53. Griese M (2002) Respiratory syncytial virus and pulmonary surfactant. Viral Immunol 15:357-363
54. McCormack FX, Whitsett JA (2002) The pulmonary collectins, SP-A and SP-D, orchestrate innate immunity in the lung. J Clin Invest 109:707-712
55. Crouch EC (2000) Surfactant protein-D and pulmonary host defense. Respir Res 1:93-108
56. Rooney SA, Young SL, Mendelson CR (1994) Molecular and cellular processing of lung surfactant. FASEB J 8:957-967
57. Van Golde LM, Batenburg JJ, Robertson B (1988) The pulmonary surfactant system: biochemical aspects and functional significance. Physiol Rev 68:374-455
58. Wright JR, Dobbs LG (1991) Regulation of pulmonary surfactant secretion and clearance. Annu Rev Physiol 53:395-414
59. Jacobs H, Jobe A, Ikegami M et al (1982) Surfactant phosphatidylcholine source, fluxes, and turnover times in 3-day-old, 10-day-old, and adult rabbits. J Biol Chem 257:1805-1810
60. Jobe A, Ikegami M, Sarton-Miller I et al (1980) Surfactant metabolism of newborn lamb lungs studied in vivo. J Appl Physiol 49:1091-1098
61. Bunt JE, Zimmermann LJ, Wattimena JL et al (1998) Endogenous surfactant turnover in preterm infants measured with stable isotopes. Am J Respir Crit Care Med 157:810-814

62. Bunt JE, Carnielli VP, Darcos Wattimena JL et al (2000) The effect in premature infants of prenatal corticosteroids on endogenous surfactant synthesis as measured with stable isotopes. Am J Respir Crit Care Med 162:844-849
63. Bunt JE, Carnielli VP, Seidner SR et al (1999) Metabolism of endogenous surfactant in premature baboons and effect of prenatal corticosteroids. Am J Respir Crit Care Med 160:1481-1485
64. Martini WZ, Chinkes DL, Barrow RE et al (1999) Lung surfactant kinetics in conscious pigs. Am J Physiol 277:E187-E195
65. Askin FB and Kuhn C (1971) The cellular origin of pulmonary surfactant. Lab Invest 25:260-268
66. Chevalier G, Collet AJ (1972) In vivo incorporation of choline- 3 H, leucine- 3 H and galactose- 3 H in alveolar type II pneumocytes in relation to surfactant synthesis. A quantitative radoautographic study in mouse by electron microscopy. Anat Rec 174:289-310
67. Oosterlaken-Dijksterhuis MA, van Eijk M, van Buel BL et al (1991) Surfactant protein composition of lamellar bodies isolated from rat lung. Biochem J 274 (Pt 1):115-119
68. Mason RJ and Voelker DR (1998) Regulatory mechanisms of surfactant secretion. Biochim Biophys Acta 1408:226-240
69. Chander A, Fisher AB (1990) Regulation of lung surfactant secretion. Am J Physiol 258:L241-L253
70. Gobran LI, Rooney SA (2004) Pulmonary surfactant secretion in briefly cultured mouse type II cells. Am J Physiol Lung Cell Mol Physiol 286:L331-:L336
71. Rooney SA (2001) Regulation of surfactant secretion. Comp Biochem Physiol A Mol Integr Physiol 129:233-243
72. Poulain FR, Allen L, Williams MC et al (1992) Effects of surfactant apolipoproteins on liposome structure: implications for tubular myelin formation. Am J Physiol Lung Cell Mol Physiol 262:L730-L739
73. Ikegami M, Korfhagen TR, Whitsett JA et al (1998) Characteristics of surfactant from SP-A-deficient mice. Am J Physiol Lung Cell Mol Physiol 275:L247-L254
74. Veldhuizen RA, Marcou J, Yao LJ et al (1996) Alveolar surfactant aggregate conversion in ventilated normal and injured rabbits. Am J Physiol 270:L152-L158
75. Magoon MW, Wright JR, Baritussio A et al (1983) Subfractionation of lung surfactant. Implications for metabolism and surface activity. Biochim Biophys Acta 750:18-31
76. Yamada T, Ikegami M, Jobe AH (1990) Effects of surfactant subfractions on preterm rabbit lung function. Pediatr Res 27:592-598
77. Miles PR, Ma JY, Bowman L (1988) Degradation of pulmonary surfactant disaturated phosphatidylcholines by alveolar macrophages. J Appl Physiol 64:2474-2481
78. Rider ED, Ikegami M, Jobe AH (1990) Intrapulmonary catabolism of surfactant-saturated phosphatidylcholine in rabbits. J Appl Physiol 69:1856-1862
79. Rider ED, Ikegami M, Jobe AH (1992) Localization of alveolar surfactant clearance in rabbit lung cells. Am J Physiol 263:L201-L209
80. Gurel O, Ikegami M, Chroneos ZC et al (2001) Macrophage and type II cell catabolism of SP-A and saturated phosphatidylcholine in mouse lungs. Am J Physiol Lung Cell Mol Physiol 280:L1266-L1272
81. Straubinger RM, Hong K, Friend DS et al (1983) Endocytosis of liposomes and intracellular fate of encapsulated molecules: encounter with a low pH compartment after internalization in coated vesicles. Cell 32:1069-1079
82. Stevens PA, Wissel H, Zastrow S et al (2001) Surfactant protein A and lipid are internalized via the coated-pit pathway by type II pneumocytes. Am J Physiol Lung Cell Mol Physiol 280:L141-L151

83. Muller WJ, Zen K, Fisher AB et al (1995) Pathways for uptake of fluorescently labeled liposomes by alveolar type II cells in culture. Am J Physiol 269:L11-L19
84. Poelma DL, Ju MR, Bakker SC et al (2004) A common pathway for the uptake of surfactant lipids by alveolar cells. Am J Respir Cell Mol Biol 30:751-758
85. Hawgood S (1992) The hydrophilic surfactant protein SP-A: Molecular biology, structure and function. In: Robertson B, van Golde LMG, Batenburg JJ (eds) Pulmonary surfactant: from molecular biology to clinical pratice. Elsevier, Amsterdam, pp 33-54
86. Horowitz AD, Moussavian B, Han ED et al (1997) Distinct effects of SP-A and SP-B on endocytosis of SP-C by pulmonary epithelial cells. Am J Physiol 273:L159-L171
87. Poelma DL, Zimmermann LJ, Scholten HH et al (2002) In vivo and in vitro uptake of surfactant lipids by alveolar type II cells and macrophages. Am J Physiol Lung Cell Mol Physiol 283:L648-L654
88. Hunt AN, Kelly FJ, Postle AD (1991) Developmental variation in whole human lung phosphatidylcholine molecular species: a comparison with guinea pig and rat. Early Hum Dev 25:157-171
89. Possmayer F, Yu SH, Weber JM et al (1984) Pulmonary surfactant. Can J Biochem Cell Biol 62:1121-1133
90. Lewis JF, Jobe AH (1993) Surfactant and the adult respiratory distress syndrome. Am Rev Respir Dis 147:218-233
91. Lewis JF, Veldhuizen RA (1995) Factors influencing efficacy of exogenous surfactant in acute lung injury. Biol Neonate 67 Suppl 1:48-60
92. Bates SR, Ibach PB, Fisher AB (1989) Phospholipids co-isolated with rat surfactant protein C account for the apparent protein-enhanced uptake of liposomes into lung granular pneumocytes. Exp Lung Res 15:695-708
93. Chander A, Claypool WD, Jr., Strauss JF 3rd et al (1983) Uptake of liposomal phosphatidylcholine by granular pneumocytes in primary culture. Am J Physiol 245:C397-C404
94. Quintero OA, Wright JR (2000) Metabolism of phosphatidylglycerol by alveolar macrophages in vitro. Am J Physiol Lung Cell Mol Physiol 279:L399-L407
95. Greene KE, Wright JR, Steinberg KP et al (1999) Serial changes in surfactant-associated proteins in lung and serum before and after onset of ARDS. Am J Respir Crit Care Med 160:1843-1850
96. Gregory TJ, Longmore WJ, Moxley MA et al (1991) Surfactant chemical composition and biophysical activity in acute respiratory distress syndrome. J Clin Invest 88:1976-1981
97. Rice WR, Sarin VK, Fox JL et al (1989) Surfactant peptides stimulate uptake of phosphatidylcholine by isolated cells. Biochim Biophys Acta 1006:237-245
98. Baritussio A, Alberti A, Quaglino D et al (1994) SP-A, SP-B, and SP-C in surfactant subtypes around birth: reexamination of alveolar life cycle of surfactant. Am J Physiol 266:L436-L447
99. Baritussio A, Benevento M, Pettenazzo A et al (1989) The life cycle of a low-molecular-weight protein of surfactant (SP-C) in 3-day-old rabbits. Biochim Biophys Acta 1006:19-25
100. Rice WR, Sarin VK, Fox JL et al (1989) Surfactant peptides stimulate uptake of phosphatidylcholine by isolated cells. Biochim Biophys Acta 1006:237-245
101. Lewis JF, Brackenbury A (2003) Role of exogenous surfactant in acute lung injury. Crit Care Med 31:S324-S328
102. Miles PR, Wright JR, Bowman L et al (1983) Incorporation of [3H]palmitate into disaturated phosphatidylcholines in alveolar type II cells isolated by centrifugal elutriation. Biochim Biophys Acta 753:107-118
103. Bourbon JR, Chailley-Heu B, Gautier B (1997) The exogenous surfactant Curosurf enhances phosphatidylcholine content in isolated type II cells. Eur Respir J 10:914-919

104. Oetomo SB, Lewis J, Ikegami M et al (1990) Surfactant treatments alter endogenous surfactant metabolism in rabbit lungs. J Appl Physiol 68:1590-1596
105. Ikegami M, Jobe A, Yamada T et al (1989) Surfactant metabolism in surfactant-treated preterm ventilated lambs. J Appl Physiol 67:429-437
106. Bunt JE, Carnielli VP, Janssen DJ et al (2000) Treatment with exogenous surfactant stimulates endogenous surfactant synthesis in premature infants with respiratory distress syndrome. Crit Care Med 28:3383-3388
107. Pettenazzo A, Ikegami M, Seidner S et al (1988) Clearance of surfactant phosphatidylcholine from adult rabbit lungs. J Appl Physiol 64:120-127
108. Pettenazzo A, Jobe A, Humme J et al (1988) Clearance of surfactant phosphatidylcholine via the upper airways in rabbits. J Appl Physiol 65:2151-2155
109. Pettenazzo A, Jobe A, Ikegami M et al (1989) Clearance of phosphatidylcholine and cholesterol from liposomes, liposomes loaded with metaproterenol, and rabbit surfactant from adult rabbit lungs. Am Rev Respir Dis 139:752-758
110. Pettenazzo A, Jobe A, Ikegami M et al (1989) In vivo clearance of natural and modified surfactant. Eur Respir J Suppl 3:S13-S15
111. Walther FJ, Hernandez-Juviel J, Bruni R et al (1998) Protein composition of synthetic surfactant affects gas exchange in surfactant-deficient rats. Pediatr Res 43:666-673
112. Veldhuizen EJ, Waring AJ, Walther FJ et al (2000) Dimeric N-terminal segment of human surfactant protein B (dSP-B(1-25)) has enhanced surface properties compared to monomeric SP-B(1-25). Biophys J 79:377-384
113. Walther FJ, Hernandez-Juviel JM, Gordon LM et al (2002) Dimeric surfactant protein B peptide sp-b(1-25) in neonatal and acute respiratory distress syndrome. Exp Lung Res 28:623-640
114. Robertson B, Johansson J, Curstedt T (2000) Synthetic surfactants to treat neonatal lung disease. Mol Med Today 6:119-124
115. Walther FJ, Gordon LM, Zasadzinski JA et al (2000) Surfactant protein B and C analogues. Mol Genet Metab 71:342-351
116. Walther FJ, Hernandez-Juviel JM, Mercado PE et al (2002) Surfactant with SP-B and SP-C analogues improves lung function in surfactant-deficient rats. Biol Neonate 82:181-187
117. Hafner D, Germann PG, Hauschke D (1998) Effects of rSP-C surfactant on oxygenation and histology in a rat-lung-lavage model of acute lung injury. Am J Respir Crit Care Med 158:270-278
118. Hafner D, Germann PG, Hauschke D (1998) Comparison of rSP-C surfactant with natural and synthetic surfactants after late treatment in a rat model of the acute respiratory distress syndrome. Br J Pharmacol 124:1083-1090
119. King RJ, Carmichael MC, Horowitz PM (1983) Reassembly of lipid-protein complexes of pulmonary surfactant. Proposed mechanism of interaction. J Biol Chem 258:10672-10680
120. King RJ (1984) Lipid-apolipoprotein interactions in surfactant studied by reassembly. Exp Lung Res 6:237-253
121. Yu SH, Possmayer F (1988) Comparative studies on the biophysical activities of the low-molecular-weight hydrophobic proteins purified from bovine pulmonary surfactant. Biochim Biophys Acta 961:337-350
122. Bachurski CJ, Pryhuber GS, Glasser SW et al (1995) Tumor necrosis factor-alpha inhibits surfactant protein C gene transcription. J Biol Chem 270:19402-19407
123. Ballard PL, Liley HG, Gonzales LW et al (1990) Interferon-gamma and synthesis of surfactant components by cultured human fetal lung. Am J Respir Cell Mol Biol 2:137-143

124. Dhar V, Hallman M, Lappalainen U et al (1997) Interleukin-1 alpha upregulates the expression of surfactant protein-A in rabbit lung explants. Biol Neonate 71:46-52
125. Whitsett JA, Clark JC, Wispe JR et al (1992) Effects of TNF-alpha and phorbol ester on human surfactant protein and MnSOD gene transcription in vitro. Am J Physiol 262:L688-L693
126. Glumoff V, Vayrynen O, Kangas T et al (2000) Degree of lung maturity determines the direction of the interleukin-1- induced effect on the expression of surfactant proteins. Am J Respir Cell Mol Biol 22:280-288

Chapter 26

Respiratory mechanics at the bedside

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Mechanical ventilation can augment lung injury and contribute to the systemic inflammatory response in patients with acute respiratory distress syndrome (ARDS) [1–3]. This ventilator-associated lung injury (VALI) can be connected with supportive care following the initial insult to the lung and is thought to arise from alveolar overdistension and repetitive alveolar collapse and re-expansion with tidal volume cycling [2]. Strategies have been proposed to minimise this injury, including low-tidal-volume ventilation, permissive hypercapnia and 'open lung' ventilation.

Over the last decade, the realisation that the physical stress of mechanical ventilation can damage lungs or amplify nonphysical injury mechanisms has generated an enormous renewal of interest in the mechanics of the injured lung. From a mechanical point of view, the respiratory system consists of two structures coupled in series, the lungs and the chest wall. The lungs and the chest wall both have characteristics of elastic structures. An elastic structure is one in which the volume of the structure is directly proportional to the pressure difference across the wall of the structure, the transmural pressure. By convention, the transmural pressure is always expressed as the internal surface pressure minus the external surface pressure. Thus, the transmural pressure of an elastic structure can be increased by elevation of the internal surface pressure or by reduction of the external surface pressure. The pressure across the chest wall (i.e. its transmural distending pressure) is the pressure difference between pleural pressure and the pressure at the body surface. As pleural pressure (Ppl) is usually not accessible at the bedside, the oesophageal pressure (Pes) is used as a surrogate parameter. As in most circumstances body surface pressure is equal to atmospheric pressure, which is the reference pressure for all other pressures, it can be regarded as zero. Therefore, the transmural distending pressure of the chest wall is usually equal to Ppl or Pes. For the lung, the transmural distending pressure is alveolar pressure minus pleural (or oesophageal) pressure, which is the transpulmonary pressure. The corresponding pressure for the total respiratory system is taken as the airway pressure (Paw). The mechanical properties of the respiratory system are classically described by a Newtonian model consisting of a resistor, representing airway resistance, and a capacitor, which represents the compliance (the change in volume associated with a given change in pressure, $C = \Delta V/\Delta P$). The mathematical inverse of compliance is elastance ($E = \Delta P/\Delta V$). Because lung and chest wall are arranged in series, the elastance of the respiratory system is the sum of the elastance of the

chest wall and the elastance of the lungs ($E_{rs} = E_{cw} + E_l$). Clinically, however, the term 'compliance' is used more frequently, and the following equation accordingly applies: $1/C_{rs} = 1/C_{cw} + 1/Cl$.

The conventional two-point quasistatic compliance of the respiratory system (C_{2P}) is calculated as:

$C_{2P} = V_T/$(end-inspiratory pressure – end-expiratory pressure)

To obtain the end-inspiratory and end-expiratory pressures, the appropriate hold functions of the ventilator are used.

At the bedside in particular, analysis of the volume–pressure relationships for the respiratory system, the lungs and the chest wall has a pivotal role. As exact quantification of alveolar overdistension, recruitment and derecruitment is not feasible at the bedside, since computed tomography analysis is the only means of achieving this [4–9], the volume–pressure relationship of the respiratory system is used as a surrogate measure of the degree of alveolar inflation and recruitment [10]. Consequently, the analysis of pressure–volume curves has evolved as the primary approach to respiratory mechanics in ARDS.

In this article, the role of respiratory mechanics data at the bedside will be discussed. Based on the model of the ARDS lung consisting of consolidated, recruitable and aerated parts, the potential applications of respiratory mechanics are: (a) determination of the severity of the disease and (b) selection of more appropriate settings for the ventilator. In this context, the potential applications of the pressure–volume curve, its traditional interpretation and new insights into its morphological correlates will be reviewed. In addition, different concepts and integrated approaches to determining recruitment will be discussed.

Early-phase ARDS lung and the pressure–volume curve

Lung injury can originate from a direct insult to the lung ('primary ARDS') or result from an extrapulmonary disease, such as sepsis, peritonitis or multiple trauma ('secondary ARDS'). In both cases, however, lesions of the alveolo–capillary barrier cause an increase in pulmonary vascular permeability, resulting in interstitial and/or alveolar oedema. The distribution of oedema is quite uniform throughout the lung parenchyma, suggesting that the increase in vascular permeability should also be evenly distributed [11]. As the total mass of the early ARDS lung is more than twice that of the normal lung, the lung progressively collapses under its own weight. The ARDS lung is uniformly affected by the primary disease, and oedema accumulates uniformly, in the same way as a sponge takes up water when it is immersed. The gas spaces are restricted by oedema, and the total gas content decreases. The increased mass causes an increased superimposed pressure, which leads in turn to 'gas squeezing' from the most dependent lung regions and progressively compresses the lung regions along the vertical axis with formation of compression atelectasis. Therefore, ARDS, initially thought to affect the lungs uniform throughout, results in an inhomogeneous pattern of injury, with radiographic densities located primarily in the dependent parts of the lung [12–14]. Other

mechanisms than this superimposed pressure in an oedematous 'heavy' lung have been found responsible for the vertical gradient, such as the increased weight of the heart [15, 16] or increases in intraabdominal pressure [17].

Thus, the ARDS lung is composed of normally inflated lung regions in the nondependent parts, consolidation and atelectasis, and an intermediate, partially collapsed part, which is prone to cyclic recruitment–derecruitment phenomena (Fig. 1).

The pressure–volume (PV) curve of the respiratory system is a classic physiological method of describing the mechanical properties of the respiratory system [18]. Its usefulness as a pulmonary function test in patients with respiratory failure was envisaged relatively early [19], and its use as a monitoring tool was introduced some years after the first description of the acute respiratory distress syndrome (RDS) [20]. The static respiratory system PV curve in acute lung injury has certain characteristics (Fig. 2). At low lung volumes, the initial flat segment with very low compliance is thought to reflect the collapse of peripheral airways and lung units [21, 22]. As insufflation proceeds, an intermediate linear segment with a steeper slope, i.e. greater cord compliance, is observed. At higher pressures, the PV curve flattens again, with a fast decrease of the slope, i.e. the compliance, in its third segment. The transition between the first flat portion and the linear part of the

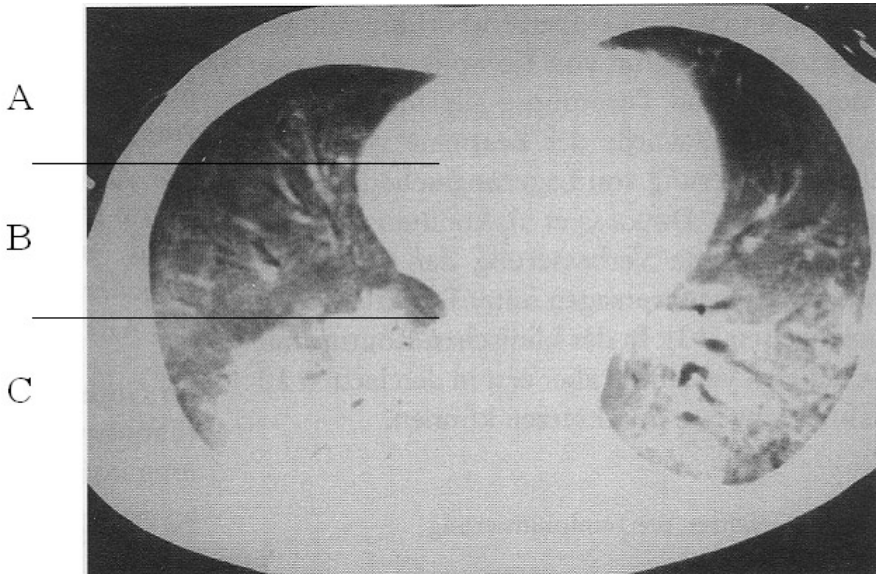

Fig. 1. Computed tomogram of the chest in a patient with ARDS, showing the typical heterogeneous distribution of opacification within the lungs. The increased density of lung tissue in dorsal regions (*A*) is caused by consolidation and atelectasis. The aerated ventral regions ('baby lung' [*B*] have the highest compliance and tend to become overdistended (volutrauma). The interface between the two areas (*C*) is prone to cyclic recruitment–derecruitment (atelectrauma)

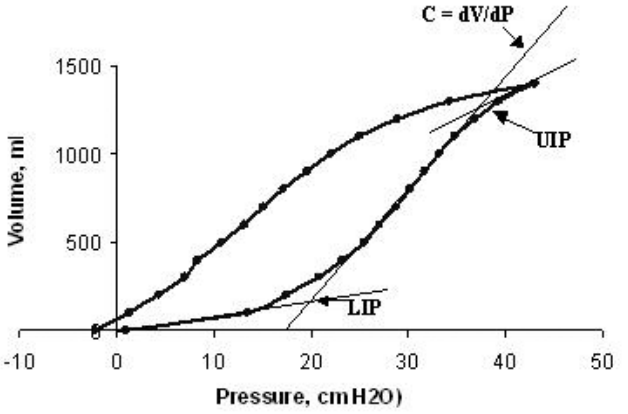

Fig. 2. Mean static pressure-volume curve after introduction of acute lung injury by saline lung lavage in pigs (*LIP* lower inflection point, *UIP* upper inflection point)

curve, termed the 'lower inflection point' (LIP), has been used as a tool in setting PEEP in patients with ARDS since the mid-1980s [23]. The theory behind its use was that there was a critical opening pressure that could be detected as a sharp inflection of the PV curve that corresponded to the recruitment of large amounts of previously collapsed units [21, 24, 25]. The pressure at the upper inflection point (UIP), in turn, was considered to indicate alveolar overdistension and/or the pressure at which alveolar recruitment ends and which should not be exceeded during mechanical ventilation [26].

Against this backdrop, there is still a great deal of interest in the PV curve, because components of the PV curve, specifically the lower and upper inflection points, have been used in attempts to reduce ventilator-induced lung injury by avoiding end-expiratory pressures below the LIP (i.e. avoiding cyclic collapse of alveoli) and end-inspiratory pressures above the UIP (i.e. avoiding overstretching) [27–30]. In addition, Ranieri et al. [3, 31] showed that avoiding collapse and overstretching reduced not only ventilator-induced lung injury, but also multiple organ failure.

The central assumptions behind the PV curves, especially the assumption that the LIP is caused by large-scale alveolar recruitment, have recently been challenged, however, on the basis of theoretical [32], experimental [7] and clinical data [4, 33]. In addition, the rationale for setting the pressure levels according to the data obtained from the inflation limb of the PV curve has also been questioned [34–36].

Throughout all attempts to interpret these findings and possible discrepancies between theoretical considerations and practical observations, it is important to keep in mind the way PV curves are generated. As nicely reviewed by Maggiore and Brochard [18], the techniques used to trace a PV curve can be static and quasistatic,

or dynamic. With the static methods (supersyringe [21, 37, 38], interrupter and multiple occlusion techniques [39–42]), the airway pressure is measured during an end-inspiratory pause, i.e. at zero flow, thus eliminating both flow-resistive and inertial pressures. Conversely, with a semistatic technique, the low-flow technique [43–45], the resistive and viscoelastic phenomena have to be taken into account. The low-flow technique offers many advantages at the bedside, as it is easy to use, requires much less time than the multiple occlusion technique, and can be done with no special equipment other than a modern ventilator that supplies a low constant flow (<15 l/min) while the patient is still connected to the ventilator [18]. Even low-flow techniques, however, represent different conditions than those in normal tidal ventilation, and the use of 'truly' dynamic PV curves instead has therefore been suggested [46–48].

It is probable, however, that rather than the technique, more importance attaches to the separation of chest wall and lung mechanics whenever abnormalities in chest wall compliance are suspected. In particular, the significant contribution of increased intraabdominal pressure to secondary ARDS has been recognised [49-51], since it results in compression atelectasis in the caudal parts, where the intraabdominal pressure tends to squeeze the lungs. In the presence of intraabdominal hypertension the distortion of total respiratory system mechanics can be due exclusively to decreased chest wall compliance while lung mechanics are (almost) normal [17, 49, 52]. Differentiation of lung and chest wall mechanics by the use of oesophageal and/or intraabdominal pressure measurements is strongly recommended in this setting [53].

Respiratory mechanics to identify the severity of disease

Respiratory system elastance (E_{rs}) has been used as an indicator of the condition of lungs and thoracic cage [23] and as a prognostic factor in patients with severe acute respiratory failure [54]. E_{rs} depends on the characteristics of the lungs and the chest wall [55], and noninvasive and repetitive measurements are easily obtained. Matamis et al. [21] have shown the relationship between changes in pulmonary mechanics and the different stages of acute RDS. In a recent experimental study in rats, Sibilla et al. [56] have shown that that in the setting of ventilator-induced lung injury induced by different 'injurious' combinations of volumes and pressures, a 50% increase in E_{rs} corresponds to an equivalent level of lung damage, irrespective of ventilatory settings and the duration of ventilation. The degree of injury was assessed by morphological analysis and lung wet-to-dry ratio measurements.

In a recent study, our group [5] assessed the effects of increasing levels of PEEP on the measurements of extravascular lung water and excess tissue volume in a saline-lavage model of acute lung injury in sheep. While stepwise increases of PEEP up to 21 cm H_2O decreased E_{rs}, neither the amount of nonaerated lung nor the transpulmonary shunt and total amount of excess tissue changed. As gas volume significantly increased, however, a more favourable gas/tissue ratio was re-established, and this more favourable ratio correlated with improved mechanics (Fig. 3).

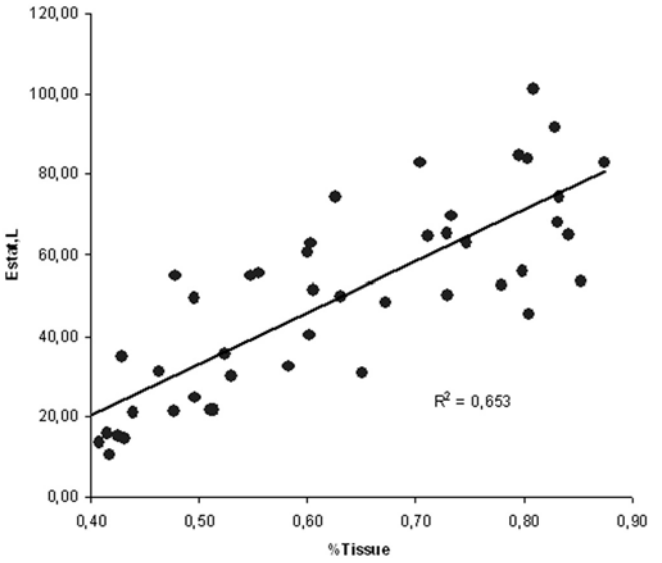

Fig. 3. Correlation between fractional tissue (%tissue = tissue volume/total lung volume) and static lung elastance (E_{stat}, L) before and after saline lavage lung injury at different levels of PEEP. While the absolute tissue volume was not changed by PEEP, the gas volume significantly increased, thereby decreasing the fractional tissue volume and Estat, L. Data from [5]

It is noteworthy, however, that at the highest level of PEEP total lung volume was increased by 50% over baseline values. It is hard to say whether a 50% increase in total volume will in fact have no without adverse consequences for the lung, despite improved mechanics and gas exchange, however. Even though no significant overdistension was demonstrable at these high volumes, there must be concerns about increased mechanical stress and strain, which may not necessarily be reflected by a 'rather crude' estimation of mechanics. What is illustrated by these data, however, is the well-known fact that recruitment always comes at a price and an increase in total lung volume may not be appreciated at the bedside because it is not possible to measure it there. As total lung volume, on the other hand, may be a major determinant for the haemodynamic depression caused by PEEP, the change in stroke volume associated with an increase in PEEP can be used to estimate changes in lung volume relative to normal functional residual capacity (FRC). If increasing airway pressures do not result in excessive lung volume changes, as will be the case in the presence of intraabdominal hypertension [53], haemodynamic compromise will be minimal. In an illustrative case report [57], for example, PEEP up to 50 cmH_2O and peak pressures as high as 100 cmH_2O were used without haemodynamic compromise in a patient with massive intraabdominal hypertension in whom surgical compression was not feasible.

For a more in-depth discussion of the relationships between lung volume and haemodynamics, the reader is referred to the chapter "*PEEP and cardiac output*" in this book.

Can the static pressure-volume curve be used to set the ventilator?

The PV curve is often suggested as a useful tool in adjustment of ventilator settings. Titration of PEEP above the LIP is thought to avoid cyclic alveolar collapse, while confining end-inspiratory plateau pressure to below the UIC should limit overdistension. According to this concept, Amato [58], in a randomised controlled trial, found a significant increase in 28-day survival by when PEEP was set at 2 cmH_2O above LIP and limiting end-inspiratory plateau pressure to 40 cmH_2O. Using the same ventilatory strategy, Ranieri et al. [3] observed a decrease in inflammatory mediators in ARDS patients.

The rationale behind the use of the inspiratory limb of the PV curve to set PEEP has been called into question, however. The presence of hysteresis on full inspiratory/expiratory PV curves (Fig. 2) seemed to indicate that the pressure necessary to open large numbers of lung units was not necessarily the same as the pressure needed to keep them open during tidal ventilation. In addition, Venegas [59], based on theoretical concerns, and Hickling, by providing a mathematical model [32, 35], suggested that recruitment occurs throughout the entire inflation limb of the PV curve. In addition, Hickling [35] showed that during an incremental PEEP trial evaluating maximum mean compliances these values did not correlate with maximal recruitment, whereas there was good correlation during a decremental PEEP trial. Further support for this concept came from computed tomography studies in oleic acid-lesioned dogs [7] and in ARDS patients [4], which showed that recruitment occurred throughout the entire inflation limb of the PV curve. In addition, these studies showed a considerable gap between estimated opening and closing pressures and indicated that—for a given pressure—there was significantly more of the lung open on the deflation limb of a PV curve than on the inflation limb. These findings cast some doubt on the validity of using an inspiratory manoeuvre to set PEEP, which is an expiratory phenomenon. In two other recent studies, the PV curves have been shown not to predict steady state lung volume during conventional ventilation [34] or high-frequency oscillatory ventilation [36].

These concepts were further addressed in a recent experimental study on two different models of lung injury (oleic acid infusion [OA] and saline lung lavage [SW]) (Luecke et al., submitted for publication), in which the regional patterns of inflation, recruitment and overinflation during static PV curves and with PEEP set below and above the lower inflection point were assessed by computed tomography. Static whole-lung PV curves were similar in both models, mainly reflecting changes in alveolar inflation or deflation. On the inspiratory limb of the PV curve, recruitment and inflation were on the same line, while there was a substantial difference between deflation and (de)recruitment on the expiratory limb. PEEP-induced recruitment at lung apex and base was at or above the (de)recruitment line on the expiratory limb and showed no relation to the whole-lung PV curve (Fig. 4).

The conclusions of these studies can be summarised by saying that neither inspiratory nor expiratory whole-lung static PV curves can be considered useful for the selection of PEEP levels intended to optimise recruitment. The positive

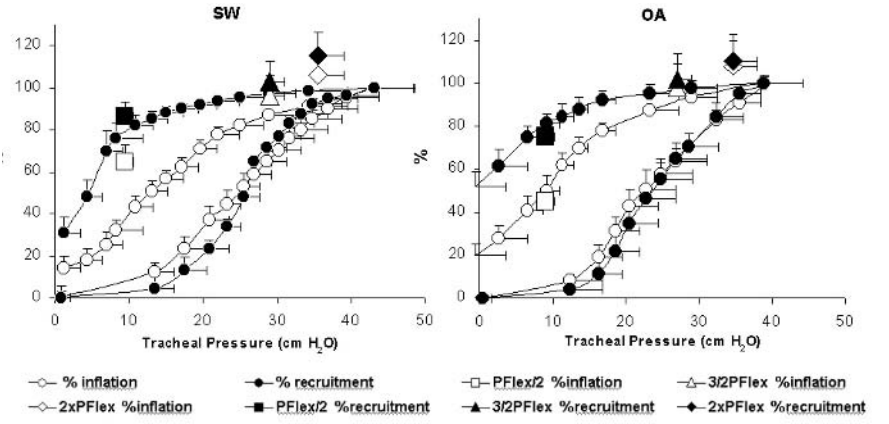

Fig. 4. Fractional inflation and recruitment at lung base after injury (*SW* saline washout group; *OA* oleic acid group). Data for PEEP at 0.5 times LIP, 1.5 times LIP and 2 times LIP are added (from T. Luecke T et al., submitted for publication)

results obtained by Amato [58] and Ranieri [3] when they set PEEP above the LIP may be simply due to the higher PEEP applied than in the control group.

According to the cited studies using computed tomography [4, 7], however, setting the level of positive end-expiratory pressure above the LIP may result in unnecessarily high levels of PEEP, which may cause too high lung volumes. That this approach might increase right ventricular (RV) outflow impedance, putting the patient at risk of acute cor pulmonale, was recently shown by Schmitt et al. [60]. In their study, two approaches to the titration of PEEP were tested in 16 ARDS patients. In the first approach, PEEP was applied in increments of 3 cmH_2O without any change in tidal volume, and the compliance of the respiratory system was calculated at each PEEP. The highest level of PEEP resulting in the highest value for compliance was used. As this approach to setting PEEP in order to maximise compliance was first described as 'optimum PEEP' by Suter et al. [61], it is termed 'Suters's PEEP' ($PEEP_S$). The second strategy for setting PEEP was based on the PV relation of the respiratory system, and PEEP was set at LIP plus 2 cmH_2O (termed 'Amato's PEEP', $PEEP_A$). A wide difference between the two PEEPs was observed, with $PEEP_A$ (13±4 cmH_2O) $PEEP_S$ (6±3 cmH_2O). RV outflow impedance, determining RV systolic function, was significantly worsened by $PEEP_A$. The same group also showed that increased RV afterload was the main factor explaining the decrease in RV stroke volume during mechanical ventilation [62], and these workers therefore strongly recommend RV protection by limitation of PEEP during mechanical ventilation [63].

Again, it should be emphasised that it is the total lung volume relative to normal FRC that has major impact on the haemodynamics, and ultimately on oxygen delivery, during positive-pressure ventilation.

How to determine recruitment at the bedside: role of respiratory mechanics and gas-exchange

Gas exchange trial

An easy method of selecting the 'optimal PEEP' at the bedside is the gas-exchange trial. Usually, different PEEP levels in the range of 5–20 cmH_2O are applied randomly or in a given order (increasing or decreasing) and gas exchange is measured. Changes in both oxygenation (PaO_2) and carbon dioxide ($PaCO_2$) are evaluated. An increase in oxygenation is likely to reflect the increase in the amount of aerated tissue present at end-expiration [64]. Numerous studies have used an increase in PaO_2 as a predictor of successful recruitment, whether established by PEEP, recruitment manoeuvre (RM) or position therapy. However, no clinical study has so far shown an association between an improvement in oxygenation and improved survival [65, 66]. Furthermore, actual recruitment has rarely been measured. In addition, even though oxygenation correlated positively with the amount of aerated and total lung volume, and shunt correlated negatively with the amount of nonaerated lung volume [5], often no correlation was observed between the change in oxygenation and the change in lung volumes measured by computed tomography. This means that a low PaO_2 is well representative of low aerated volume and a high Q_{VA}/Q_T correlates with a high nonaerated volume, but neither oxygenation parameter was predictive for the increase in aerated volume or the decrease in nonaerated volume after the application of PEEP.

We usually see an improvement in oxygenation by at least 10–15 mmHg (whatever inspired oxygen fraction is used) as a positive response to the gas exchange trial. On the other hand, the changes in $PaCO_2$ must be taken into account, which they usually are not when a PEEP trial is performed. However, we believe that a change in $PaCO_2$ (at constant minute ventilation) may be even more informative than changes in oxygenation. It must be remembered that a change of 40 mmHg in oxygenation (i.e. from 60 to 100 mmHg) causes a change in oxygen content similar to the change in carbon dioxide content of 5 mmHg (i.e. from 40 to 45 mmHg). Our hypotheses are: (a) a decrease in carbon dioxide during the PEEP test probably means prevalent alveolar recruitment, (b) no change in $PaCO_2$ indicates a balance between recruitment and overdistension, and (c) even small increases in $PaCO_2$ is probably indicative of prevalent overdistension. Thus, we believe that when a gas exchange trial is performed changes in both PaO_2 and $PaCO_2$ must be taken into account to optimise the selection of PEEP.

Respiratory mechanics trial

Other authors have suggested the use of respiratory mechanics to select PEEP [25, 52, 56], hypothesising that the best compliance of the respiratory system should indicate the level of PEEP at which the lung is in optimum balance between recruitment and overdistension. An alternative mode for selecting PEEP by using respiratory mechanics has been suggested by Ranieri et al. [67]: using the pressure

time curve during constant-flow ventilation and analysing the shape of the curve. This interesting approach, however, has not been yet validated in the clinical setting. New forms of continuous monitoring of collapse and decollapse, as with electrical impedance tomography, are still in the experimental stage [68].

Anyway, we also believe that when present, improvements in respiratory compliance probably indicate more open lung relative to overdistension. Unchanged compliance may indicate an equal increase between opening and overdistension, while a reduction in respiratory compliance may point to prevalent overdistension. However, this use of respiratory system compliance is limited by the fact that respiratory compliance does not always parallel changes in aeration and that even if it does these changes may be small and their sensitivity low.

Moreover, the respiratory system compliance may be not representative of the mechanical behaviour of the lung in the presence of altered chest wall compliance such as is found in patients with increased intraabdominal pressure [69, 70, 52].

Oxygen transport

Some groups [71, 61] have proposed setting optimal PEEP with reference mainly to its effects on oxygen delivery. In other words, they propose considering the interaction between the level of oxygenation and its effects on haemodynamics as the main effect of PEEP. This approach has the advantage that it is a relatively integrated approach between gas exchange and haemodynamics. However, its limiting factor is that with this method it is possible to reach acceptable oxygen delivery (greater than 600 ml O_2/min) even with relatively low levels of PEEP that are known not to optimise alveolar opening [72]. In other words, it is likely that a safe level of oxygenation will be obtained with this method, but it is also very likely that collapse and decollapse of the alveolar units will continue to occur.

Selection of 'optimal PEEP': an integrated approach

Recently, integrated approaches to the selection of optimal PEEP have been proposed; these use (1) oxygenation and respiratory mechanics; (2) lung morphology determined by chest X-ray and/or CT scan, respiratory mechanics and oxygenation.

Oxygenation and respiratory mechanics

An interesting integrated approach of gas exchange and respiratory mechanics has been proposed by Bohm and Lachmann [73] and recently investigated in animal [7, 74, 75] and human studies [4]. It consists of a first part to open up the lung (increasing plateau and PEEP levels) and a second part to keep the lung open (progressively decreasing the PEEP levels).

For this procedure, the ventilatory setting should be switched from volume to

pressure control mode, with the level of the previous inspiratory plateau pressure on volume control serving as a guide to find the appropriate plateau pressure for pressure control ventilation. Otherwise, the plateau pressure during volume control ventilation minus 5 cmH_2O can be chosen. The levels of PEEP can initially be the same as in the volume control mode. With an inspiratory/expiratory ratio of 1:1, both PEEP levels and plateau inspiratory pressures are successively incremented in steps of 3–5 cmH_2O. Levels exceeding 20/60 cmH_2O for PEEP and plateau inspiratory pressure are necessary only occasionally. During the process of opening the lungs, the PaO_2 helps to guide this effort, because it is the only parameter that reliably correlates with the amount of lung tissue that participates in gas exchange. Moreover, a more than proportional increase in the tidal volume following an increase in airway pressure also indicates alveolar recruitment. It is important that during the manoeuvre (opening procedure) a sufficient intravascular volume is maintained and it may be necessary to administer additional fluids and/or give inotropic support during the opening procedure. This type of haemodynamic support will be superfluous at lower airway pressures.

If a further increase in airway pressure does not result in a parallel increase in PaO_2, plateau inspiratory pressures can be carefully reduced, because by this stage reopened alveoli are present, which no longer require such high intrapulmonary pressures to keep open. The PaO_2 should, however, remain high despite the reduction in airway pressures until the critical level of pressure is reached at which the least compliant parts of the lungs start to collapse. Should this occur, the inspiratory pressures should be increased to the previously determined values for a short period. The lung tissue is thus fully recruited again, and the pressures should be reduced consecutively to levels about 2–3 cmH_2O above the closing pressure.

As discussed above, changes in CO_2 should also always be kept in mind when this test is performed, as CO_2 (and dead space) can indirectly measure the amount of 'overdistension' induced by application of different airways pressures. We believe that the following is a reasonable alternative approach:

1) Stabilise haemodynamics and ensure that an appropriate volume status is reached with or without the use of vasoactive drugs.
2) Perform the PEEP test in volume control using the parameters suggested by the NIH low-tidal-volume study (i.e. 6 ml/kg IBW and a respiratory rate yielding a pH and PCO_2 as close as possible to physiological values) and an FiO_2 that will lead to at least 88–90% Sat O_2 at PEEP 5 cmH_2O. Then randomly apply different PEEP levels (from 5–20 cmH_2O), always preceded by a recruitment manoeuvre. The choice of the recruitment manoeuvre is the individual decision of the physician in charge. Different alternatives are available: (1) the classic recruitment manoeuvre at 40 cmH_2O for 10–40 s; (2) increase in PEEP, by 5-cmH_2O steps; (3) an increase in PEEP, keeping the tidal volume and respiratory rate constant to achieve 40 cmH_2O. We personally prefer this third approach, which has been reported to be more effective in improving oxygenation and to have a less negative effect on haemodynamics at least in animal studies (J.J. Marini and C.M. Lim, personal communication). As always, the recruitment pressure should be titrated according to the value of the intraabdominal pressure, as

determined by bladder pressure measurement. If the intraabdominal pressure is lower than 12 mmHg the recruitment pressure of 40 cmH_2O is considered high enough (as the properties of the chest wall are likely to be normal). If the intraabdominal pressure is higher than 12 mmHg the recruitment pressure should be increased to 50–60 cmH_2O (as the properties of the chest wall are likely to be abnormal).

3) Measure oxygenation, PCO_2 and compliance (as the simple ratio between tidal volume applied and the difference between the plateau pressure and total PEEP) at each step of PEEP. Improvement for each parameter is considered if oxygenation and compliance increase by at least 10 % from baseline and PCO_2 decreases by at least 1 mmHg. It is likely that if only one parameter improves less recruitment can be expected than when two or three of these parameters improve alt the same time.

Oxygenation, respiratory mechanics and lung morphology

Another integrated approach using respiratory mechanics and lung morphology has been suggested by Rouby et al. [76]. Briefly, these authors perform a chest X-ray or CT scan at a PEEP of 5 cmH_2O. If it shows a diffuse loss of aeration (diffuse and bilateral hyperdensities, 'white lungs') they plot a PV curve to determine the UIP and then perform a PEEP trial at 10, 15, 20, and 25 cmH_2O, with a pressure limitation 2 cmH_2O below the UIP. If the morphological study shows bilateral hyperdensities predominantly in the lower lobes, they suggest performing a PEEP trial at 5, 8, 10 and 12 cmH_2O. The optimal PEEP level is defined as the PEEP allowing the highest PaO_2 and $SatO_2$ at the lowest FiO_2. If the optimal PEEP level is not reached and if it does not allow for reduction of FiO_2 below 0.5, other supportive therapies are used, such as prone position, inhaled nitric oxide, an almitrine trial and finally extracorporeal membrane oxygenation.

All these recommendations for selection of the optimal PEEP levels are based on the hypothesis that PEEP is not only useful for improving oxygenation by keeping open previously collapsed alveoli, but is also a 'therapeutic' strategy that can be implemented to avoid collapse and decollapse of the alveolar units, thus preventing ventilator associated lung injury. It may also be possible, however, that keeping the diseased lung 'closed' and avoiding recruitment (e.g. in lobar pneumonia) is not dangerous and may even be beneficial. Experimental studies have shown that keeping part of the lung closed can result in less lung damage than in controls and improves lung function and survival [77, 78]. In our opinion, we should be ready to consider and study this perspective, and extracorporeal lung assistance should also be reevaluated from this angle [79].

References

1. Chiumello D, Pristine G, Slutsky AS (1999) Mechanical ventilation affects local and systemic cytokines in an animal model of acute respiratory distress syndrome. Am J Respir Crit Care Med 160:109-116
2. Dreyfuss D, Saumon G (1998) Ventilator-induced lung injury: lessons from experimental studies. Am J Respir Crit Care Med 157:294-323
3. Ranieri VM, Suter PM, Tortorella C et al (1999) Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. JAMA 282:54-61
4. Crotti S, Mascheroni D, Caironi P et al (2001) Recruitment and derecruitment during acute respiratory failure: a clinical study. Am J Respir Crit Care Med 164:131-140
5. Luecke T, Roth H, Herrmann P et al (2003) decreases atelectasis and extravascular lung water but not lung tissue volume in surfactant-washout lung injury. Intensive Care Med 29:2026-2033
6. Luecke T, Roth H, Joachim A et al (2004) Effects of end-inspiratory and end-expiratory pressures on alveolar recruitment and derecruitment in saline-washout-induced lung injury -- a computed tomography study. Acta Anaesthesiol Scand 48:82-92
7. Pelosi P, Goldner M, McKibben A et al (2001) Recruitment and derecruitment during acute respiratory failure: an experimental study. Am J Respir Crit Care Med 164:122-130
8. Rouby JJ, Lu Q, Vieira S (2003) Pressure/volume curves and lung computed tomography in acute respiratory distress syndrome. Eur Respir J Suppl 42:S27-S36
9. Rouby JJ, Puybasset L, Cluzel P et al (2000) Regional distribution of gas and tissue in acute respiratory distress syndrome. II. Physiological correlations and definition of an ARDS Severity Score. CT Scan ARDS Study Group. Intensive Care Med 26:1046-1056
10. Hall JB (1998) Respiratory system mechanics in adult respiratory distress syndrome. Stretching our understanding. Am J Respir Crit Care Med 158:1-2
11. Sandiford P, Province MA, Schuster DP (1995) Distribution of regional density and vascular permeability in the adult respiratory distress syndrome. Am J Respir Crit Care Med 151:737-742
12. Gattinoni L, Caironi P, Pelosi P et al (2001) What has computed tomography taught us about the acute respiratory distress syndrome? Am J Respir Crit Care Med 164:1701-1711
13. Gattinoni L, Mascheroni D, Torresin A et al (1986) Morphological response to positive end expiratory pressure in acute respiratory failure. Computerized tomography study. Intensive Care Med 12:137-142
14. Pelosi P, D'Andrea L, Vitale G, Pesenti A, Gattinoni L (1994) Vertical gradient of regional lung inflation in adult respiratory distress syndrome. Am J Respir Crit Care Med 149:8-13
15. Albert RK, Hubmayr RD (2000) The prone position eliminates compression of the by the heart. Am J Respir Crit Care Med 161:1660-1665
16. Malbouisson LM, Busch CJ, Puybasset L et al (2000) Role of the heart in the loss of aeration characterizing lower lobes in acute respiratory distress syndrome. CT Scan ARDS Study Group. Am J Respir Crit Care Med 161:2005-2012
17. Quintel M, Pelosi P, Caironi P et al (2004) An increase of abdominal pressure increases pulmonary edema in oleic acid-induced lung injury. Am J Respir Crit Care Med 169:534-541
18. Maggiore S, Brochard L (2000) Pressure-volume curve in the critically ill. Curr Opin Crit Care 6:1-10
19. Bone RC (1976) Diagnosis of causes for acute respiratory distress by pressure-volume curves. Chest 70:740-746

20. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE (1967) Acute respiratory distress in adults. Lancet 2:319-323
21. Matamis D, Lemaire F, Harf A et al (1984) Total respiratory pressure-volume curves in the adult respiratory distress syndrome. Chest 86:58-66
22. Petty TL, Silvers GW, Paul GW, Stanford RE (1979) Abnormalities in lung elastic properties and surfactant function in adult respiratory distress syndrome. Chest 75:571-574
23. Gattinoni L, Pesenti A, Caspani ML et al (1984) The role of total static lung compliance in the management of severe ARDS unresponsive to conventional treatment. Intensive Care Med 10:121-126
24. Gattinoni L, Pesenti A, Avalli L et al (1987) Pressure-volume curve of total respiratory system in acute respiratory failure. Computed tomographic scan study. Am Rev Respir Dis 136:730-736
25. Gattinoni L, Pesenti A, Bombino M et al (1988) Relationships between lung computed tomographic density, gas exchange, and PEEP in acute respiratory failure. Anesthesiology 69:824-832
26. Roupie E, Dambrosio M, Servillo G et al (1995) Titration of tidal volume and induced hypercapnia in acute respiratory distress syndrome. Am J Respir Crit Care Med 152:121-128
27. Maggiore SM, Jonson B, Richard JC et al (2001) Alveolar derecruitment at decremental positive end-expiratory pressure levels in acute lung injury: comparison with the lower inflection point, oxygenation, and compliance. Am J Respir Crit Care Med 164:795-801
28. Nagano O, Tokioka H, Ohta Y et al (2001) Inspiratory pressure-volume curves at different positive end-expiratory pressure levels in patients with ALI/ARDS. Acta Anaesthesiol Scand 45:1255-1261
29. Richard JC, Maggiore SM, Jonson B et al (2001) Influence of tidal volume on alveolar recruitment. Respective role of PEEP and a recruitment maneuver. Am J Respir Crit Care Med 163:1609-1613
30. Servillo G, Svantesson C, Beydon L et al (1997) Pressure-volume curves in acute respiratory failure: automated low flow inflation versus occlusion. Am J Respir Crit Care Med 155:1629-1636
31. Ranieri VM, Giunta F, Suter PM et al (2000) Mechanical ventilation as a mediator of multisystem organ failure in acute respiratory distress syndrome. JAMA 284:43-44
32. Hickling KG (1998) The pressure-volume curve is greatly modified by recruitment. A mathematical model of ARDS lungs. Am J Respir Crit Care Med 158:194-202
33. Jonson B, Richard JC, Straus C et al (1999) Pressure-volume curves and compliance in acute lung injury: evidence of recruitment above the lower inflection point. Am J Respir Crit Care Med 159:1172-1178
34. Downie JM, Nam AJ, Simon BA (2004) Pressure-volume curve does not predict steady-state lung volume in canine lavage lung injury. Am J Respir Crit Care Med 169:957-962
35. Hickling KG (2001) Best compliance during a decremental, but not incremental, positive end-expiratory pressure trial is related to open-lung positive end-expiratory pressure: a mathematical model of acute respiratory distress syndrome lungs. Am J Respir Crit Care Med 163:69-78
36. Luecke T, Meinhardt JP, Herrmann P et al (2003) Setting mean airway pressure during high-frequency oscillatory ventilation according to the static pressure-volume curve in surfactant-deficient lung injury: a computed tomography study. Anesthesiology 99:1313-1322

37. Gattinoni L, Mascheroni D, Basilico E et al (1987) Volume/pressure curve of total respiratory system in paralysed patients: artefacts and correction factors. Intensive Care Med 13:19-25
38. Janney CD (1959) Super-syringe. Anesthesiology 20:709-711
39. Gottfried SB, Rossi A, Calverley PM, Zocchi L et al (1984) Interrupter technique for measurement of respiratory mechanics in anesthetized cats. J Appl Physiol 56:681-690
40. Rossi A, Gottfried SB, Higgs BD et al (1985) Respiratory mechanics in mechanically ventilated patients with respiratory failure. J Appl Physiol 58:1849-1858
41. Rossi A, Gottfried SB, Zocchi L et al (1985) Measurement of static compliance of the total respiratory system in patients with acute respiratory failure during mechanical ventilation. The effect of intrinsic positive end-expiratory pressure. Am Rev Respir Dis 131:672-677
42. Sydow M, Burchardi H, Zinserling J et al (1991) Improved determination of static compliance by automated single volume steps in ventilated patients. Intensive Care Med 17:108-114
43. Lu Q, Vieira SR, Richecoeur J et al (1999) A simple automated method for measuring pressure-volume curves during mechanical ventilation. Am J Respir Crit Care Med 159:275-282
44. Rodriguez L, Marquer B, Mardrus P et al (1999) A new simple method to perform pressure-volume curves obtained under quasi-static conditions during mechanical ventilation. Intensive Care Med 25:173-179
45. Svantesson C, Drefeldt B, Sigurdsson S et al (1999) A single computer-controlled mechanical insufflation allows determination of the pressure-volume relationship of the respiratory system. J Clin Monit Comput 15:9-16
46. Karason S, Sondergaard S, Lundin S et al (2000) Evaluation of pressure/volume loops based on intratracheal pressure measurements during dynamic conditions. Acta Anaesthesiol Scand 44:571-577
47. Karason S, Sondergaard S, Lundin S et al (2000) A new method for non-invasive, manoeuvre-free determination of "static" pressure-volume curves during dynamic/therapeutic mechanical ventilation. Acta Anaesthesiol Scand 44:578-585
48. Mols G, Brandes I, Kessler V et al (1999) Volume-dependent compliance in ARDS: proposal of a new diagnostic concept. Intensive Care Med 25:1084-1091
49. Gattinoni L, Pelosi P, Suter PM et al (1998) Acute respiratory distress syndrome caused by pulmonary and extrapulmonary disease. Different syndromes? Am J Respir Crit Care Med 158:3-11
50. Pelosi P, Bottino N, Chiumello D et al (2003) Sigh in supine and prone position during acute respiratory distress syndrome. Am J Respir Crit Care Med 167:521-527
51. Pelosi P, D'Onofrio D, Chiumello D et al (2003) Pulmonary and extrapulmonary acute respiratory distress syndrome are different. Eur Respir J Suppl 42:S48-S56
52. Ranieri VM, Brienza N, Santostasi S et al (1997) Impairment of lung and chest wall mechanics in patients with acute respiratory distress syndrome: role of abdominal distension. Am J Respir Crit Care Med 156:1082-1091
53. Malbrain ML (2004) Is it wise not to think about intraabdominal hypertension in the ICU? Curr Opin Crit Care 10:132-145
54. Mancebo J, Benito S, Martin M et al (1988) Value of static pulmonary compliance in predicting mortality in patients with acute respiratory failure. Intensive Care Med 14:110-114
55. Pelosi P, Cereda M, Foti G et al (1995) Alterations of lung and chest wall mechanics in patients with acute lung injury: effects of positive end-expiratory pressure. Am J Respir Crit Care Med 152:531-537

56. Sibilla S, Tredici S, Porro A et al (2002) Equal increases in respiratory system elastance reflect similar lung damage in experimental ventilator-induced lung injury. Intensive Care Med 28:196-203
57. Suwanvanichkij V, Curtis JR (2004) The use of high positive end-expiratory pressure for respiratory failure in abdominal compartment syndrome. Respir Care 49:286-290
58. Amato MB, Barbas CS, Medeiros DM et al (1998) Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 338:347-354
59. Venegas JG, Harris RS, Simon BA (1998) A comprehensive equation for the pulmonary pressure-volume curve. J Appl Physiol 84:389-395
60. Schmitt JM, Vieillard-Baron A, Augarde R et al (2001) Positive end-expiratory pressure titration in acute respiratory distress syndrome patients: impact on right ventricular outflow impedance evaluated by pulmonary artery Doppler flow velocity measurements. Crit Care Med 29:1154-1158
61. Suter PM, Fairley B, Isenberg MD (1975) Optimum end-expiratory airway pressure in patients with acute pulmonary failure. N Engl J Med 292:284-289
62. Vieillard-Baron A, Loubieres Y, Schmitt JM et al (1999) Cyclic changes in right ventricular output impedance during mechanical ventilation. J Appl Physiol 87:1644-1650
63. Vieillard-Baron A, Jardin F (2003) Why protect the right ventricle in patients with acute respiratory distress syndrome? Curr Opin Crit Care 9:15-21
64. Suter PM, Fairley HB, Isenberg MD (1978) Effect of tidal volume and positive end-expiratory pressure on compliance during mechanical ventilation. Chest 73:158-162
65. Acute Respiratory Distress Syndrome Network (2000) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 342:1301-1308
66. Gattinoni L, Tognoni G, Pesenti A et al (2001) Effect of prone positioning on the survival of patients with acute respiratory failure. N Engl J Med 345:568-573
67. Ranieri VM, Zhang H, Mascia L et al (2000) Pressure-time curve predicts minimally injurious ventilatory strategy in an isolated rat lung model. Anesthesiology 93:1320-1328
68. Kunst PW, Bohm SH, Vazquez de Anda G et al (2000) Regional pressure volume curves by electrical impedance tomography in a model of acute lung injury. Crit Care Med 28:178-183
69. Pelosi P, Croci M, Calappi E et al (1995) The prone positioning during general anesthesia minimally affects respiratory mechanics while improving functional residual capacity and increasing oxygen tension. Anesth Analg 80:955-960
70. Pelosi P, Ravagnan I, Giurati G et al (1999) Positive end-expiratory pressure improves respiratory function in obese but not in normal subjects during anesthesia and paralysis. Anesthesiology 91:1221-1231
71. Ranieri VM, Giuliani R, Cinnella G et al (1993) Physiologic effects of positive end-expiratory pressure in patients with chronic obstructive pulmonary disease during acute ventilatory failure and controlled mechanical ventilation. Am Rev Respir Dis 147:5-13
72. Gattinoni L, Pelosi P, Crotti S et al (1995) Effects of positive end-expiratory pressure on regional distribution of tidal volume and recruitment in adult respiratory distress syndrome. Am J Respir Crit Care Med 151:1807-1814
73. Bohm S, Lachmann B (1996) Pressure Control Ventilation: Putting a mode into a perspective. Int J Intensive Care 4:45-55
74. Rimensberger PC, Cox PN, Frndova H et al (1999) The open lung during small tidal volume ventilation: concepts of recruitment and "optimal" positive end-expiratory pressure. Crit Care Med 27:1946-1952

75. Rimensberger PC, Pache JC, McKerlie C et al (2000) Lung recruitment and lung volume maintenance: a strategy for improving oxygenation and preventing lung injury during both conventional mechanical ventilation and high-frequency oscillation. Intensive Care Med 26:745-755
76. Rouby JJ, Lu Q, Goldstein I (2002) Selecting the right level of positive end-expiratory pressure in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 165:1182-1186
77. Hickling KG, Wright T, Laubscher K et al (1998) Extreme hypoventilation reduces ventilator-induced lung injury during ventilation with low positive end-expiratory pressure in saline-lavaged rabbits. Crit Care Med 26:1690-1697
78. Rossi N, Kolobow T, Aprigliano M et al (1998) Intratracheal pulmonary ventilation at low airway pressures in a ventilator-induced model of acute respiratory failure improves lung function and survival. Chest 114:1147-1157
79. Gattinoni L, Pesenti A, Bombino M et al (1993) Role of extracorporeal circulation in adult respiratory distress syndrome management. New Horiz 1:603-612

Chapter 27

PEEP and cardiac output

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Cyclic opening and closing of atelectatic alveoli with tidal breathing is known to be a basic mechanism leading to ventilator-induced lung injury [1]. To prevent alveolar cycling and derecruitment in acute lung injury, high levels of PEEP have been found necessary to counterbalance the increased lung mass resulting from oedema, inflammation and infiltrations and to maintain normal functional residual capacity (FRC) [2]. Therefore, the application of high levels of PEEP is recommended [3], although 'aggressive' mechanical ventilation using high levels of PEEP to maintain or restore oxygenation during acute lung injury can markedly affect cardiac function in a complex and often unpredictable fashion.

Except for that from the failing ventricle, PEEP usually decreases cardiac output, a well-known fact since the classic studies published by Cournand et al. [4], in which the effects of positive-pressure ventilation were measured. The conclusion was that positive-pressure ventilation restricted the filling of the right ventricle because the elevated intrathoracic pressures restricted venous flow into the thorax, thereby reducing cardiac output. This formulation of intrathoracic responses to positive-pressure ventilation is still the basis of our present-day understanding of the cardiopulmonary interactions induced by PEEP; although precise responses to PEEP have not been simple to prove and the intrathoracic responses appear multiple and complex.

As heart rate usually does not change with PEEP [5], the entire fall in cardiac output is a consequence of a reduction in left ventricular stroke volume (SV). Therefore, the discussion on PEEP-induced changes in cardiac output can be confined to analysis of changes in SV and its determinants, i.e. preload, afterload, contractility and ventricular compliance.

Before considering how PEEP affects the determinants of SV, however, we must emphasise that ventilation with PEEP, like any other active or passive ventilatory manoeuvre, primarily affects cardiac function by changing lung volume and intrathoracic pressure (ITP) [6]. To understand the direct cardiocirculatory consequences of respiratory failure, it is therefore necessary to understand the effects of changes in lung volume, factors controlling venous return, diastolic interactions between the ventricles and the effects of intrathoracic pressures on cardiac, specifically left ventricular, function.

This review will attempt to integrate basic mechanisms into the global mechanisms of PEEP and relate these concepts to patient care. Analysis will focus on (1) the relationships between lung volume and intrathoracic pressure and (2) using

these relationships, specifically assess the four primary components of the circulatory system that are affected by ventilation: systemic venous return, right ventricular (RV) output, left ventricular (LV) filling and LV output [7].

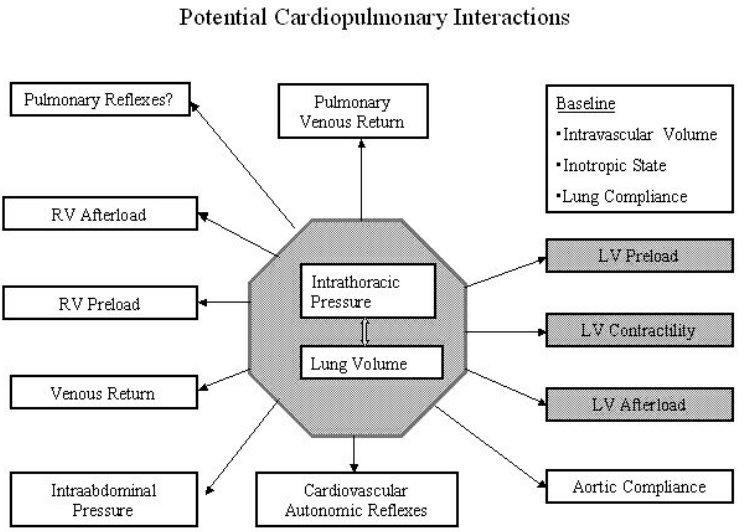

Fig. 1. Schematic representation of potential cardiopulmonary interactions with changes in intrathoracic pressure and lung volume (Redrawn from [8]). To get a more focused view of these numerous interactions, all haemodynamic effects of ventilation can simply be grouped into processes, which – by changing lung volume and ITP – affect LV preload, contractility and afterload [6]

Relations between airway pressure, intrathoracic pressure and lung volume

There is a lot of confusion both in the literature and at the bedside in understanding and applying the concept of intrathoracic pressure (ITP) during mechanical ventilation. As outlined by Scharf [9], it must be clear that the term *intrathoracic pressure* does not per se specify a pressure. Rather, it is necessary to ask, 'what intrathoracic pressure, oesophageal, pleural, cardiac fossa, or cardiac surface?' To confuse matters even further, it is common practice to equate changes in airway pressure (Paw) with changes in both ITP and lung volume.

Although positive-pressure ventilation increases lung volume only by increasing Paw, the degree to which both ITP (which can be oesophageal [Pes], pleural [Ppl] or pericardial [Ppc]) and lung volume increase will be a function of airway resistance as well as of lung and chest wall compliance. Bearing in mind that the heart is a pressure chamber within a pressure chamber, i.e. the thorax, the question

of how much of the externally applied Paw (or PEEP) is actually transmitted to the intrathoracic structures is of pivotal importance, especially in attempts to measure and interpret filling pressures of the heart in order to define its loading conditions. The catheter (central venous or pulmonary artery) measures an intravascular pressure relative to atmosphere. The interpretation of haemodynamic data during positive-pressure ventilation, however, requires thinking in terms of *transmural* pressures, which is the pressure difference acting across the wall of a vessel or cardiac chamber, i.e. outside pressure subtracted from inside pressure. As neither the pericardial pressure, which is the outside pressure for the right and left ventricle, nor the pleural pressure is directly accessible in clinical practice, the oesophageal pressure (Pes) is commonly used as the outside pressure. Thus, transmural LV pressure is clinically measured as LV intracavitary pressure minus oesophageal pressure, assuming that Pes represents cardiac surface pressure. While this is a common assumption, when the pericardium is intact, changes in cardiac volume may render it invalid [10].

In summary, there are two important limitations that make it difficult to assess PEEP-induced changes in cardiac function:

First, true transmural filling pressures of the right and left ventricles are not available, and surrogate estimates using oesophageal pressure have to be used instead. Second, predicting how much Paw is transmitted to the pericardial space is difficult at best. According to O'Quin [11], it is possible to estimate how changes in alveolar pressure (ΔPalv) translate into changes in ITP (ΔITP), assuming that the compliances of the lung (C_L) and chest wall (C_{CW}) are in series and homogeneous:

$\Delta ITP/\Delta Palv = 1/(1+ C_{CW}/C_L)$

A precise value for C_{CW}/ C_L is not generally known, and the validity of the underlying assumptions is rather approximate. Nevertheless, the above equation is helpful for making rough predictions. In most healthy subjects, C_L is nearly the same as C_{CW} during normal tidal volume (0.2 l/cmH_2O). In this situation, $\Delta ITP/\Delta Palv = ½$ or half of the PEEP applied would be expected to be transmitted to ITP. Whereas a popular rule of thumb is to subtract half of the applied PEEP from haemodynamic measurements, this rule is helpful only when the patient's chest wall and lung compliance are normal [12]. A decrease in lung compliance has been shown to decrease the transmission of Paw to intrathoracic structures (commonly measured as Ppl) [13, 14], while these findings have been challenged by O'Quin [11], who measured juxtacardiac Ppl and found that the fractional change in Ppl vs Paw was only slightly decreased after acute lung injury in a canine model. These results were confirmed by Scharf and Ingram [15] and Romand et al. [16], who were able to show that the primary determinant of change in Ppl (or ITP) during positive-pressure breathing is the amount of lung inflation, and not a specific change in compliance. Thus, the PEEP-induced change in total intrathoracic volume, which actually has to be considered in the diseased lung, when total volume can be increased due to extensive oedema even if the aerated lung volume is actually decreased, ultimately determines the changes in ITP and the concomitant haemodynamic effects.

In summary, it is extremely difficult to attain any degree of accuracy in predicting the amount to which increases in airway pressure, induced either by PEEP or positive-pressure ventilation, will increase intrathoracic pressure in an individual patient with acute lung injury; attempts are potentially hazardous [17]. Nevertheless, in attempts to understand the haemodynamic effects of PEEP in an individual patient, the most important question to keep in mind is: 'To what extent will PEEP change total lung volume and ITP, and how will these changes ultimately affect LV preload, contractility and afterload?'

Effects of PEEP

As proposed by Pinsky [6], all haemodynamic effects of positive-pressure ventilation and PEEP can simply be grouped into processes which – by changing lung volume and intrathoracic pressure – affect left ventricular preload, afterload and contractility (Fig. 1).

Left ventricular preload

The effects of PEEP on LV preload are dependent on changes in systemic venous return, right ventricular output and left ventricular filling. Owing to the complexity of these changes, the single factors will be discussed separately.

Determinants of venous return

The sensitivity of systemic venous return to respiratory-induced changes has been described in the classic experiments by Guyton et al. [18, 19]. The basic principle is that the systemic venous return is the major determinant of circulation and is equal to LV output in steady state conditions [7, 20, 21]. Guyton et al. [19] demonstrated that the right atrial pressure (RAP) represents the outflow pressure (back-pressure) for venous return. The relationship between RAP and venous return is displayed by the venous return curve (Fig.2, left upper panel). The pressure gradient driving blood from the periphery to the right atrium can be defined as the difference between the pressures in the upstream reservoirs, referred to as mean circulatory pressure (MCP) or mean systemic pressure (Pms) relative to RAP. Mean systemic pressure, defined as the RAP at the point of zero flow, is a function of blood volume, peripheral vasomotor tone and the distribution of blood within the vasculature [22]. As RAP increases, venous return decreases until RAP is equal to the mean systemic pressure. As RAP decreases, VR increases until the point of flow limitation (FL) is reached. The slope of the VR curve is equal to 1/RV. The relationship between right atrial end-diastolic pressure (representing preload) and cardiac output is the familiar Frank–Starling relationship ([9], Fig.2, right upper panel). The superimposition of the venous return curve and the Frank–Starling curve on the same set of axes (Fig. 2, lower panel) was the creative insight of Guyton et al. [18] and provided an immensely useful conceptual framework for studying cardiovascular

control [23]. Since, in steady state, cardiac output must be equal to venous return, the point at which the two systems exist in equilibrium is represented by the point of intersection of the cardiac function (Frank–Starling) and venous return curves [9]. Thus for any given set of cardiac function and venous return curves there is only one combination of RAP and cardiac output (=VR) at which steady state conditions apply (Fig. 2, lower panel, point A).

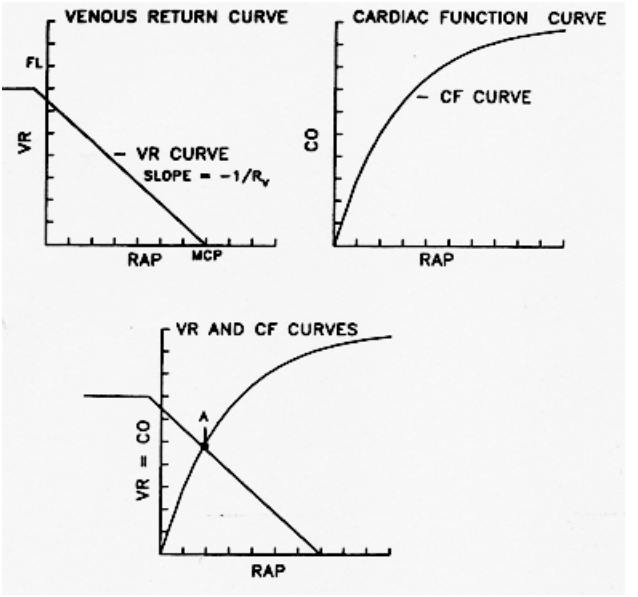

Fig. 2. Venous return (*VR*) and cardiac function (*CF*) curves. As right atrial pressure (*RAP*) increases, venous return decreases until RAP equals mean circulatory pressure (*MCP*). As RAP decreases, VR increases until the point of flow limitation (*FL*). The slope of the VR curve is equal to 1/RV. The CF curve is essentially a form of the Frank–Starling curve. In steady state the system exists at the point of intersection of the curves (point *A*). (Reprinted from [9] with permission)

Venous return

Since the right atrium is a highly compliant structure, RAP will reflect variations in intrathoracic pressure (ITP). Any increase in PEEP, by increasing lung volume and thus ITP, is expected to decrease venous return by decreasing the pressure gradient in a manner demonstrated in Fig. 3. The cardiac function curve is displaced to the right by the amount by which ITP is increased, thus maintaining the same transmural pressure–cardiac output relationships. Postulating that mean circulatory pressure (MCP) does not change with PEEP, this would move the intersection of the cardiac function and the venous return curves 'downward' on the venous return curve [9]. As a result, the gradient for venous return (MCP-RAP) decreases, decelerating venous blood flow [24], decreasing RV filling and consequently, decreasing RV stroke volume [25-28].

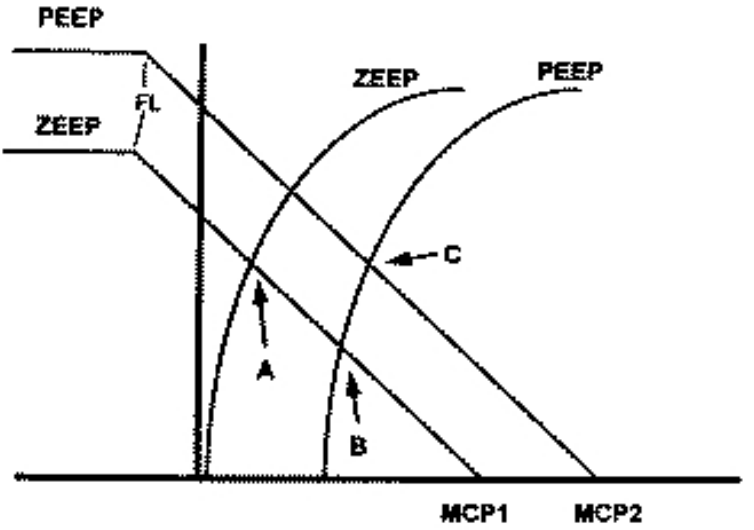

Fig. 3. Theoretic effects of PEEP on venous return (*VR*) and cardiac output (*CO*). PEEP causes an increase in ITP and a right shift in the cardiac function curve. If there were no change in the VR curve, then CO and VR would decrease (from point *A* to point *B*). However, if there is a compensatory increase in mean circulatory pressure (from MCP_1 to MCP_2), then the system will exist in equilibrium at point *C*, at which VR and CO will be maintained relative to ZEEP conditions. MCP can increase either by an increase in stressed volume or by sympathoadrenal stimulation. (Reprinted from [9], with permission)

However, as first suggested by Scharf et al. [29] and later demonstrated in experimental studies [30, 31], PEEP also increases MCP, thus preserving the gradient for venous return. Recently, Jellinek et al. [32], were able to confirm that positive airway pressure increased RAP and MCP equally in patients during general anaesthesia for implantation of defibrillator devices.

Whereas the pressure gradient for venous return was not altered by PEEP in these studies, venous return and cardiac output invariably fell, indicating an increase in resistance of the venous conduits. According to Fessler et al. [30], PEEP may either (a) decrease the calibre of the conducting veins by constriction or compression, resulting in reduced flow at the same driving pressure through an increase in ohmic resistance (e.g. by abdominal pressurisation) or (b) increase the pressure around a portion of the veins in excess of RAP.

If RAP were below a critical closing pressure (P_{CRIT}) of the veins, a condition termed a 'vascular waterfall' is said to exist. This term was first applied to blood flow through the pulmonary circulation when alveolar pressure exceeded left atrial pressure [33]. In these circumstances, the *effective* downstream pressure for venous return is P_{CRIT}, not RAP. If PEEP were to elevate P_{CRIT} in some parts of the circulation in excess of RAP, then the effective pressure gradient for venous flow

from those regions could fall despite an unaltered (MCP–RAP) difference [34] and flow limitation at PEEP would occur at higher pressures than with ZEEP. In fact, in canin studies Fessler et al. [35] were able to demonstrate a PEEP-induced vascular collapse at the inferior vena cava consistent with a vascular waterfall [36] or zone 2 condition [37], causing the back-pressure to venous return to be located upstream of the right atrium. With PEEP, the vessels collapsed at higher pressure than normal, i.e. there was an increase in P_{CRIT} of these veins caused by direct mechanical compression from the inflating lungs and/or mechanical compression from the intra-abdominal contents, especially the liver [9, 37, 38].

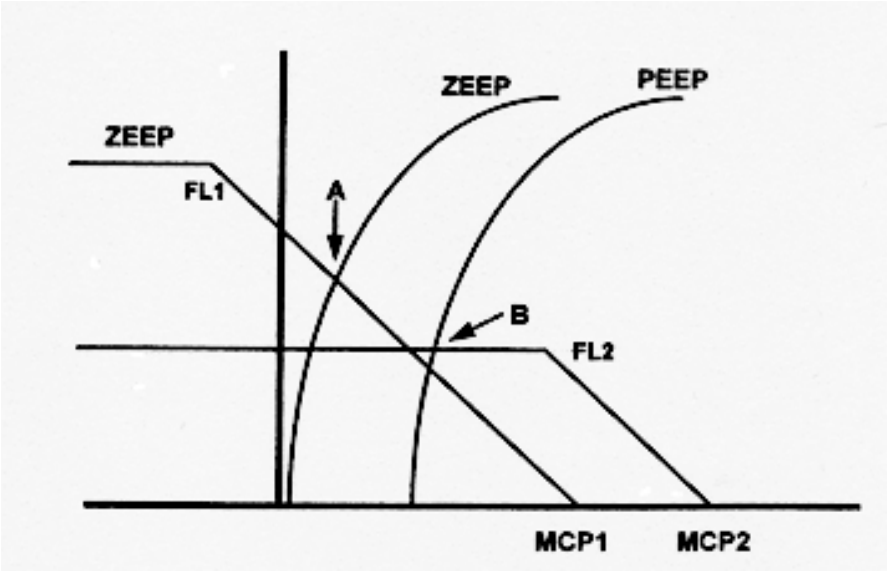

Fig. 4. Another, more likely scheme for the changes in venous return with PEEP. If there is an increase in the pressure, at which flow limitation occurs, then the ability of an increase in mean circulatory pressure to buffer PEEP-induced decreases in venous return is markedly smaller. FL1, flow-limiting point at ZEEP; FL2, flow-limiting point at PEEP. (Reprinted from [10], with permission)

Whether this concept is applicable in humans on mechanical ventilation and PEEP, however, is still a matter of debate. While a PEEP-induced collapse of the inferior vena cava in humans is very unlikely for anatomical reasons, Vieillard-Baron et al. [39] were able to demonstrate a high collapsibility index of the thoracic part of the superior vena cava (SVC). As in humans, the part of venous return devoted to SVC flow is close to 25%, it is not surprising that a marked and sudden reduction in the size of this vessel had discernible consequences for RV filling. On the contrary, however, no tendency towards collapse could be observed in the

surgical patients studied by Jellinek et al. [32]. These differences can be readily explained by the volume status of the individual patient. In haemodynamically stable, volume-loaded cardiac surgical patients, for example, increases in airway pressure up to 20 cmH_2O did not affect venous return and cardiac output, primarily because of an in-phase-associated pressurisation of the abdominal compartment associated with compression of the liver and squeezing of the lungs [40]. Systemic venous return depends on baseline filling status, which will substantially influence the effects of increasing airway pressure – and thus lung inflation – on stroke volume and cardiac output. This fact explains why in patients with acute lung injury, baseline right atrial pressure was most sensitive in predicting the subsequent haemodynamic depression induced by a apnoeic positive airway pressure of 30 cmH_2O [41]. Patients with baseline RAP mmHg demonstrated a more profound haemodynamic depression than patients with higher baseline RAP, potentially placing these patients at risk of organ hypoperfusion.

In summary, the effects of PEEP on venous return can show wide interindividual variation, depending on the changes in RAP, MCP, intra-abdominal pressure and baseline volume status.

Right ventricular output

The pumping capability of the right ventricle depends on RV filling volume (preload), RV contractility and the pressure against which the RV ejects (afterload). While PEEP decreases RV preload by impairing systemic venous return, it will also increase RV afterload. The exact interaction among RV ejection pressure, pulmonary input impedance and RV systolic function is difficult to define, because RV ejection is more 'continuous' in nature than LV contraction, uses LV contractile force to develop a majority of its intraluminal pressure via the shared muscle fibres of the interventricular septum, and ejects into a vascular system with a highly variable but usually low-impedance pulmonary vascular circuit [17, 42]. In a simplified manner, however, RV afterload can be estimated as maximal RV systolic wall stress [43]. Thus, RV afterload, by the LaPlace equation, is a function of the product of RV end-diastolic volume and RV end-systolic pressure [43]. Especially during ventilation with PEEP, exact assessment of these parameters is difficult, however, because of (a) the uncertainties in calculation of transmural pressures, as discussed above, and (b) because of the difficulties in obtaining adequate measurements of RV volume owing to the complex geometry of the RV and its position in the thorax [44]. Increases in transmural pulmonary artery pressure, which is the actual RV ejection pressure, increases RV afterload, thus impeding RV ejection [44]. If the RV does not empty as much as before, stroke volume will decrease and RV end-systolic volume will increase [43], increasing RV wall stress and thus afterload further, eventually leading to acute cor pulmonale and cardiovascular collapse. As outlined by Pinsky [17], the pericardium has an important role in minimising these potentially detrimental right-sided interactions, markedly limiting RV overdistension. In fact, one of the primary physiological roles of the pericardium appears to be to limit RV overdistension.

Positive-pressure ventilation and PEEP can modify pulmonary vascular resistance (PVR), and thus RV afterload, by any of several mechanisms. First, PEEP may reduce PVR by reducing increased pulmonary vasomotor tone owing to hypoxic pulmonary vasoconstriction. If ventilation with PEEP recruits collapsed alveoli, thereby increasing regional alveolar pO_2 above the critical threshold of 60 mmHg, hypoxic pulmonary vasoconstriction will be reduced, pulmonary vasomotor tone will fall and RV ejection will improve [45, 46].

Second, PEEP changes PVR by changing lung volume. PVR is related to lung volume in a bimodal fashion, with resistance to flow being minimal near functional residual capacity. As lung volume increases from residual volume to functional residual capacity (FRC), PVR decreases and vascular capacitance increases. As lung volumes continue to increase from FRC to total lung capacity, PVR increases and vascular capacitance decreases. This biphasic behaviour is explained by postulating two different types of intraparenchymal vessels. Vessels located within alveolar septa (intra-alveolar vessels) are compressed as lung volume increases, while vessels located in the corners where alveoli join or within peribronchial spaces (extra-alveolar vessels) are exposed to expanding forces when lung volume increases. At lung volumes below FRC, the effects on extra-alveolar vessels predominate and PVR decreases. As lung volume increases above FRC, effects on intra-alveolar vessels predominate and PVR rises again [47]. At higher lung volumes and airway pressures, alveolar pressure is elevated relative to pulmonary artery and left atrial pressure [48], which expands zone II regions of the lung [49], where alveolar pressure is the effective pressure against which RV ejects [34].

In summary, the effects of PEEP on RV output depend on (a) how PEEP changes lung volume relative to normal FRC, (b) on the extent to which it can alleviate hypoxic pulmonary vasoconstriction and finally (c) on the overall change in pulmonary arterial pressure. Brunet et al. [50], for example, demonstrated an inverse correlation between changes in RV function, estimated by RV end-diastolic volume (RVEDV) and RV ejection fraction (RVEF), and the increase in mean pulmonary artery pressure. In an ovine saline lavage model of acute lung injury, Luecke et al. [51] found RVEDV and RVEF to be well preserved up to a PEEP of 21 cmH_2O, supporting the findings by Cheatham et al. obtained in ARDS patients [52]. While these data show that RV dysfunction is not an inevitable result of therapy with PEEP, an echocardiographic study from Jardin's group [53] has demonstrated a 25% incidence of acute cor pulmonale due to increased right ventricular outflow impedance in ARDS patients submitted to protective ventilation. The same group also provided echocardiographic evidence that the way PEEP is managed in ARDS may have significant consequences for RV outflow impedance [54] and that increased RV afterload is the main parameter explaining the decrease in RV stroke volume in ARDS patients [55]. Based on these findings, they strongly recommend RV protection during mechanical ventilation [56] by limitation of PEEP and avoidance of hypercapnic acidosis, which may adversely affect RV performance by inducing pulmonary arteriolar vasoconstriction, leading to pulmonary hypertension [57].

LV filling and ventricular interdependence

Any decrease in systemic venous return and thus, RV inflow, must, within a few heart beats, result in decreased pulmonary venous return and inflow to the left ventricle because the two ventricles pump in series. Analogous to systemic venous return, pulmonary venous return to the left ventricle is regulated by the driving pressure and the impedance of flow, which in this case are transmural pulmonary venous pressure and transmural left atrial pressure, respectively [12].

In addition to this passive coupling of the right and left ventricles, PEEP may have more direct mechanical effects on LV filling and, thus, on LV preload. Since the two ventricles share common fibre bundles and a common interventricular septum, coexist within the same pericardial space and are surrounded by a fixed cardiac fossa volume, any increase in RV volume must limit LV filling. This parallel interaction between the ventricles causing the function of one ventricle to influence the function of the other is called *ventricular interdependence* [58, 59]. Classically, ventricular interdependence is thought to occur as increases in RV volume decrease LV diastolic compliance, LV preload and LV output. RV end-diastolic volume increases during spontaneous inspiration, transiently shifting the intraventricular septum from its neutral position into the LV [60]. As the RV dilates, LV diastolic compliance is reduced, reducing LV end-diastolic volume. This may also occur if the application of PEEP results in acute cor pulmonale. However, RV volumes can also decrease during positive-pressure ventilation and PEEP, reducing ventricular interdependence and allowing LV volumes to increase for the same filling pressures [17, 61, 62]. In addition to shifts of the interventricular septum, increasing intrathoracic pressures may also change the overall shape of the LV cavity owing to nonuniformity of changes in cardiac surface pressures [63, 64].

As reviewed by Fessler [34], during mechanical ventilation with PEEP, these factors have been difficult to tease apart, because of complex interaction between cardiac and lung volume. In animals, PEEP has been shown to cause flattening of the LV, which is greatest at the free wall [65, 66]. In humans, PEEP increases the radius of the curvature of the septum [67–69]. PEEP has been shown in some studies to decrease LV compliance [68, 70], which may be due to changes in LV conformation or increased rigidity of the distended surrounding lung [70]. Others have failed to find reduced LV compliance during PEEP [71] or have shown it only when RV dilatation is exaggerated by high levels of PEEP and RV ischaemia [72]. In another study [73], the leftward shift of the LV end-diastolic transmural pressure–volume curve observed at high levels of PEEP in patients with ARDS was related to overestimation of transmural pressure rather than to decreased LV diastolic compliance (Fig. 5). Bearing in mind the nonuniformity of cardiac surface pressures, it is difficult at best to obtain adequate estimates of transmural LV filling pressures at higher levels of PEEP and to assess LV compliance. Therefore, no final conclusions about the effect of PEEP on LV compliance are possible. Changes in LV conformation induced by PEEP, while of mechanical interest, probably have little impact on cardiac output on PEEP [34, 74].

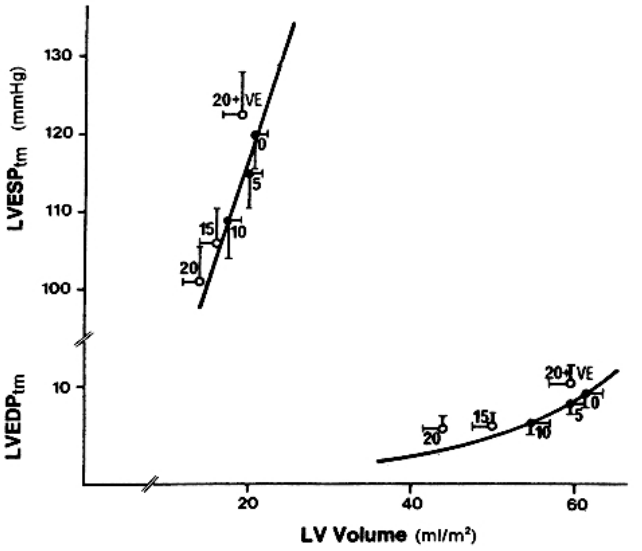

Fig. 5. Effects of continuous positive-pressure ventilation on end-diastolic (*ED*) and end-systolic (*ES*) volume (*V*)–transmural pressure (tm) relationship in the left ventricle (*LV*). *Closed circles* represent mean volume–transmural pressure coordinates at low levels of PEEP (0, 5, 10 cmH_2O), and the *continuous lines* are drawn through these points to indicate typical volume–transmural pressure curves. *Open circles* represent the mean volume–transmural pressure coordinates at high levels of PEEP (15, 20, and 20 cm H_2O with volume expansion (*VE*). Both ESV and EDV are reduced at the same pressures, indicating leftward displacement of the volume–transmural pressure curves at high levels of PEEP. (From [73], with permission)

In summary, LV preload during PEEP is predominantly affected by the decrease in systemic venous return and/or the decrease in RV output (*series* effects), while direct, *parallel* interactions may have limited effects, unless acute cor pulmonale is present.

LV output (contractility and afterload)

As stated for the right ventricle, the pumping capability of the left ventricle depends on LV filling volume (preload), LV contractility and the pressure against which the LV ejects (afterload). While PEEP decreases LV preload, its effect on LV contractility probably has generated more controversy than any other aspect of heart–lung interactions. This arose in part from difficulty in defining myocardial function and, once it was defined, difficulty in measuring it [34]. One commonly used estimate of myocardial function is the Starling relationship, i.e. the relationship between filling pressure of a ventricle and mechanical output (SV, CO, work, power). While

this relationship is physiologically relevant, because normal pumping of the ventricles requires that they deliver appropriate amounts of blood to the tissues at acceptably low filling pressures [75], it poses special problems during mechanical ventilation at high intrathoracic pressures: The Starling relationship describes a relationship between ventricular preload and output. Preload is end-diastolic volume, and a function curve relating ED volume to mechanical output is therefore a more accurate representation of the Frank–Starling effect. Unfortunately, filling pressures (pulmonary capillary wedge or RAP) are usually more readily available than volume, and the inability to accurately measure changes in LV volumes during ventilatory manoeuvres still represents a major limitation in the investigations of heart–lung interactions [6, 51]. As discussed above, however, these filling pressures are measured relative to ambient pressure and correction for transmural filling pressures (intracavitary minus cardiac surface) is difficult. Therefore, characterisation of ventricular performance, especially during high intrathoracic pressure, in terms of function curves relating filling pressures to output is a 'black box' approach; alterations in diastolic compliance (see above) produce effects that are indistinguishable from alterations in contractile performance [75]. Accordingly, a more attractive approach is to examine the relationship between LV end-diastolic volume and CO on PEEP. This has been attempted by numerous techniques in animal and human studies [5, 51, 67, 69, 71–73, 76–78], which have generally failed to demonstrate a decrease in LV function (Fig. 6).

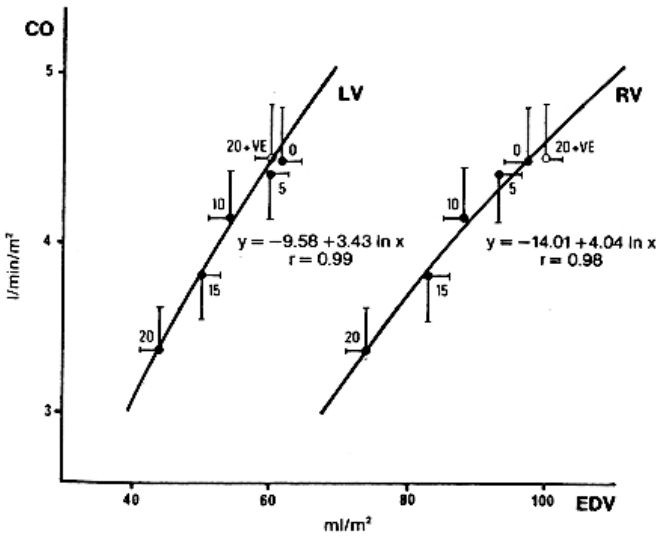

Fig. 6. Starling relationship between cardiac output (*CO*) and end-diastolic volume (*EDV*) of the right ventricle (*RV*) (*right curve*) and left ventricle (*LV*) (*left curve*) as airway pressure progressively increases from 0 (*upper right data point*) to 20 cmH_2O (*lower left data point*). Note that volume expansion at PEEP 20 cmH_2O (20 + VE) entirely reversed the decrease in RVEDV and LVEDV and restored CO. (From [73], with permission)

The Starling curve slope, however, like the most commonly employed clinical indices of ventricular contractile function (e.g. ejection fraction, shortening velocity, fractional area shortening), is affected by changing external loading conditions [75]. Therefore, as an alternative to characterisation of systolic function in terms of stress and shortening, Suga and Sagawa proposed an elastance approach, i.e. the analysis of end-systolic pressure–volume relationships (ESPVR) [79, 80]. Briefly, instantaneous pressure–volume diagrams of consecutive cardiac cycles are recorded while changing loading conditions and the point of maximal elastance (pressure/volume) is measured from each beat (termed E_{max}). The parameters of that line, its slope and its intercept can be used to define myocardial contractility [34]. Although subsequent studies could not confirm the initially proposed load-independence and linearity of the ESPVR [81], the ESPVR has proved to be a useful conceptual approach to assessment of contractile function [75]. While the problem of assessing transmural pressures during PEEP still exists with this approach, errors in estimating cardiac surface pressures would be more likely to affect the intercept of an ESPV curve than its slope [34]. In animal studies [78, 82] the slope of the ESPVR is not altered by PEEP, which supports the conclusion that contractility is unchanged.

In contrast to its effect on the RV, PEEP has been shown to decrease LV afterload. PEEP increases the pressure around structures in the thorax and, to a lesser extent, in the abdominal cavity relative to atmospheric pressure. Because the rest of the circulation is normally at atmospheric pressure, this results in a pressure differential, with most of the systemic circulation being under lower pressure than the LV and the thoracic aorta [12]. Thus, increased intrathoracic pressure, when arterial pressure is constant, decreases the force necessary to eject blood from the LV in a manner exactly analogous to decreased arterial pressure with constant intrathoracic pressure [83–85]. Again, however, problems arise with the concept of intrathoracic pressure and the exact calculation of effective transmural pressure: In these studies, LV afterload was measured as LV end-systolic transmural pressure, calculated as LV end-systolic cavitary minus oesophageal pressure. This assumes that oesophageal pressure represents cardiac surface pressure. While this is a common assumption, when the pericardium is intact changes in cardiac volume may render this assumption invalid [10]. When the heart is small, changes in intrathoracic pressure (ITP) are transmitted to the cardiac surface and the effect of pericardial elasticity on cardiac surface pressure is small. On the other hand, with cardiac dilatation, the elasticity of the pericardium becomes greater and may have greater effects on LV surface pressure. This is because cardiac surface pressure is the arithmetic sum of ITP and pericardial elastic pressure. As the heart becomes larger, pericardial elastic pressure becomes an increasingly important component of cardiac surface pressure during PEEP [86]. This means that changes in oesophageal pressure may not be a good indicator of cardiac surface pressure when the heart is dilated and may result in inaccurate overestimations of LV transmural pressure [10]. Therefore, it is difficult to assess whether the PEEP-induced afterload reduction is actually due to a reduction in LV end-systolic transmural pressure or simply related to the commonly observed decrease in mean arterial pressure.

Whatever the major component of PEEP-induced reduction in LV afterload may be, that decrease in afterload usually does not translate into increased cardiac output, as the adverse effects on LV filling usually predominate. The failing heart, however, is more sensitive to decreased afterload. As patients with congestive heart failure (CHF) are usually hypervolaemic, they are also less sensitive to decreased preload [87]. Therefore, in a manner analogous to the effects of vasodilators in CHF, cardiac output could rise when PEEP is applied to patients with poor myocardial function [10]. Besides these direct mechanical effects, however, the beneficial effects of PEEP in these patients may also be mediated by poorly understood reflex vasodilatation [88].

How to assess the effects of PEEP on circulatory function in the ICU?

Summarising the complex effects of positive-pressure ventilation with PEEP on cardiocirculatory function, the most important facts to keep in mind at the bedside are the potentially detrimental consequences for venous return and RV afterload. As these effects are ultimately mediated by increased lung volumes, leading to potential alveolar overdistension, it is important to be aware that ventilator-associated lung injury due to high lung volumes at the same time can result in 'ventilator-associated heart injury'. Therefore, monitoring lung volumes would be a major component to limit adverse haemodynamic effects, but unfortunately it is not feasible to date. If this is put the other way round, however, monitoring the haemodynamic effects of individual PEEP settings does make it possible to draw some inferences about the resulting lung volume changes. A number of studies have shown that measurements of cardiac or intrathoracic volumes are clearly superior to filling pressures for assessment cardiac preload during mechanical ventilation with PEEP [51, 52, 89–92]. Given the problems when calculating 'true' transmural filling pressures, as discussed above, and that the individual pressure–volume relationship (i.e. the ventricular compliance) is not known, these findings are well explained and limit the use of filling pressures, especially at high levels of PEEP. Combined with continuous cardiac output measurements by rapid-response thermodilution technique and/or pulse contour-derived techniques [93, 94], volume-based techniques can be regarded as state-of-the-art monitoring of cardiac function during ventilation with PEEP. In addition, echocardiography can be a powerful tool to assess RV function, especially if acute cor pulmonale is a concern [53, 95, 96], as well as to estimate LV function [97-99]. How respiratory mechanics, as well as arterial and mixed/central venous blood gas analysis, might be used to titrate PEEP in order to limit its potentially detrimental effects on cardiocirculatory function, is discussed by the authors in depth elsewhere in this book.

References

1. Dreyfuss D, Saumon G (1998) Ventilator-induced lung injury. Lessons from experimental studies. Am J Respir Crit Care Med 157:294-330
2. Maggiore SM, Jonson B, Richard JC et al (2001) Alveolar derecruitment at decremental positive end-expiratory pressure levels in acute lung injury: comparison with the lower inflection point, oxygenation, and compliance. Am J Respir Crit Care Med 164:795-801
3. Rouby JJ, Lu Q, Goldstein I (2002) Selecting the right level of positive end-expiratory in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 165:1182-1186
4. Cournand A, Motley HL, Werko L et al (1948) Physiological studies of the effects of intermittent positive pressure breathing on cardiac output in man. Am J Physiol 152:162-174
5. Viquerat CE, Righetti A, Suter PM (1983) Biventricular volumes and function in patients with adult respiratory distress syndrome ventilated with PEEP. Chest 83:509-514
6. Pinsky M (1997) The hemodynamic consequences of mechanical ventilation: an evolving story. Int Care Med 23:493-503
7. Robotham JL, Peters J, Takata M (1993) Cardiorespiratory interactions. In: Pulmonary and critical care medicine, vol 3. Mosby-Year Book, St Louis, pp 1-25
8. Peters J Robotham JL (1987) Hemodynamic effects of increased intrathoracic pressure. In: Vincent JL, Suter PM (eds) Cardiopulmonary interactions in acute respiratory failure. Springer-Verlag, Berlin-Heidelberg-New York, pp 120-133
9. Scharf S (1996) Ventilatory support in cardiac failure. In: Kvetan, V, Dantzker DR (eds) The critically ill cardiac patient. Lippincott-Raven, Philadelphia, pp 29-45
10. Scharf S (2000) Ventilatory support in the failing heart. In: Scharf, SM, Pinsky, MR, Magder, S (eds): Respiratory-circulatory interactions in health and disease. Marcel Dekker, New York, pp 519-550
11. O'Quin R, Marini JJ (1983) Pulmonary artery occlusion pressure: clinical physiology, measurement, and interpretation. Am Rev Respir Dis 128:319-326
12. Klinger J (1996) Hemodynamics and positive end-expiratory pressure in critically ill patients. Crit Care Clin North Am 12:841-864
13. Chapin JC, Downs JB, Douglas ME, et al (1979) Lung expansion, airway pressure transmission, and positive end-expiratory pressure. Arch Surg 114:1193-1197
14. Mirro R, Busija D, Green R et al (1987) Relationship between mean airway pressure, cardiac output, and organ blood flow with normal and decreased respiratory compliance. J Pediatr 111:101-106
15. Scharf SM, Ingram RH Jr (1977) Effects of decreasing lung compliance with oleic acid on the cardiovascular response to PEEP. Am J Physiol 233:H635-H641
16. Romand JA, Shi W, Pinsky MR (1995) Cardiopulmonary effects of positive pressure ventilation during acute lung injury. Chest 108:1041-1048
17. Pinsky M (2001) Hemodynamic effects of ventilation and ventilatory maneuvers. In: Scharf, SM, Pinsky, MR, Magder, S (eds) Respiratory-circulatory interactions in health and disease. Marcel Dekker, New York, pp 183-218
18. Guyton AC (1955) Determination of cardiac output by equating venous return curves cardiac response curves. Physiol Rev 35:123-129
19. Guyton AC, Lindsey AW, Abernathy B et al (1957) Venous return at various right atrial pressures and the normal venous return curve. Am J Physiol 189:609-615
20. Pinsky M (1984) Instantaneous venous return curves in intact canine preparation. J Appl Physiol 56:765-771

21. Robotham JL, Peters J (1989) Mechanical effects of intrathoracic pressure on ventricular performance. In: Scharf SM (ed) Heart-lung interactions in health and disease, vol 46. Marcel Dekker, New York, pp 251-283
22. Goldberg HS, Rabson J (1981) Control of cardiac output by systemic vessels. Circulatory adjustments to acute and chronic respiratory failure and the effect of therapeutic interventions. Am J Cardiol 47:696-702
23. Fessler HE, Permutt S (1995) Interaction between the circulatory and ventilatory pumps. In: Roussos C (ed) The thorax. Marcel Dekker, New York, pp 1621-1640
24. Pinsky MR (1984) Determinants of pulmonary arterial flow variation during respiration. J Appl Physiol 56:1237-1245
25. Chevalier PA, Weber KC, Engle JC et al (1972) Direct measurements of right and left heart outputs in a Valsalva-like maneuver in dogs. Proc Soc Exp Biol Med 139:1429-1437
26. Guntheroth WG, Gould R, Butler J et al (1974) Pulsatile flow in pulmonary artery, capillary, and vein in the dog. Cardiovasc Res 8:330-337
27. Pinsky MR (1984) Instantaneous venous return curves in an intact canine preparation. J Appl Physiol 56:765-771
28. Scharf SM, Brown R, Saunders N et al (1980) Hemodynamic effects of positive-pressure inflation. J Appl Physiol 49:124-131
29. Scharf SM, Caldini P, Ingram RH Jr (1977) Cardiovascular effects of increasing airway pressure in the dog. Am J Physiol 232:H35-H43
30. Fessler HE, Brower RG, Wise RA et al (1991) Effects of positive end-expiratory on the gradient for venous return. Am Rev Respir Dis 143:19-24
31. Nanas S, Magder S (1992) Adaptations of the peripheral circulation to PEEP. Am Rev Respir Dis 146:688-693
32. Jellinek H, Krenn H, Oczenski W et al (2000) Influence of positive airway pressure on the pressure gradient for venous return in humans. J Appl Physiol 88:926-932
33. Permutt S, Bromberger-Barnea B et al (1962) Alveolar pressure, pulmonary venous pressure, and the vascular waterfall. Med Thorac 19:239-260
34. Fessler HE (2001) Mechanical ventilation with PEEP. In: Scharf, SM, Pinsky, MR, Magder, S (eds) Respiratory-circulatory interactions in health and disease. Marcel Dekker, New York, pp 807-835
35. Fessler HE, Brower RG, Shapiro EP et al (1993) Effects of positive end-expiratory pressure and body position on pressure in the thoracic great veins. Am Rev Respir Dis 148:1657-1664
36. Permutt S, Riley RL (1963) Hemodynamics of collapsible vessels with tone: the vascular waterfall. J Appl Physiol 18:924-932
37. Takata M, Wise RA, Robotham JL (1990) Effects of abdominal pressure on venous return: abdominal vascular zone conditions. J Appl Physiol 69:1961-1972
38. Moreno AH, Burchell AR, Van der Woude R et al (1967) Respiratory regulation of splanchnic and systemic venous return. Am J Physiol 213:455-465
39. Vieillard-Baron A, Augarde R, Prin S et al (2001) Influence of superior vena caval zone condition on cyclic changes in right ventricular outflow during respiratory support. Anesthesiology 95:1083-1088
40. van den Berg PC, Jansen JR, Pinsky MR (2002) Effect of positive pressure on venous return in volume-loaded cardiac surgical patients. J Appl Physiol 92:1223-1231
41. Jellinek H, Krafft P, Fitzgerald RD et al (2000) Right atrial pressure predicts hemodynamic response to apneic positive airway pressure. Crit Care Med 28:672-678
42. Mebazaa A, Karpati P, Renaud E et al (2004) Acute right ventricular failure-from pathophysiology to new treatments. Intensive Care Med 30:185-196

43. Maughan WL, Shoukas AA, Sagawa K et al (1979) Instantaneous pressure-volume relationship of the canine right ventricle. Circ Res 44:309-315
44. Tulevski, II, Romkes H, Dodge-Khatami A et al (2002) Quantitative assessment of the pressure and volume overloaded right ventricle: imaging is a real challenge. Int J Cardiovasc Imaging 18:41-51
45. Marshall BE, Hanson CW, Frasch F et al (1994) Role of hypoxic pulmonary vasoconstriction in pulmonary gas exchange and blood flow distribution. 2. Pathophysiology. Intensive Care Med 20:379-389
46. Marshall BE, Marshall C, Frasch F et al (1994) Role of hypoxic pulmonary vasoconstriction in pulmonary gas exchange and blood flow distribution. 1. Physiologic concepts. Intensive Care Med 20:291-297
47. Burton AC, Patel DJ (1958) Effect on pulmonary vascular resistance of inflation of the rabbit lungs. J Appl Physiol 12:239-246
48. Whittenberger JL, McGregor GM, Berglund E et al (1960) Influence of state of inflation of the lung on pulmonary vascular resistance. J Appl Physiol 15:878-882
49. West JB, Dollery CT, Naimark A (1964) Distribution of blood flow in isolated lung; relation to vascular and alveolar pressures. J Appl Physiol 19:713-724
50. Brunet F, Dhainaut JF, Devaux JY et al (1988) Right ventricular performance in patients with acute respiratory failure. Intensive Care Med 14 Suppl 2:474-477
51. Luecke T, Roth H, Herrmann P et al (2004) Assessment of cardiac preload and left ventricular function under increasing levels of positive end-expiratory pressure. Intensive Care Med 30:119-126
52. Cheatham ML, Nelson LD, Chang MC et al (1998) Right ventricular end-diastolic volume index as a predictor of preload status in patients on positive end-expiratory pressure. Crit Care Med 26:1801-1806
53. Vieillard-Baron A, Schmitt JM, Augarde R et al (2001) Acute cor pulmonale in acute respiratory distress syndrome submitted to protective ventilation: incidence, clinical implications, and prognosis. Crit Care Med 29:1551-1555
54. Schmitt JM, Vieillard-Baron A, Augarde R et al (2001) Positive end-expiratory pressure titration in acute respiratory distress syndrome patients: impact on right ventricular outflow impedance evaluated by pulmonary artery Doppler flow velocity measurements. Crit Care Med 29:1154-1158
55. Vieillard-Baron A, Loubieres Y, Schmitt JM et al (1999) Cyclic changes in right ventricular output impedance during mechanical ventilation. J Appl Physiol 87:1644-1650
56. Vieillard-Baron A, Jardin F (2003) Why protect the right ventricle in patients with acute respiratory distress syndrome? Curr Opin Crit Care 9:15-21
57. Viitanen A, Salmenpera M, Heinonen J (1990) Right ventricular response to hypercarbia after cardiac surgery. Anesthesiology 73:393-400
58. Scharf SM, Brown R (1982) Influence of the right ventricle on canine left ventricular function with PEEP. J Appl Physiol 52:254-259
59. Weber KT, Janicki JS, Shroff S et al (1981) Contractile mechanics and interaction of the right and left ventricles. Am J Cardiol 47:686-695
60. Brinker JA, Weiss JL, Lappe DL et al (1980) Leftward septal displacement during right ventricular loading in man. Circulation 61:626-633
61. Janicki JS, Weber KT (1980) The pericardium and ventricular interaction, distensibility, and function. Am J Physiol 238:H494-H503
62. Olsen CO, Tyson GS, Maier GW et al (1983) Dynamic ventricular interaction in the conscious dog. Circ Res 52:85-104
63. Cassidy SS, Schwiep F (1989) Cardiovascular effects of positive end-expiratory pressure

In: Scharf SM (ed) Heart-lung interactions in health and disease, vol 46. Marcel Dekker, New York, pp 463-506
64. Santamore WP, Bove AA, Heckman JL (1984) Right and left ventricular pressure-volume response to positive end-expiratory pressure. Am J Physiol 246:H114-H119
65. Cassidy SS, Mitchell JH, Johnson RL Jr (1982) Dimensional analysis of right and left ventricles during positive-pressure ventilation in dogs. Am J Physiol 242:H549-H556
66. Cassidy SS, Ramanathan M (1984) Dimensional analysis of the left ventricle during PEEP: relative septal and lateral wall displacements. Am J Physiol 246:H792-H805
67. Cassidy SS, Eschenbacher WL, Robertson CH Jr et al (1979) Cardiovascular effects of positive-pressure ventilation in normal subjects. J Appl Physiol 47:453-461
68. Haynes JB, Carson SD, Whitney WP et al (1980) Positive end-expiratory pressure shifts left ventricular diastolic pressure-area curves. J Appl Physiol 48:670-676
69. Jardin F, Farcot JC, Boisante L et al (1981) Influence of positive end-expiratory pressure on left ventricular performance. N Engl J Med 304:387-392
70. Lloyd TC, Jr. (1982) Mechanical cardiopulmonary interdependence. J Appl Physiol 52:333-339
71. Fewell JE, Abendschein DR, Carlson CJ et al (1981) Continuous positive-pressure ventilation does not alter ventricular pressure-volume relationship. Am J Physiol 240:H821-H826
72. Schulman DS, Biondi JW, Zohgbi S et al (1992) Left ventricular diastolic function during positive end-expiratory pressure. Impact of right ventricular ischemia and ventricular interaction. Am Rev Respir Dis 145:515-521
73. Dhainaut JF, Devaux JY, Monsallier JF et al (1986) Mechanisms of decreased left ventricular preload during continuous positive pressure ventilation in ARDS. Chest 90:74-80
74. Veddeng OJ, Myhre ES, Risoe C et al (1992) Selective positive end-expiratory pressure and intracardiac dimensions in dogs. J Appl Physiol 73:2016-2020
75. LeWinter MM, Osol G (2001) Normal physiology of the cardiovascular system. In: Fuster V, Alexander RW, O'Rouke RA (eds), Hurst's The heart, 10th edn. McGraw-Hill, New York, pp 63-98
76. Berglund JE, Halden E, Jakobson S et al (1994) Echocardiographic analysis of cardiac function during high PEEP ventilation. Intensive Care Med 20:174-180
77. Huemer G, Kolev N, Kurz A et al (1994) Influence of positive end-expiratory pressure on right and left ventricular performance assessed by Doppler two-dimensional echocardiography. Chest 106:67-73
78. Johnston WE, Vinten-Johansen J, Santamore WP et al (1989) Mechanism of reduced cardiac output during positive end-expiratory pressure in the dog. Am Rev Respir Dis 140:1257-1264
79. Sagawa K (1981) The end-systolic pressure-volume relation of the ventricle: definition, modifications and clinical use. Circulation 63:1223-1227
80. Suga H, Sagawa K, Shoukas AA (1973) Load independence of the instantaneous pressure-volume ratio of the canine left ventricle and effects of epinephrine and heart rate on the ratio. Circ Res 32:314-322
81. Kass DA, Maughan WL (1988) From 'Emax' to pressure-volume relations: a broader view. Circulation 77:1203-1212
82. Crottogini AJ, Willshaw P, Barra JG et al (1988) End-systolic pressure-volume relationships in dogs during ventilation with PEEP. Am J Physiol 254:H664-H670
83. Fessler HE, Brower RG, Wise RA et al (1992) Effects of systolic and diastolic positive pleural pressure pulses with altered cardiac contractility. J Appl Physiol 73:498-505

84. Pinsky MR, Matuschak GM, Klain M (1985) Determinants of cardiac augmentation by elevations in intrathoracic pressure. J Appl Physiol 58:1189-1198
85. Pinsky MR, Summer WR, Wise RA et al (1983) Augmentation of cardiac function by elevation of intrathoracic pressure. J Appl Physiol 54:950-955
86. Takata M, Robotham JL (1991) Ventricular external constraint by the lung and pericardium during positive end-expiratory pressure. Am Rev Respir Dis 143:872-875
87. Pouleur H, Covell JW, Ross J Jr (1980) Effects of nitroprusside on venous return and central blood volume in the absence and presence of acute heart failure. Circulation 61:328-337
88. Genovese J, Huberfeld S, Tarasiuk A et al (1995) Effects of CPAP on cardiac output in pigs with pacing-induced congestive heart failure. Am J Respir Crit Care Med 152:1847-1853
89. Diebel LN, Myers T, Dulchavsky S (1997) Effects of increasing airway pressure and PEEP on the assessment of cardiac preload. J Trauma 42:585-590; discussion 590-591
90. Diebel LN, Wilson RF, Tagett MG et al (1992) End-diastolic volume. A better indicator of preload in the critically ill. Arch Surg 127:817-821; discussion 821-822
91. Durham R, Neunaber K, Vogler G et al (1995) Right ventricular end-diastolic volume as a measure of preload. J Trauma 39:218-223; discussion 223-224
92. Lichtwarck-Aschoff M, Zeravik J, Pfeiffer UJ (1992) Intrathoracic blood volume accurately reflects circulatory volume status in critically ill patients with mechanical ventilation. Intensive Care Med 18:142-147
93. Ferris SE, Konno M (1992) In vitro validation of a thermodilution right ventricular ejection fraction method. J Clin Monit 8:74-80
94. Goedje O, Hoeke K, Lichtwarck-Aschoff M et al (1999) Continuous cardiac output by femoral arterial thermodilution calibrated pulse contour analysis: comparison with pulmonary arterial thermodilution. Crit Care Med 27:2407-2412
95. Jardin F, Vieillard-Baron A (2003) Right ventricular function and positive pressure ventilation in clinical practice: from hemodynamic subsets to respirator settings. Intensive Care Med 29:1426-1434
96. Vieillard-Baron A, Prin S, Chergui K et al (2002) Echo-Doppler demonstration of acute cor pulmonale at the bedside in the medical intensive care unit. Am J Respir Crit Care Med 166:1310-1319
97. Denault AY, Gorcsan J 3rd, Mandarino WA et al (1997) Left ventricular performance assessed by echocardiographic automated border detection and arterial pressure. Am J Physiol 272:H138-H147
98. Gorcsan J 3rd (1999) Assessment of left ventricular systolic function using color-coded tissue Doppler echocardiography. Echocardiography 16:455-463
99. Gorcsan J 3rd, Denault A, Mandarino WA et al (1996) Left ventricular pressure-volume relations with transesophageal echocardiographic automated border detection: comparison with conductance-catheter technique. Am Heart J 131:544-552

Chapter 28

Expiratory flow limitation and intrinsic PEEP

J. Milic-Emili

The highest pulmonary ventilation that a subject can achieve is ultimately limited by the highest flow rates that can be generated. Most normal subjects and endurance-trained athletes do not exhibit expiratory flow limitation even during maximal exercise [1,2]. In contrast, patients with chronic obstructive pulmonary disease (COPD) may exhibit flow limitation even at rest, as first suggested by Hyatt [1]. This was based on the observation that patients with severe COPD often breathe tidally along their MEFV curve. The presence of expiratory flow limitation during tidal breathing promotes dynamic pulmonary hyperinflation, with concomitant increase of inspiratory work, impairment of inspiratory muscle function and adverse effects on haemodynamics [3], and may contribute to dyspnoea [4].

Conventionally, flow limitation (FL) is assessed by comparison of the tidal expiratory flow volume ($V,\dot{}$-V) to corresponding MEFV curves. Patients in whom, at comparable lung volumes, tidal flows are similar to those obtained during forced expiratory vital capacity (FVC) manoeuvre are considered to have FL [1]. As discussed below, this approach has both theoretical and practical limitations. Nevertheless, it has been the kernel for understanding respiratory dynamics. Accordingly, it is useful to review it in some detail.

Fig. 1 depicts the flow-volume ($V,\dot{}$-V) loops at rest and during maximal exercise, together with the corresponding maximal $V,\dot{}$-V curves of a normal subject and a patient with severe airway obstruction. In the normal subject, even during maximal exercise, the flows are less than maximal (i.e. there is no FL). In this case, the increase of tidal volume during exercise is obtained as a result of both an increase in end-inspiratory and a decrease in end-expiratory lung volume compared to rest, and the work of breathing during exercise is sustained by activity of both inspiratory and expiratory muscles. In contrast, in patients with severe airway obstruction, maximal expiratory flows may be reached even at rest. In this case, the increase of tidal volume during exercise must be accompanied by increases in end-expiratory volume and inspiratory flow [6,7]. This pattern of breathing, in which the ratio of inspiratory time to total cycle duration falls to 0.3 or less as compared to normal values of 0.4 to 0.5, may be considered an adaptation to expiratory FL. However, the increase is volume is associated with an expansion of the thoracic cage to a point at which the inspiratory muscles operate inefficiently. Furthermore, the dynamic hyperinflation causes: (a) an increase in inspiratory work through a decrease in the static volume-pressure curve; and (b) a high inspiratory threshold pressure that has been labelled intrinsic PEEP [3]. With severe dynamic hyperinflation, this

phenomenon becomes self-limiting because the changes in volume and inspiratory flow require too high force development by the inspiratory muscles. Thus, in patients with severe airway obstruction, inspiratory muscle fatigue may limit exercise performance. This explains why detection of tidal expiratory FL is of great clinical importance.

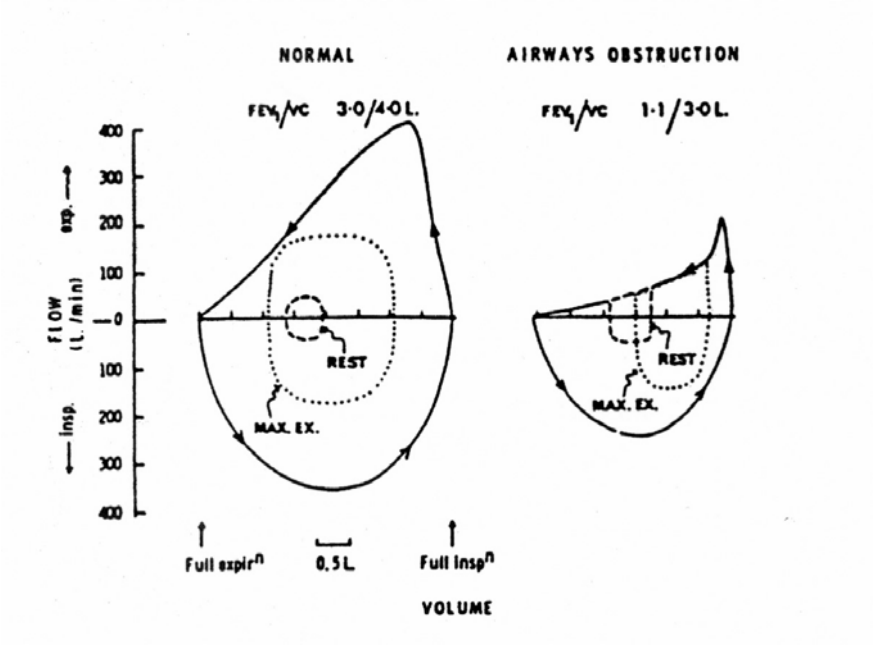

Fig. 1. Flow-volume curves obtained from a normal subject and from a patient with chronic obstructive pulmonary disease. Spontaneous flow-volume loops at rest (*dashed lines*) and maximum exercise (Max Ex, *dotted line*) are compared with maximum flow-volume loops (*outer solid lines*). FEV_1, Forced expiratory volume in one second, *V*, vital capacity [5]

The conventional approach for detecting expiratory FL, as shown in Fig. 1, has an important practical limitation because, as a result of thoracic gas compression during the FVC manoeuvre, the tidal and maximal $V,\dot{}$-V curves have to be measured with a body plethymograph [8]. This implies that such measurements are usually confined to resting breathing in sitting position. Apart from this, there are several other factors that make assessment of FL based on comparison of tidal and maximal $V,\dot{}$-V curves problematic: (a) volume-dependent changes in airway resistance and lung recoil during maximal inspiration prior to the FVC manoeuvre, and (b) the time-dependent viscoelastic behaviour of pulmonary tissues and time-dependent lung emptying due to time-constant inequality [9, 10]. These mechanisms imply that the maximal flows which can be reached during expiration depend on the volume and time history of the preceding inspiration. Furthermore, since the previous volume and time history automatically varies between tidal and

maximal inspiration, assessment of FL based on comparison of tidal and maximal $\dot{V}$-V curves commonly leads to erroneous conclusions, even if the measurements are made with body plethysmography [11, 12]. Recently, however, an alternate technique (NEP, negative expiratory pressure method) has been introduced to detect expiratory FL during tidal breathing. NEP does not require either performance of FVC manoeuvres on the part of the patient or a body plethysmograph [13, 14]. Accordingly, this method can also be applied to mechanically ventilated patients [13]. The NEP method has been validated by concomitant determination of iso-volume flow-pressure relationships [13].

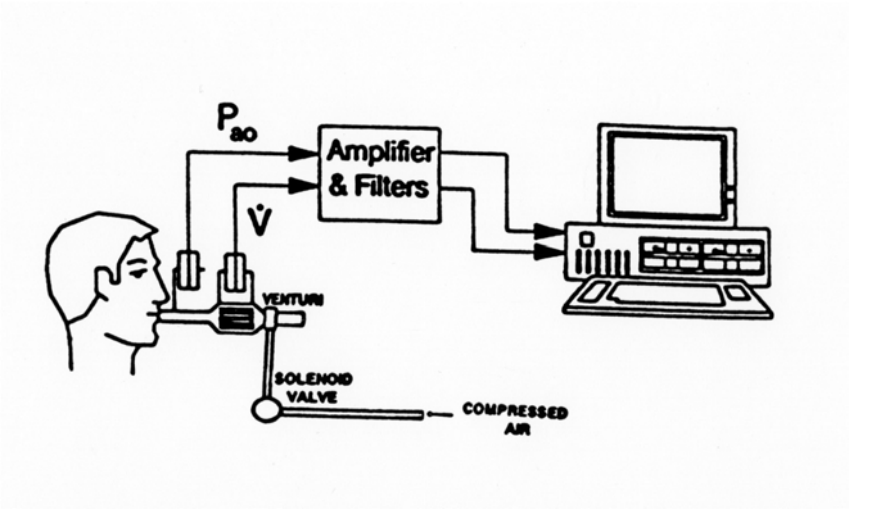

Fig. 2. Schematic diagram of equipment setup for the negative expiratory pressure (NEP) test. *Pao* Pressure at airway opening, $\dot{V}$ = flow. Volume is obtained by numerical integration of the signal. During the study, the time course of flow, volume and pressure are continuously monitored on the computer screen, together with the corresponding flow-volume curves [4]

NEP method for detection of expiratory flow limitation

Fig. 2 illustrates the experimental setup used to detect expiratory FL with NEP. It consists of a pneumotachograph and a Venturi device that is activated by opening a rapid solenoid valve [4]. During NEP, negative pressure is applied at the mouth during tidal expiration (usually about -3 to -5 cm H_2O) and the ensuing $\dot{V}$-V curve is compared with that of the previous control expiration. Therefore, with this technique the volume and time history, as well as the intrathoracic pressures during expiration with NEP are the same as in the preceding control breath [15]. If application of NEP elicits increased flow over the entire range of the control tidal volume, the patient is not flow limited (Fig. 3, left). In contrast, if with NEP the subject exhales along part or the entire control $\dot{V}$-V curve, FL is present (Fig. 3,

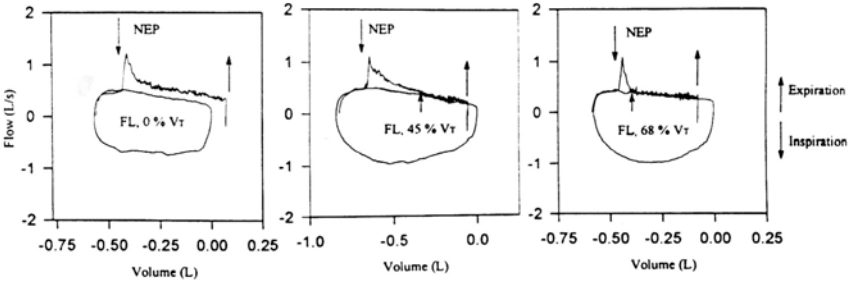

Fig. 3. Flow-volume loops of NEP test breaths and preceding control breaths in three representative COPD patients seating at rest. No flow-limitation (*FL*) (*left*), FL over last 45% of control expired tidal volume (*VT*) (*middle*), FL over 68% VT (*right*). *Long arrows* Onset of NEP, *short arrows* onset of FL. Zero volume is end-expiratory lung volume of control breaths [4]

middle and right). The FL portion of the tidal expiration can be expressed as percentage fraction of the control tidal volume (%VT). In the two FL subjects in Fig. 3, flow limitation amounted to 45 and 68% VT, respectively. If expiratory flow limitation is present when NEP is applied, there is a transient increase of flow (spike in Fig. 3, right) that mainly reflects enhanced dynamic airway compression and sudden reduction in volume of the compliant oral and neck structures [14, 15]. Such spikes are useful markers of FL.

Flow limitation and chronic dyspnoea

Intuitively, one would expect patients with the most severe airway obstruction, as assessed with routine lung function measurements, to be the most dyspnoeic. However, some patients with severe airway obstruction are minimally symptomatic, whereas others with little objective dysfunction appear to be very dyspnoeic [16]. In fact, many studies have shown that the correlation between chronic dyspnoea and FEV_1 is weak (see [4]). In contrast, FL, as measured with the NEP technique, is a much better predictor of chronic dyspnoea then FEV_1 [4,11,12]. Using the NEP technique, it has been shown that assessment of FL based on comparison of tidal with maximal $\dot{V}$-V curves is inaccurate even when volume is measured with a body plethysmograph in order to avoid thoracic gas-compression artefacts [11, 12].

Flow limitation and exercise capacity

Since in COPD the reduced exercise capacity shows only a weak relation to FEV_1 and FVC [4, 17], it has been concluded that other factors, such as peripheral muscle

weakness, deconditioning and impaired gas exchange play a predominant role in reducing exercise tolerance [18]. A recent study, however, has shown that in COPD there is a relatively strong correlation (r=0.81) between resting IC and exercise capacity [19]. Accordingly, lung-function impairment is probably an important cause of decreased exercise tolerance in many COPD patients. Indeed, because of expiratory FL, the maximal tidal volume (and hence ventilation) is necessary closely related to resting IC [15].

In conclusion, the NEP technique provides a simple and reliable tool for detecting expiratory FL both at rest and during exercise. The method does not require body plethysmography, does not depend on patient cooperation and coordination, and can be applied in any desired body posture.

References

1. Hyatt RE (1961) The interrelationship of pressure, flow and volume during various respiratory maneuvers in normal and emphysematous patients. Am Rev Respir Dis 83:676-683
2. Mota S, Casan P, Drobnic F et al (1999) Expiratory flow limitation during exercise in competition cyclists. J Appl Physiol 86:611-616
3. Gottfried SB (1991) The role of PEEP in the mechanically ventilated COPD patient. In:Roussos C, Marini JJ (eds) Ventilatory Failure. Springer-Verlag, Berlin, pp 392-418
4. Eltayara L, Becklake MR, Volta CA et al (1996) Relationship of chronic dyspnea and flow limitation in COPD patients. Am J Respir Crit Care Med 154:1726-1734
5. Leaver DG, Pride NB (1971) Flow-volume curves and expiratory pressures during exercise in patients with chronic air-flow obstruction. Scan J Respir Dis Suppl 77:23-27
6. Stubbing DG, Pengelly LD, Morse JLC et al (1980) Pulmonary mechanics during exercise in subjects with chronic air-flow obstruction. J Appl Physiol 49:511-515
7. Grimby G, Stiksa J (1970) Flow-volume curves and breathing patterns during exercise in patients with obstructive lung disease. Scan J Clin Lab Invest 25:303-313
8. Ingram RH Jr, Schilder DP (1966) Effect of gas compression on pulmonary pressure, flow and volume relationship. J Appl Physiol 47:1043-1050
9. Koulouris NG, Rapakoulias P, Rassidakis A et al (1995) Dependence of FVC maneuver on time course of preceding inspiration in patients with restrictive lung disease. Eur Respit J 8:306-313
10. D'Angelo E, Robatto E, Calderini M et al (1991) Pulmonary and chest wall mechanics in anaesthetized paralyzed humans. J Appl Physiol 70:2602-2610
11. Murciano D, Pichot M-H, Boczkowski J et al (1997) Expiratory flow limitation in stable asthmatic patients during resting breathing. Am J Respir Crit Care Med 156:752-757
12. Boczkowski J, Murciano D, Picho M-H et al (1997) Expiratory flow limitation in stable asthmatic patients during resting breathing. Am J Respir Crit Care Med 156:752-757
13. Valta P, Corbeil C, Lavoie A et al (1994) Detection of expiratory flow limitation during mechanical ventilation. Am J Respir Crit Care Med 150:1311-1317
14. Koulouris NG, Valta P, Lavoie A et al (1995) A simple method to detect expiratory flow limitation during spontaneous breathing. Eur Respir J 8:306-313
15. Koulouris NG, Dimpoulou I, Valta P et al (1996) Detection of expiratory flow limitation during exercise in COPD patients. J Appl Physiol 82:723-731
16. Fletcher CM (1961) Bronchitis: an international symposium. Assen: The Netherlands Discussion. Thomas CC (ed), Springfield IL, pp 212-214

17. Jones NG, Jones G, Edwards RHT (1971) Exercise tolerance in chronic airway obstruction. Am Rev Respir Dis 103:477-494
18. Gosselink R, Troosters T, Decramer M (1997) Exercise training in COPD patients: the basic questions. Eur Respir J 10:2884-2891
19. Murariu C, Ghezzo H, Milic-Emili J et al (1998) Exercise limitation in obstructive lung disease. Chest 114:965-968

Chapter 29

Mechanical ventilation strategies for lung protection

N.R. MacIntyre

Lung injury from positive pressure ventilation

Numerous animal studies have shown that the lung is subject to physical injury during mechanical ventilation [1–13]. Two mechanisms appear to be important in producing this injury. The first is a physical stretch injury resulting from inflation of lung regions beyond their physiologic maximum. Interestingly, such stretch injury is due not only to maximal end-inspiratory stretch, but also to tidal stretch, rate of stretch and frequency of stretch [14–16]. All these factors produce a tissue injury characterised by inflammation, oedema formation, hyaline membranes and the release of inflammatory mediators into the circulation. Lungs with a heterogeneous distribution of disease are at particular risk of this injury, because healthier regions will be preferentially overdistended when a positive-pressure breath is delivered. The second mechanism is a shearing injury that results from repeated opening and closing of atelectatic but potentially recruitable alveoli in an injured lung. The use of expiratory pressure to prevent alveolar de-recruitment can help ameliorate this injury [17–19].

To minimise this injury potential, mechanical ventilation goals should be twofold. The first goal should be to provide enough positive end-expiratory pressure (PEEP) to maintain recruitment of the 'recruitable' alveoli while at the same time not applying so much PEEP that healthier regions are unnecessarily overdistended. The second goal should be to avoid a PEEP–tidal volume(Vt) combination that unnecessarily overdistends lung regions at end-inspiration. These goals embody the concept of a 'lung-protective' mechanical ventilation strategy.

Determining the risk of lung injury from underrecruitment and overdistension in the lung

Conceptually, the upper and lower inflection points on a static pressure–volume (PV) plot should be the best guide to determining lung recruitment and overdistension [20, 21]. These inflection points are thought to represent the attainment of optimal recruitment (rise in compliance at the lower inflection point) and the development of overdistension (reduction in compliance at the upper inflection point). However, the 'whole-lung' PV plot that is clinically available reflects an amalgam of the mechanical properties of numerous lung regions with potentially

widely varying regional PV relationships [22]. It is thus over-simplistic to assume that the lower and upper inflection points measured are the ideal points for PEEP and Vt.

Another concern with the static PV plot is that it is technically difficult to perform and often requires heavy sedation or paralysis. A new technique, single-breath 'slow-flow' pressure–volume measurement (so called because the slow inspiratory flow minimises resistive pressures so that a single dynamic measurement can approximate the true static plot) might make this mechanical assessment more clinically useful [23].

Even without complex PV assessments, clinicians can still use routinely monitored parameters to assess the risk of stretch lung injury. Conceptually, overdistension is likely to occur when lung regions are subjected to transalveolar pressures exceeding the normal physiological maximum of 30–35 cmH_2O [24]. Indeed, animal studies have almost uniformly verified the importance of exceeding this 'stretch' level in the production of lung injury [1–13]. In mechanically ventilated patients, the end-inspiratory intra-alveolar pressure (reflected in the 'plateau' airway pressure under no-flow conditions) is a reasonable approximation of end-inspiratory transalveolar pressure if chest wall compliance is near normal. In patients with abnormal chest wall compliance (e.g. bindings, obesity) or abdominal distension, however, the plateau pressure may grossly overestimate this transalveolar pressure [22]. An oesophageal balloon to measure pleural pressure can be helpful in these conditions. Because tidal stretch also appears to be important in the production of lung injury [26, 27], tidal volumes in excess of the normal physiological tidal volume (e.g. 5–7 ml/kg) may also indicate a risk of stretch injury.

Determination of adequate recruitment may be more problematic. Static compliance improvements derived from changes in ventilator settings correlate with improved recruitment, but these measurements are time consuming and sometimes require patient sedation/paralysis. Fortunately, improvements in gas exchange also generally correlate with improved recruitment, and the PaO_2/FiO_2 ratio is often used as a surrogate for recruitment assessment. It must be remembered, however, that pressures required for recruitment of the most badly pathologic regions may produce overdistension in healthier regions. Aggressive recruitment strategies with positive airway pressure must thus be balanced against the risk of producing overdistension injury.

Mechanical ventilation strategies for providing lung protection

Frequency–tidal volume settings

The tidal breath should be 5–7 ml/kg, as shown by recent randomised trial results [26, 27], and the resulting end-inspiratory plateau pressure should be <30–35 cmH_2O. The set ventilator frequency is generally used to control the CO_2. A reasonable starting point is a normal frequency of between 12 and 20 breaths per minute. Increasing the frequency will increase minute ventilation and will generally

increase CO_2 clearance. At some point, however, air trapping will develop as a result of inadequate expiratory times. Under these conditions, minute ventilation will either start to fall off (pressure-targeted ventilation) or airway pressures will start to rise (volume-targeted ventilation). In general, this begins to happen at breathing frequencies of approximately 35 breaths per minute, although it can occur at much lower frequencies if the inspiratory-to-expiratory ratio is high or the time constant for lung emptying (resistance × compliance) is very high.

Efforts to provide protection against overdistension may lead to compromise of the alveolar ventilation and the development of hypercapnia ('permissive' hypercapnia). As long as the pH remains above 7.1–7.2, this appears to be well tolerated in most patients (exceptions might include those with central nervous system injuries and those with unstable cardiovascular systems). A new technique, tracheal gas insufflation, flushes the endotracheal tube free of CO_2 during expiration, which can be helpful in these circumstances.

PEEP/FiO_2

The goal of PEEP application is to maintain the patency of alveoli that are opened (recruited) by a positive-pressure breath. In this sense, PEEP acts in such a way as to prevent derecruitment. It follows therefore that the initial implementation, a reimplementation or an increase in PEEP should be accompanied by a 'volume recruitment' manoeuvre. Recommended strategies include lung inflation to near maximum (i.e. pressures of 30–40 cmH_2O) for 30–60 s.

The appropriate PEEP level can be determined by applying either mechanical or gas-exchange criteria [20, 21, 26–29]. Mechanical criteria involve assessments that attempt to ensure that PEEP recruits recruitable alveoli while not over distending alveoli already recruited. Two bedside approaches have been reported: (1) use of pressure–volume curves to set the PEEP above the lower inflection point on the PV curve [20, 21]; and (2) use of a step increase in PEEP to determine the PEEP level that gives the best compliance [28]. As noted previously, both of these approaches are technically challenging and time consuming.

The use of gas-exchange criteria to guide PEEP application involves balancing PaO_2 goals, FiO_2 goals and lung distension goals. In general, these strategies provide some minimal level of PEEP at one extreme (e.g. a minimal PEEP of 5 cm H_2O is unlikely to produce overdistension) and some maximal level of PEEP at the other extreme (e.g. a maximal PEEP of 24 cmH_2O will still maintain plateau pressures –35 cmH_2O with a minimal Vt). In between these extremes, PEEP and FiO_2 are adjusted to maintain an oxygenation goal. Examples of values compiled in two tables and found to have equivalence by the ARDS Network are given in Table 1. Note that this approach may not produce the maximal PaO_2/FiO_2 ratio or the minimal shunt, especially if used with a low-tidal-volume strategy [26]. This trade-off, however, is important in protecting the from overdistension.

Table 1. PEEP/FiO_2 values from tables used during two NIH ARDS Network studies, which were found to be equivalent. The clinical target is a PO_2 of 55–80 mmHg or SpO_2 of 88–95%. If the patient is below these target values, move up the table to the right; if above, move down the table to the left

FiO_2	0.30	0.30	0.40	0.40	0.50	0.50	0.60	0.70	0.70	0.70	0.80	0.80	0.90	0.90	0.90	1.0	1.0	1.0	1.0
PEEP[a]	5	5	5	8	8	10	10	10	10	12	14	14	14	16	18	18	20	22	24
PEEP[b]	12	14	14	16	16	18	20	20	20	20	20	22	22	22	22	22	24	24	24

[a] PEEP values used in the original ARDS Network Trial [26]
[b] PEEP values used in the more recent NIH ARDS Network ALVEOLI trial [30]

Inspiratory-to-expiratory timing ratio

Setting the inspiratory time and the inspiratory-to-expiratory ratio (I:E) involves several considerations. The normal I:E ratio is roughly 1:2-1:4. This produces the most comfort and thus is the initial setting most frequently used. The flow graphic should also be assessed to ensure that an expiratory time that is adequate to avoid air trapping is present.

Prolongation of the I:E beyond the physiological range of 1:2–1:4 can be employed as an alternative to increasing PEEP for recruitment of lung units and improvement of ventilation–perfusion relationships in severe respiratory failure [31–33]. Generally, inspiratory time prolongation is reserved for patients in whom the plateau pressure from the PEEP-Vt combination has approached 30–35 cmH_2O and/or potentially toxic concentrations of FiO_2 are being used without meeting SaO_2 or oxygen delivery goals. Inspiratory time prolongation has several important physiological effects. First, a longer inspiratory time results in a longer alveolar conducting airway gas mixing time. Second, a longer inspiratory time can give slower filling alveolar units time to be ventilated and recruited. Finally, if expiratory time is inadequate for lung emptying, air trapping and intrinsic PEEP (PEEPi) can develop. A number of studies have shown improved gas exchange as a consequence of longer inspiratory times, but it is difficult to sort out which physiological mechanism is responsible. Indeed, long inspiratory times without air trapping have been shown in one study to improve PaO_2, while others have supported the argument that improved PO_2 occurs only as a consequence of $PEEP_i$ development.

Several other aspects of long inspiratory times strategies need to be considered when this technique is used. First, the development of air trapping has different effects on pressure- vs volume-targeted ventilation. Second, although long inspiratory times are often used with pressure-controlled breaths to utilise the rapid initial flow pattern and the pressure-limiting feature, long inspiratory time strategies have also been used with volume-targeted breaths, generally by addition of an inspiratory pause. Third, a long inspiratory time will increase mean airway pressure and can thus reduce cardiac filling. Fourth, in the presence of air trapping, the mean alveolar pressure will be higher than the mean airway pressure, making

monitoring of intrathoracic pressure more difficult. Fifth, lengthening the inspiratory-to-expiratory ratio beyond 1:1 also results in quite some discomfort to the patient and usually requires heavy sedation and/or paralysis. A novel approach to improving comfort with this strategy is the use of a pressure relief mechanism. This permits spontaneous breathing during the long inflation period and has been termed airway pressure release ventilation (APRV– also called BIPAP in Europe) [34]. Finally, it must be emphasised that the inspiratory time approach to limiting maximal pressure has not been evaluated in any meaningful outcome study. Indeed, it is conceivable that long inspiratory times, in and of themselves, may be potentially injurious.

Clinical evidence that lung protective strategies are effective

Perhaps the most important study to address this issue is the recently reported NIH ARDS Network study of ventilator management [26]. In this trial, over 800 patients were randomised to either a low-stretch strategy (Vt=6 ml/kg ideal body weight) or a high-stretch strategy (Vt=12 ml/kg ideal body weight). Importantly, the high-stretch strategy resulted in plateau pressures above the overdistension threshold (i.e. 30–35 cmH_2O) while the low-stretch strategy produced plateau pressures below this. The results showed a statistically significant 25% reduction in mortality in the low-stretch group despite the fact that the patients in this group actually had a lower PaO_2/FiO_2 ratio during the first 2 days of the trial. Also of note was that fact that there were fewer cases of other organ failures and inflammatory cytokine values were lower in the low-stretch group. This study provides compelling evidence that ventilator management strategies designed to prevent overdistension not only protect the lung from injury but also reduce systemic inflammation and improve mortality.

Future directions

There are still a number of important open questions about the use of lung-protective strategies during conventional mechanical ventilation. First, are there other aspects of the tidal breath pressure/volume pattern (e.g. frequency, flow magnitude, inspiratory time, tidal stretch) that affect injury? Second, what are the optimal trade-offs in gas exchange, pH and FiO2 when aggressive reductions in minute ventilation are planned? Third, where is the optimal PEEP setting with regard to PV plots? Indeed, does it matter? Fourth, what is the role of positioning (especially to the prone position) in redistribution of lung water, lung perfusion and lung ventilation so as to optimise a lung-protective strategy? Finally, do these lung-protective principles also apply to nonparenchymal lung disease (e.g. obstructive diseases)? Logic would suggest that overdistension injury can also occur in any lung disease if excessive pressures and volumes are directed at healthier regions of the lung.

Potential nonconventional respiratory support strategies and adjuncts that might enhance lung protection include two approaches: high-frequency ventilation

(HFV) and techniques to alter surface-active properties. HFV, by providing low maximal pressures and high recruitment pressures might be the 'ultimate' lung-protective strategy for a positive-pressure ventilatory support system. Indeed, in infants at risk for overdistension injury HFV has been shown to offer benefit, and a recent randomised trial in adults also suggests an outcome benefit [35]. Surface-active properties can be altered by surfactant administration [36], and the need for high distending pressures should be reduced accordingly. Surfactant replacement in the adult was unsuccessful in early trials, but with newer preparations (which include surfactant proteins) and better delivery strategies this approach may prove useful in the future.

Conclusions

Robust data suggest that both maximal and tidal overdistension of lung regions can produce both direct lung injury and a release of inflammatory mediators into the circulation. Animal data also suggest that additional injury results from repetitive alveolar recruitment–derecruitment. Ventilator management strategies aimed at limiting maximal distension (and optimising recruitment) are called lung-protective strategies. Because minute ventilation can be compromised by these strategies, gas exchange may suffer in a trade-off for this protection. Recent clinical trial results showing mortality benefits of lung protection, however, provide strong evidence that this trade-off is worthwhile.

References

1. Webb HH, Tierney DF (1974) Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressure. Protection by positive end-expiratory pressure. Am Rev Respir Dis 199:556-565
2. Hernandez LA, Coker PJ, May S et al (1990) Mechanical ventilation increases microvascular permeability in oleic acid injured lungs. J AppI Physiol 69:2057-2061
3. Kolobow T, Moretti MP, Fumagalli R et al (1987) Severe impairment in lung function induced by high peak airway pressure during mechanical ventilation. Am Rev Respir Dis 135:312-315
4. Dreyfuss D, Soler P, Basset G et al (1988) High inflation pressure pulmonary edema. Am Rev Respir Dis 137:1159-1164
5. Dreyfuss D, Basset G, Soler P et al (1985) Intermittent positive-pressure hyperventilation with high inflation pressures produces pulmonary microvascular injury in rats. Am Rev Respir Dis 132:880-884
6. Bowton DL, Kong DL (1989) High tidal volume ventilation produces increased lung water in oleic acid injured rabbit lungs. Crit Care Med 17:908-911
7. Parker JC Townsley MI, Rippe B et al (1984) Increased microvascular permeability in dog lungs due to high peak airway pressures. J Appl Physiol 57:1809-1816
8. Parker JC, Hernandez LA, Peevy KJ (1993) Mechanisms of ventilator-induced lung injury. Crit Care Med 21:131-143

9. Parker JC, Hernandez LA, Longenecker GL, Peevy K, Johnson W (1990) Lung edema caused by high peak inspiratory pressures in dogs. Am Rev Respir Dis 142:321-328
10. Tsuno K, Prato P, Kolobow T (1990) Acute lung injury from mechanical ventilation at moderately high airway pressures. J Appl Physiol 69:956-961
11. Tsuno K, Miura K, Takeya M et al (1991) Histopathologic pulmonary changes from mechanical ventilation at high peak airway pressures. Am Rev Respir Dis 143:1115-1120
12. Dreyfuss D, Saumon G (1993) The role of tidal volume, FRC and end inspiratory volume in the development of pulmonary edema following mechanical ventilation. Am J Respir Crit Care Med 148:1194-1203
13. Muscedere JG, Mullen JB, Gan K et al (1994) Tidal ventilation at low airway pressure can augment lung injury. Am J Respir Crit Care Med 149:1327-1334
14. Rich BR, Reickert CA, Sawada S et al (2000) Effect of rate and inspiratory flow on ventilator induced lung injury. J Trauma 49:903-911
15. Simonson DA, Adams AB, Wright LA et al (2004) Effects of ventilatory pattern on experimental lung injury caused by high airway pressure. Crit Care Med 32:781-786
16. Slutsky AS (2001) Basic science in ventilator-induced lung injury: implications for the bedside (see comment). Am J Respir Crit Care Med 163:599-600
17. Wyszogrodski L, Kyei-Aboagye K, Taeusch HW et al (1975) Surfactant inactivation by hyperventilation: conservation by end expiratory pressure. J Appl Physiol 38:461-466
18. Ranieri VM, Eissa NT, Corbeil C et al (1991) Effects of positive end expiratory pressure on alveolar recruitment and gas exchange in patients with the adult respiratory distress syndrome. Am Rev Respir Dis 144:544-551
19. Sandhar BK, Niblett DJ, Argiras EP et al (1988) Effect of positive end expiratory pressure on hyaline membrane formation in a rabbit model of the neonatal respiratory distress syndrome. Intensive Care Med 14:538-546
20. Putensen C, Bain M, Hormann C (1993) Selecting ventilator settings according to the variables derived from the quasi static pressure volume relationship in patients with acute lung injury. Anesth Analg 77:436-447
21. Gattiononi L, Pesenti A, Avalli L et al (1987) Pressure-volume curve of total respiratory system in acute respiratory failure: computed tomographic scan study. Am Rev Respir Dis 136:730-736
22. Hickling KG (2002) Reinterpreting the pressure-volume curve in patients with acute respiratory distress syndrome. Curr Opin Crit Care 8:32-38
23. Ranieri VM, Giuliani R, Fiore T et al (1994) Volume pressure curve of the respiratory system predicts effects of PEEP in ARDS: occlusion vs constant flow technique. Am J Respir Crit Care Med 149:19-27
24. ACCP Consensus Group (1993) Mechanical ventilation. Chest 104:1833-1859
25. Ranieri VM, Brienza N, Santostasi S et al (1997) Impairment of lung and chest wall mechanics in patients with acute respiratory distress syndrome: role of abdominal distension. Am J Respir Crit Care Med 156:1082-1091
26. NIH ARDS Network (2000) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 342:1301-1308
27. Amato MB, Barbas CSV, Medievos DM et al (1998) Effect of a protective ventilation strategy on mortality in ARDS. N Engl J Med 338:347-354
28. Suter PM, Fairley HB, Isenberg MD (1975) Optimic end expiratory pressure in patients with acute pulmonary failure. N Engl J Med 292:284-289
29. Gattinoni L, Pelosi P, Crotti S, Valenza F (1995) Effects of positive end expiratory pressure on regional distribution of tidal volume and recruitment in adult respiratory distress syndrome. Am J Respir Crit Care Med 151:1807-1814

30. ARDS Network (2002) A comparison of a high or a low PEEP strategy on outcomes in ARDS (ALVEOLI Trial). Paper presented at the American Thoracic Society Meeting, Seattle, 2002
31. Cole AGH, Weller SF, Sykes MK (1984) Inverse ratio ventilation compared with PEEP in adult respiratory failure. Intensive Care Med 10:227-232
32. Tharratt RS, Allen RP, Albertson TE (1988) Pressure controlled inverse ratio ventilation in severe adult respiratory failure. Chest 94:755-762
33. Armstrong BW, MacIntyre NR (1995) Pressure controlled inverse ratio ventilation that avoids air trapping in ARDS. Crit Care Med 23:279-285
34. Putensen C, Zech S, Wrigge H et al (2001) Long term effects of spontaneous breathing during ventilatory support in patients with ALI. Am J Respir Crit Care Med 164:43-49
35. Derdak S, Mehta S, Stewart TE et al (Multicenter Oscillatory Ventilation for Acute Respiratory Distress Syndrome Trial [MOAT] Study Investigators) (2002) High-frequency oscillatory ventilation for acute respiratory distress syndrome in adults: a randomized, controlled trial. Am J Respir Crit Care Med 166:801-808
36. Jobe AH (1993) Pulmonary surfactant therapy. N Engl J Med 328:861-868

Chapter 30

Recruitment and oxygenation

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The provision of adequate gas exchange with the least possible pulmonary and systemic damage is the therapeutic goal of mechanical ventilation in patients with acute respiratory distress syndrome (ARDS). Mechanical ventilation itself can promote and perpetuate lung injury. Both end-inspiratory overdistension and end-expiratory cycling collapse of lung units, which causes mechanical stress and repetitive share forces, induces cytokine release into the lung parenchyma and the systemic circulation [1, 2] and may thereby contribute to ventilator-associated lung injury [3]. The use of low tidal volumes (~6 ml/kg body weight) to limit end-inspiratory pressure reduces the mortality of patients with ARDS [4, 5] and has been recommended definitively for such patients [3].

However, a reduction in tidal volume is responsible for a significant lung volume loss corresponding to alveolar derecruitment [6]. Collapsed lung tissue increases the likelihood of infection, activates inflammation [7, 8] and requires higher airway pressure and fraction of inspired oxygen (FiO_2) [9].

There is some controversy about the usefulness and safety of different techniques for alveolar recruitment. The use of higher PEEP (to prevent derecruitment), recruitment manoeuvres, high-frequency ventilation, prone position and spontaneous breathing have been proposed as adjunctive lung-protective strategies for reversal or prevention of low tidal volume-related derecruitment.

Recruitment by PEEP

The use of PEEP to improve oxygenation in patients with ARDS was first reported by Ashbaugh et al. [10] in 1967 first. Crotti et al. [11] have shown that P_aO_2 increases with PEEP (5, 10, 15 or 20 cmH_2O) regardless of what plateau pressure is applied (30 or 35 cmH_2O), and that the increases in P_aO_2 with the increase of PEEP are well correlated with the shift of poorly aerated tissue to aerated tissue in densitometric analyses of thoracic computed tomography (CT) scans. Earlier investigations by Gattinoni [12] have also demonstrated that end-inspiratory collapse of lung tissue is inversely related to PaO_2. PEEP improves oxygenation by avoiding expiratory derecruitment, reducing shunt and improving ventilation–perfusion match, but tidal ventilation in addition to PEEP might also cause alveolar overdistension, increased dead space ventilation and decreased cardiac output (at least if an increase in intrathoracic pressure is not compensated by adequate fluid admini-

stration) and oxygen delivery [13]. There is some controversy about the optimal PEEP setting. Some authors recommend high PEEP levels [4, 14], while others advise low settings [15]. A recently published study by the American ARDS Network [16] addressed the issue of using either higher PEEP or higher FIO_2. Unfortunately, this study was broken off early and was hampered by some methodical problems, so that a definite answer is lacking. From a physiological point of view, the potential for recruitment might be dependent on the type and distribution of lung disease, which means that not every patient's lung can be easily recruited.

Analysis of pressure–volume (PV) curves, representing the static relationship between inflation or deflation pressure and volume of the respiratory system, have been used to optimise PEEP settings. It has been suggested that PEEP set above the lower inflection point (LIP) of the PV curve (P_{lip}) leads to an increased recruitment of collapsed lung units [17], a higher weaning rate, a lower incidence of barotraumas and a higher 28-day survival rate [4]. Moreover PEEP above P_{lip} decreases the levels of cytokines in BAL fluid of ARDS patients, suggesting a reduction of lung inflammation [18] attributable to a reduction in share forces.

Other investigators have found that a PEEP setting based on P_{lip} may be insufficient to keep the lung open. They report that derecruitment indicated by an increased shunt occurs at pressure levels above P_{lip} [19]. Crotti et al. [11] found that recruitment and derecruitment occur along the entire VP curve of the respiratory system. Using a mathematical model of ARDS lungs, Hickling et al. [20] suggest that tidal compliance during an incremental PEEP trial is not useful for prediction of open-lung PEEP, but may have some value during decremental PEEP trial.

Different techniques for measurement of static PV curves can lead to different results, and the interpretation of the results has been questioned [13, 21]. Thus, the use of the P_{lip} of the PV curve does not seem to be an adequate way of finding an optimal PEEP setting. Different methods of setting PEEP, such as optimising the shunt, using dynamic PV curves (stress index) [22] and using the deflation limb of the PV curve, should be further investigated [23].

Recruitment manoeuvres

PEEP can only prevent derecruitment, and many studies have shown that very high pressures are necessary to reopen collapsed lung regions [24, 25] and that these lung units may be stabilised with lower pressure levels when reopened.

A recruitment manoeuvre (RM) is a sustained increase in airway pressure with the goal of opening collapsed lung tissue. RMs can be performed in different ways. A *sustained high-pressure recruitment manoeuvre* is usually performed by maintaining high CPAP levels (up to 60 cmH2O) for 20–40 s. The effect of a sustained high-pressure RM on oxygenation is controversially discussed. Different studies have demonstrated an increment in the P_aO_2/FIO_2 ratio [4], a persistent improvement in oxygen saturation 4 h after a RM [26] and an increase in PaO_2 induced by a RM that was observed after 1 h [27]. Other authors have shown that the improvement of oxygenation can only be observed immediately after a RM and is lost after 20 min [28].

Intermittent sighs are implemented by periodically increasing PEEP, tidal volume or inspiratory time. Pelosi et al. [29] observed an increase of P_aO_2/FIO_2 ratio, a larger lung volume and a smaller venous admixture in patients with ARDS ventilated with a lung-protective strategy with three consecutive sighs per minute at 45 cmH_2O plateau pressure than in patients who had the same protective strategy except without sights. Barbas et al. [30] compared three cycles of PCV of 40 cmH_2O for 6 s vs three cycles of PCV of progressive plateau pressure levels (40, 50, 60 cmH_2O) and observed a further increment in the P_aO_2/FIO_2 ratio after 1 h and 6 h without haemodynamic impairment in the progressive plateau pressure group.

Intermittent stepwise PEEP levels are a type of RM consisting in short-time steps of tidal ventilation with fixed pressure control and progressive PEEP levels (20, 25, 35 and so on up to 45 cmH_2O), followed by a PEEP titration strategy (stepwise decrements in PEEP until PaO_2 declines) to keep the lung open.

This strategy has been shown to be capable of perpetuating the benefits of recruitment after 6 h. There was an immediate decrease in PaO2 when PEEP was reduced to below the titrated pressure (unpublished data, Okamato 2003, cited in [31]).

Origin of ARDS and different models of ALI

Pelosi et al. [29] suggested that the effect of RMs in terms of recruitment might depend on the underlying disease. Gattinoni et al. [32] demonstrated that PEEP-induced recruitment was significantly higher in extrapulmonary ARDS, in which alveolar collapse and interstitial oedema is predominant, whereas no recruitment was observed with PEEP in pulmonary ARDS. However, data published by other investigators suggest that the success of RMs probably depends on respiratory mechanics. Grasso et al. [33] investigated the effects of a RM in ARDS patients; they found that pulmonary ARDS was equally distributed in responders and nonresponders and observed a higher transpulmonary pressure in responders than in nonresponders.

The response to three consecutive RMs in three different models of canine acute lung injury (ALI) was evaluated by Van der Kloot [34]. Lung injury was induced by saline lavage, oleic acid and *Escherichia coli* instillation (pneumonia). RMs were beneficial only in the saline lavage model. The animals with pneumonia, which were characterised by lung inflammation and consolidation, responded poorly to PEEP and RMs in terms of alveolar recruitment.

Side effects and limitations

The application of periodic or sustained high airway pressure is not without potential problems. In patients with pre-existing bullous lung disease or air leaks the potential risk of the development of barotauma has to be considered. Transient desaturation and hypotension are the most frequently observed side effects of RMs. Grasso et al. [33] observed a significant decrease in cardiac output and in mean arterial pressure during a RM in nonresponders, whereas in responders the hae-

modynamics remained unchanged during the recruitment manoeuvre. The authors claim that this difference is caused by a higher chest wall elastance in nonresponders, resulting in a greater transmission of airway pressure to pleural pressure during the RM.

The effects of RMs on cerebral perfusion in patients with cerebral lesions and ALI were evaluated by Bein et al. [35]. Recruitment manoeuvres resulted in decreased jugular bulb oxygen saturation and decreased cerebral perfusion pressures, caused by increased intracranial pressure and decreased mean arterial pressure. These data imply that RM should be used with caution, especially in patients with intracranial hypertension.

In some studies [28] RMs did not improve or even worsened gas exchange in a fraction of subjects. Musch et al. [36] investigated the use of RMs in sheep with polysorbate 80 lavage-induced ALI. They found that if lung inflation resulted predominantly in overexpansion of aerated regions rather than in alveolar recruitment, the increase in pulmonary vascular resistance in this aerated region could divert perfusion toward nonaerated areas.

It can be that multiple RM are necessary, and the oxygenation benefit of the RM is rapidly lost if PEEP is inadequately adjusted to prevent derecruitment after an RM [26]. The success of any RM probably depends on a combination of factors, such as pressure level, time [31] and mechanism of lung injury (extra- and intrapulmonary ARDS). Detection of the kind of patients who will benefit from RMs seems to be an important task.

Until further safety studies have addressed possible side effects of RM, e.g. studies on microscopic tissue damage and pulmonary and systemic inflammatory responses, we cannot recommend routine application of RMs in patients with ALI.

Prone position

Prone positioning in ARDS results in improved oxygenation and facilitates a reduction in the FIO_2 or PEEP level [37, 38]. This effect is caused by a high recruiting force in dependent, compressed lung regions [39] and reduction of low-ventilation-perfusion units and pulmonary shunt [40]. Differences in regional ventilation and perfusion in patients in the prone vs the supine position are responsible for this improvement in ventilation/perfusion matching [41].

Lim at al. [42] compared the effect of low PEEP (2 cmH_2O below P_{lip}) and high PEEP (2 cmH_2O above P_{lip}) in the supine and the prone position in a canine lavage-injury model. They demonstrated that prone positioning enhances the improvement in oxygenation by low PEEP settings and reduces the side effects of high PEEP on haemodynamics.

In a recent study, Cakar et al. [43] investigated the oxygenation response to a RM (30 s sustained inflation at 60 cmH_2O) performed in prone and supine positions in a canine oleic acid-induced ALI. Prone position improved oxygenation, and the oxygenation benefit of prone position was carried over to the supine position. Moreover, oxygenation improved in both groups after RM, but a higher

PEEP (15 cmH_2O) was required to maintain oxygenation benefit in the supine position than in the prone position (8 cmH_2O). As demonstrated by Hering et al., prone positioning, when used in ALI patients, while associated with a small increase in intra-abdominal pressure, contributes to improved arterial oxygenation and systemic blod flow without affecting renal perfusion and function [44] or hepato-splanchnic function [45]. However, a first randomised controlled multicentre trial failed to demonstrate a beneficial effect of prone positioning on mortality in patients with ALI [46]. Post hoc analysis suggests that patients with most severe hypoxaemia seem to derive a survival benefit from prone positioning [46]. Ongoing trials will provide more evidence about a possible influence of prone positioning on clinical outcome.

Spontaneous breathing

During controlled mechanical ventilation the diaphragm is relaxed and its displacement will mainly be in non-dependent, anterior regions, because of the lower impedance of abdominal organs in the upper than in the lower abdominal regions. During spontaneous breathing (SB), posterior muscle sections of the diaphragm move more than the anterior tendon plate [47, 48]. In parallel with the displacement of the diaphragm ventilation seems to be distributed to upper, nondependent lung regions in mechanically ventilated subjects [49, 50], in contrast to the well-known preferential distribution to dependent lung regions during SB.

Spontaneous breathing is possible in any phase of the mechanical ventilator cycle with airway pressure release ventilation (APRV), a technique that provides ventilatory support by way of time-cycled switching between two different CPAP levels [51–53]. In patients with severe ALI, unsupported SB with APRV has been observed to improve aterial blood oxygenation over that in patients with controlled mechanical ventilation alone [54–56] or breath-to-breath inspiratory assistance with pressure support ventilation [56]. Moreover, this clinical investigation and other experimental studies [57, 58] have shown a reduction in intrapulmonary shunting. Wrigge et al. [59] recently demonstrated an increase in oxygenation (Fig. 1a) and oxygen delivery as well as a substantial and progressive improvement of end-expiratory lung volume (EELV) with SB (Fig. 1b), whereas oxygenation, oxygen delivery and EELV remained low in the absence of SB in a porcine model of oleic acid-induced lung injury. Another major finding in this CT study was that SB was associated with considerably less nonaerated lung tissue and increased aeration (Fig. a). The negative correlation (r^2=0.62) between EELV and amount of nonaerated lung (Fig. 2b) combined with the correlation between venous admixture (r^2=0.61) suggests that recruitment of non aerated lung tissue is the major factor for improvement of EELV during APRV with SB and that redistribution of gas to dependent, well perfused lung regions mainly explains improved oxygenation and reduction in intrapulmonary shunt during spontaneous breathing. This hypothesis is supported by additional, not jet published results of this investigation showing a redistribution of tidal ventilation to dependent juxtadiaphragmatic lung

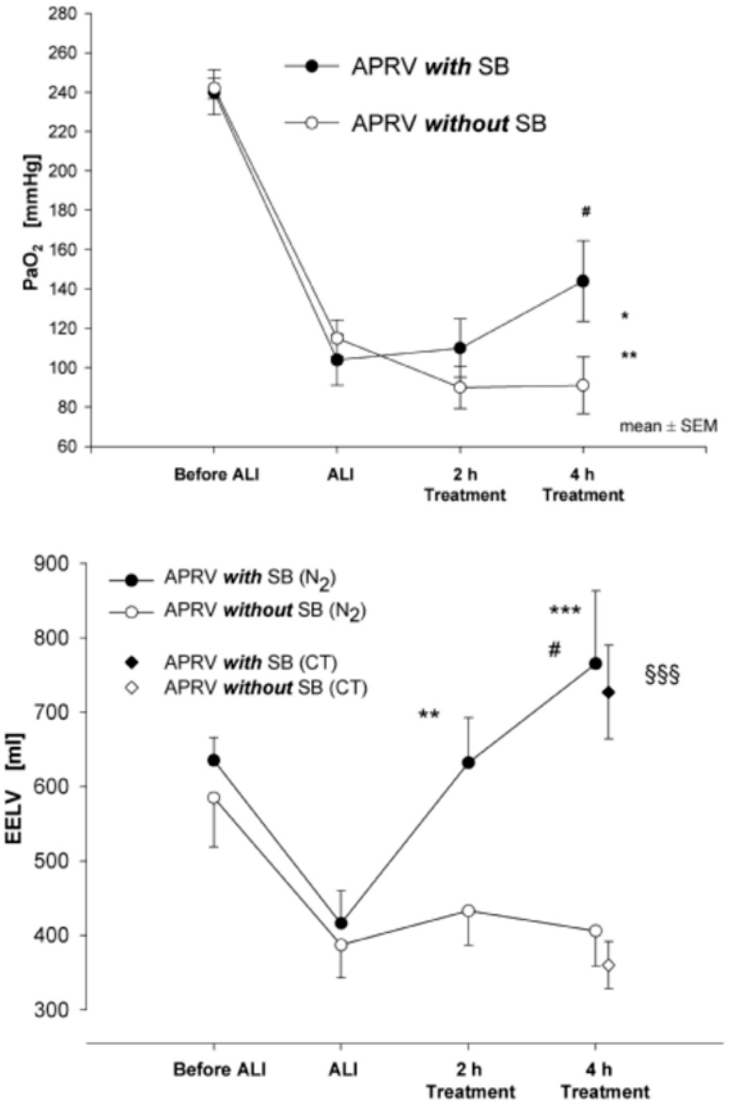

Fig. 1a. Time-course of oxygenation for airway pressure release ventilation (*APRV*) with and without spontaneous breathing (*SB*). Statistical significance: **P*<0.001 for differences from time-course in patients with lung injury; ***P*<0.01 for interaction of factors time and ventilatory mode; #*P*<0.05 APRV with versus without SB

Fig. 1b. Time-course of end-expiratory lung volume (*EELV*) for airway pressure release ventilation (*APRV*) with and without spontaneous breathing (*SB*) measured by N_2 washout and after 4 h of specific treatment using computed tomography (*CT*) densitometry. ***P*<0.01; ****P*<0.001 for comparison with lung injury; #*P*<0.05 for difference in APRV with vs without SB measured by N_2 washout; §§§*P*.001 for difference in APRV with vs without SB determined by CT analysis

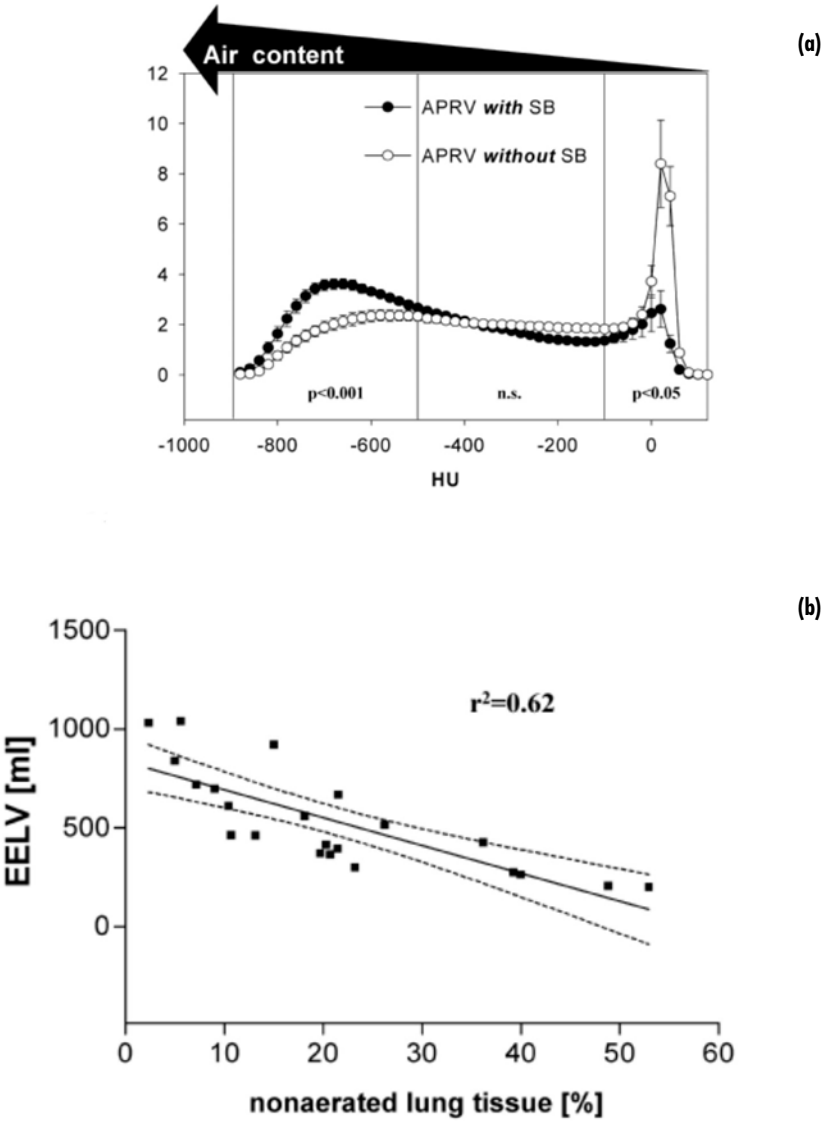

Fig. 2a. Densitometry of the whole lungs from spiral computed tomography (CT) at end-expiration. Histogram shows normalised lung volume for Hounsfield units (HU) ranging from –1,000 to +100, plotted as mean±SEM of all animals. Aeration categories (hyperinflated –900 to –1,000, normally aerated –500 to –900, poorly aerated –100 to –500, nonaerated 100 to –100) are marked and were statistically compared between APRV with and without SB.
Fig. 2b. Linear correlation of EELV and relative amount of nonaerated lung revealed the equation EELV=-1410 × nonaerated lung + 833, r^2 = 0.62, P<0.001.

regions as well as a reduction of cyclic alveolar collapse during SB.

High frequency oscillatory ventilation (HFOV)

HFOV aims to maintain an open lung volume by the application of a constant mean airway pressure (mPaw) similar to continuous positive airway pressure used in conventional mechanical ventilation [60]. Oxygenation is mainly achieved by increasing mean Paw [61]. Ventilation mechanisms during HFOV are more dependent on facilitate diffusion, rather than bulk flow of gas that occurs with conventional ventilation [62]. Ventilation is primarily achieved by superimposing an oscillatory pressure amplitude (?P). The oscillatory excursions promote cyclic tidal ventilation delivery and facilitate ventilation. Maximum ventilation occurs with the highest ?P and lowest frequency settings.

Ideally, HFOV maintains the lung in an open, recruited state and results in small tidal volumes with minimal stretch injury [63] and minimal potential for atelectatic trauma caused by cyclic alveolar collapse.

Patients with serve ARDS were treated with HFOV using an open-lung strategy by Fort et al. [64]. After the transition to HFOV, patients demonstrated significant improvements in PaO_2/FIO_2, which persisted for the first 48 h of treatment. Derdak et al. [65] randomised ARDS patients to conventional ventilation or HFOV. Patients who received HFOV showed a significant improvement in oxygenation. However, this difference did not persist beyond 24 h.

Van Genderingen et al. [66] used electrical impedance tomography to analyse the regional lung volume during a PV manoeuvre on conventional ventilation and during a recruitment-derecruitment manoeuvre on HFOV. They demonstrated that lung opening during the conventional PV manoeuvre was distributed nonuniformly, whereas deflation was more homogeneous. HFOV seemed to have a homogenising effect on lung volume distribution, as no large regional differences were found during either inflation or deflation. Other findings were a larger lung volume and impedance reached at the highest imposed airway pressure during HFOV than with a conventional PV manoeuvre. This suggests that HFOV is more potent in recruiting nonaerated lung units than a static airway pressure.

In a recently published prospective, randomized trial comparing HFOV and conventional ventilation [65] HOFV was found to be effective and safe. However, no significant difference in mortality rate was observed.

Monitoring of recruitment

Computed tomography (CT)

Computed tomography (CT) is the state of the art to evaluate regional lung aeration. However, it is not available at bedside and it is associated with radiation load.

Electrical impedance tomography (EIT)

The method is based on the fact that changes in regional air content modifies the electrical properties of lung tissue [67], which can be determined in a thoracic cross-section. EIT is a dynamic technique that quantifies changes in electrical impedance. It is safe, noninvasive and available at the bedside. In the future, EIT will allow visualisation of a three-dimensional thoracic image. This will allow clinicians to recruit ARDS lungs and adjust PEEP to the ideal level, as well as maintaining an open lung and homogeneous ventilation [68].

Conclusions

Although lung protective ventilatory strategies have been shown to reduce the mortality rate in patients with ALI, reduction of tidal volume to 6 ml/kg of predicted body weight may be responsible for alveolar derecruitment. Higher PEEP levels should reduce derecruitment which might be associated with low tidal volume mechanical ventilation. Despite beneficial results in small randomised controlled clinical trials favouring the use of high PEEP, data obtained in a large study comparing higher PEEP against higher FIO_2 have not yet convincingly demonstrated that high PEEP is superior, but have at least shown that high PEEP can safely be used in ALI and ARDS.

Small tidal volume-related lung volume loss can be recovered by different types of RM. Indeed, a sufficiently high PEEP level is necessary to prevent a loss of lung volume after a RM. It is not known whether these manoeuvres have a benefit over other recruitment interventions, such as high PEEP levels, prone position or spontaneous breathing. RMs cannot be generally recommended until further safety data are available. Suitable patients must be selected.

Prone positioning may be a useful and safe component of therapy in selected patients with severe ARDS who have not responded to other recruitment interventions, even if a beneficial effect of prone positioning on mortality in patients with ALI has not been demonstrated.

HFOV is an alternative method of mechanical ventilation for patients with severe ARDS and should be considered if FIO_2 requirements exceed 60% and the inspiratory plateau pressure cannot be maintained below 30 cmH_2O.

Suppression of SB is not necessary unless it is required for specific reasons (e.g. treatment of increased intracranial pressure). SB with APRV not only reduces the need for sedation to adapt the patient to the ventilator, but also improves both

systemic blood flow and arterial blood oxygenation over that obtained with controlled mechanical ventilation. SB promotes reopening of the collapsed and consolidated lung and increases EELV. Moreover, SB redistributes end-expiratory aeration and tidal ventilation to dependent, well-perfused lung regions.

References

1. Chiumello D, Pristine G, Slutsky AS (1999) Mechanical ventilation affects local and systemic cytokines in an animal model of acute respiratory distress syndrome. Am J Respir Crit Care Med 160:109-116
2. Ranieri VM, Suter PM, Tortorella C et al (1999) Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. JAMA 282:54-61
3. (1999) International Consensus Conferences in Intensive Care Medicine: Ventilator-associated Lung Injury in ARDS. Official conference report cosponsored by the American Thoracic Society, The European Society of Intensive Care Medicine and The Société de Réanimation de Langue Française, and was approved by the ATS Board of Directors, July 1999. Am J Respir Crit Care Med 160:2118-2124
4. Amato MB, Barbas CS, Medeiros DM et al (1998) Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 338:347-354
5. The Acute Respiratory Distress Syndrome Network (2000) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 342:1301-1308
6. Richard JC, Maggiore SM, Jonson B et al (2001) Influence of tidal volume on alveolar recruitment. Respective role of PEEP and a recruitment maneuver. Am J Respir Crit Care Med 163:1609-1613
7. Slutsky AS, Tremblay LN (1998) Multiple system organ failure. Is mechanical ventilation a contributing factor? Am J Respir Crit Care Med 157:1721-1725
8. Dreyfuss D, Saumon G (1998) From ventilator-induced lung injury to multiple organ dysfunction? Intensive Care Med 24:102-104
9. Richard JC, Maggiore S, Mercat A (2003) Where are we with recruitment maneuvers in patients with acute lung injury and acute respiratory distress syndrome? Curr Opin Crit Care 9:22-27
10. Ashbaugh DG, Bigelow DB, Petty TL et al (1967) Acute respiratory distress in adults. Lancet II:319-323
11. Crotti S, Mascheroni D, Caironi P et al (2001) Recruitment and derecruitment during acute respiratory failure: a clinical study. Am J Respir Crit Care Med 164:131-140
12. Gattinoni L, Pesenti A, Bombino M et al (1988) Relationships between lung computed tomographic density, gas exchange, and PEEP in acute respiratory failure. Anesthesiology 69:824-832
13. Villar J (2003) Positive end-expiratory pressure or no positive end-expiratory pressure: is that the question to be asked? Crit Care 7:192
14. Kirby RR, Downs JB, Civetta JM et al (1975) High level positive end expiratory pressure (PEEP) in acute respiratory insufficiency. Chest 67:156-163
15. Carroll GC, Tuman KJ, Braverman B et al (1988) Minimal positive end-expiratory pressure (PEEP) may be "best PEEP". Chest 93:1020-1025

16. Brower RG, Lanken PN, MacIntyre N et al (2004) Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med 351:327-336
17. Gattinoni L, Pesenti A, Avalli L (1987) Pressure-volume curve of total respiratory system in acute respiratory failure. Computed tomographic scan study. Am Rev Respir Dis 136:730-736
18. Ranieri VM, Suter PM, Tortorella C et al (1999) Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. JAMA 282:54-61
19. Meyer EC, Barbas CS, Grunauer MA et al (1998) PEEP at Pflex cannot guarantee a full open lung after a high pressure recruitment maneuver in ARDS patients (abstract). Am J Respir Crit Care Med 157:A694
20. Hickling KG (2001) Best compliance during a decremental, but not incremental, positive end-expiratory pressure trial is related to open-lung positive end-expiratory pressure: a mathematical model of acute respiratory distress syndrome lungs. Am J Respir Crit Care Med 163:69-78
21. Wilson TA, Anafi RC, Hubmayr RD (2001) Mechanics of edematous lungs. J Appl Physiol 90:2088-2093
22. Grasso S, Terragni P, Mascia L et al (2004) Airway pressure-time curve profile (stress index) detects tidal recruitment/hyperinflation in experimental acute lung injury. Crit Care Med 32:1018-1027
23. Medoff BD, Harris RS, Kesselman H et al (2000) Use of recruitment maneuvers and high-positive end-expiratory pressure in a patient with acute respiratory distress syndrome. Crit Care Med 28:1210-1216
24. Rothen HU, Sporre B, Engberg G et al (1995) Reexpansion of atelectasis during general anaesthesia may have a prolonged effect. Acta Anaesthesiol Scand 39:118-125
25. Gattinoni L, Pelosi P, Crotti S et al (1995) Effects of positive end-expiratory pressure on regional distribution of tidal volume and recruitment in adult respiratory distress syndrome. Am J Respir Crit Care Med 151:1807-1814
26. Lapinsky SE, Aubin M, Mehta S et al (1999) Safety and efficacy of a sustained inflation for alveolar recruitment in adults with respiratory failure. Intensive Care Med 25:1297-1301
27. Lim CM, Koh Y, Park W et al (2001) Mechanistic scheme and effect of "extended sigh" as a recruitment maneuver in patients with acute respiratory distress syndrome: a preliminary study. Crit Care Med 29:1255-1260
28. Villagra A, Ochagavia A, Vatua S et al (2002) Recruitment maneuvers during lung protective ventilation in acute respiratory distress syndrome. Am J Respir Crit Care Med 165:165-170
29. Pelosi P, Cadringher P, Bottino N et al (1999) Sigh in acute respiratory distress syndrome. Am J Respir Crit Care Med 159:872-880
30. Barbas CSV, SIlva E, Garrido A et al (2001) Recruitment maneuvers with different pressure control levels in ARDS patients (abstract). Am J Respir Crit Care Med 163:A163
31. Valente Barbas CS (2003) Lung recruitment maneuvers in acute respiratory distress syndrome and facilitating resolution. Crit Care Med 31:S265-S271
32. Gattinoni L, Pelosi P, Suter PM et al (1998) Acute respiratory distress syndrome caused by pulmonary and extrapulmonary disease. Different syndromes? Am J Respir Crit Care Med 158:3-11
33. Grasso S, Mascia L, Del Turco M et al (2002) Effects of recruiting maneuvers in patients with acute respiratory distress syndrome ventilated with protective ventilatory strategy. Anesthesiology 96:795-802

34. Kloot TE, Blanch L, Melynne YA et al (2000) Recruitment maneuvers in three experimental models of acute lung injury. Effect on lung volume and gas exchange. Am J Respir Crit Care Med 161:1485-1494
35. Bein T, Kuhr LP, Bele S et al (2002) Lung recruitment maneuver in patients with cerebral injury: effects on intracranial pressure and cerebral metabolism. Intensive Care Med 28:554-558
36. Musch G, Harris RS, Vidal Melo MF et al (2004) Mechanism by which a sustained inflation can worsen oxygenation in acute lung injury. Anesthesiology 100:323-330
37. Chatte G, Sab JM, Dubois JM et al (1997) Prone position in mechanically ventilated patients with severe acute respiratory failure. Am J Respir Crit Care Med 155:473-478
38. Pelosi P, Tubiolo D, Mascheroni D et al (1998) Effects of the prone position on respiratory mechanics and gas exchange during acute lung injury. Am J Respir Crit Care Med 157:387-393
39. Albert RK, Hubmayr RD (2000) The prone position eliminates compression of the lungs by the heart. Am J Respir Crit Care Med 161:1660-1665
40. Pappert D, Rossaint R, Slama K et al (1994) Influence of positioning on ventilation-perfusion relationships in severe adult respiratory distress syndrome. Chest 106:1511-1516
41. Lamm WJ, Graham MM, Albert RK (1994) Mechanism by which the prone position improves oxygenation in acute lung injury. Am J Respir Crit Care Med 150:184-193
42. Lim CM, Koh Y, Chin JY et al (1999) Respiratory and haemodynamic effects of the prone position at two different levels of PEEP in a canine acute lung injury model. Eur Respir J 13:163-168
43. Cakar N, der Kloot TV, Youngblood M et al (2000) Oxygenation response to a recruitment maneuver during supine and prone positions in an oleic acid-induced lung injury model. Am J Respir Crit Care Med 161:1949-1956
44. Hering R, Wrigge H, Vorwerk R et al (2001) The effects of prone positioning on intraabdominal pressure and cardiovascular and renal function in patients with acute lung injury. Anesth Analg 92:1226-1231
45. Hering R, Vorwerk R, Wrigge H et al (2002) Prone positioning, systemic hemodynamics, hepatic indocyanine green kinetics, and gastric intramucosal energy balance in patients with acute lung injury. Intensive Care Med 28:53-58
46. Gattinoni L, Tognoni G, Pesenti A et al (2001) Effect of prone positioning on the survival of patients with acute respiratory failure. N Engl J Med 345:568-573
47. Froese AB, Bryan AC (1974) Effects of anesthesia and paralysis on diaphragmatic mechanics in man. Anesthesiology 41:242-255
48. Kleinman BS, Frey K, VanDrunen M et al (2002) Motion of the diaphragm in patients with chronic obstructive pulmonary disease while spontaneously breathing versus during positive pressure breathing after anesthesia and neuromuscular blockade. Anesthesiology 97:298-305
49. Tokics L, Hedenstierna G, Svensson L et al (1996) V/Q distribution and correlation to atelectasis in anesthetized paralyzed humans. J Appl Physiol 81:1822-1833
50. Rehder K, Sessler AD, Rodarte JR (1977) Regional intrapulmonary gas distribution in awake and anesthetized-paralyzed man. J Appl Physiol 42:391-402
51. Downs JB, Stock MC (1987) Airway pressure release ventilation: a new concept in ventilatory support. Crit Care Med 15:459-461
52. Stock MC, Downs JB, Frolicher DA (1987) Airway pressure release ventilation. Crit Care Med 15:462-466
53. Baum M, Benzer H, Putensen C et al (1989) Biphasic positive airway pressure (BIPAP) – a new form of augmented ventilation. Anaesthesist 38:452-458

54. Putensen C, Zech S, Wrigge H et al (2001) Long-term effects of spontaneous breathing during ventilatory support in patients with acute lung injury. Am J Respir Crit Care Med 164:43-49
55. Sydow M, Burchardi H, Ephraim E et al (1994) Long-term effects of two different ventilatory modes on oxygenation in acute lung injury. Comparison of airway pressure release ventilation and volume-controlled inverse ratio ventilation. Am J Respir Crit Care Med 149:1550-1556
56. Putensen C, Mutz NJ, Putensen-Himmer G et al (1999) Spontaneous breathing during ventilatory support improves ventilation-perfusion distributions in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 159:1241-1248
57. Putensen C, Rasanen J, Lopez FA et al (1994) Effect of interfacing between spontaneous breathing and mechanical cycles on the ventilation-perfusion distribution in canine lung injury. Anesthesiology 81:921-930
58. Putensen C, Rasanen J, Lopez FA (1994) Ventilation-perfusion distributions during mechanical ventilation with superimposed spontaneous breathing in canine lung injury. Am J Respir Crit Care Med 150:101-108
59. Wrigge H, Zinserling J, Neumann P et al (2003) Spontaneous breathing improves lung aeration in oleic acid-induced lung injury. Anesthesiology 99:376-384
60. Froese AB (1997) High-frequency oscillatory ventilation for adult respiratory distress syndrome: let's get it right this time! Crit Care Med 25:906-908
61. Brazelton TB III, Watson KF, Murphy M et al (2001) Identification of optimal lung volume during high-frequency oscillatory ventilation using respiratory inductive plethysmography. Crit Care Med 29:2349-2359
62. Chang HK (1984) Mechanisms of gas transport during ventilation by high-frequency oscillation. J Appl Physiol 56:553-563
63. Goddon S, Fujino Y, Hromi JM et al (2001) Optimal mean airway pressure during high-frequency oscillation: predicted by the pressure-volume curve. Anesthesiology 94:862-869
64. Fort P, Farmer C, Westerman J et al (1997) High-frequency oscillatory ventilation for adult respiratory distress syndrome – a pilot study. Crit Care Med 25:937-947
65. Derdak S, Mehta S, Stewart TE et al (2002) High-frequency oscillatory ventilation for acute respiratory distress syndrome in adults: a randomized, controlled trial. Am J Respir Crit Care Med 166:801-808
66. Van Genderingen HR, van Vught AJ, Jansen JR (2004) Regional lung volume during high-frequency oscillatory ventilation by electrical impedance tomography. Crit Care Med 32:787-794
67. Nopp P, Rapp E, Pfutzner H et al (1993) Dielectric properties of lung tissue as a function of air content. Phys Med Biol 38:699-716
68. Victorino JA, Borges JB, Okamoto VN et al (2004) Imbalances in regional lung ventilation: a validation study on electrical impedance tomography. Am J Respir Crit Care Med 169:791-800

Chapter 31

Lung oedema in acute lung injury

S. Nunes

Lung oedema

Lung oedema occurs when transudation or exudation from the pulmonary capillaries exceeds the capacity of the lymphatic drainage. In its more severe forms there is free fluid in the alveoli [1].

The alveolar–capillary barrier is formed by the microvascular endothelium and the alveolar epithelium. Alveolar oedema results thus from (1) transudation of fluid from the pulmonary microcirculation into the interstitial space (across the endothelium), (2) movement of fluid within the interstitium and (3) movement of fluid from the interstitial space into the alveoli (across the epithelium).

Passage of fluid across the pulmonary microvascular endothelium is promoted by the hydrostatic pressure differential between capillary and interstitium, but counteracted by the osmotic pressure of the plasma proteins. This relationship is described by the Starling equation [1]. Transudation across the alveolar epithelium seems to occur only in the presence of epithelial damage or when the interstitial pressure increases above a critical level [2]. On the basis of this knowledge, it is possible to classify pulmonary oedema according to its main aetiologies: (1) hydrostatic pulmonary oedema (increased capillary pressure due to hypervolaemia, left heart failure, or left-to-right cardiac shunt), (2) permeability pulmonary oedema (increased permeability of the alveolar–capillary barrier) and (3) lung oedema due to decreased osmotic pressure of the plasma proteins (reduced plasma albumin concentration).

Permeability lung oedema in acute lung injury

Acute lung injury (ALI) and its most severe form, acute respiratory distress syndrome (ARDS), are characterised by the impairment of gas exchange and respiratory mechanics. These syndromes progress through different stages, each with different physiopathological, histopathological and radiological manifestations. Permeability pulmonary oedema typically occurs during the acute or exsudative phase of the disease. This type of oedema results from the loss of integrity of the alveolar–capillary membrane, allowing albumin and other macromolecules to enter the alveoli. The osmotic pressure gradient that opposes transudation is then lost. The oedema fluid has a protein content approaching that of plasma. Radio-

graphic findings are usually indistinguishable from those of hydrostatic pulmonary oedema [3]. Infiltrates can be patchy or asymmetrical, and pleural effusions are common [4]. Alveolar filling, consolidation and atelectasis occur predominantly in the dependent lung, whilst other areas may be relatively spared [5].

The alveolar–capillary membrane can be damaged either by direct insult (pneumonia, pulmonary contusion, aspiration, near-drowning, smoke or toxic chemical inhalation), or indirectly through the effects of systemic inflammatory response on the lung. Furthermore, experimental evidence indicates that excessive volumes and pressures generated by mechanical ventilation can cause permeability pulmonary oedema in the uninjured lung [6] and enhanced oedema in the injured lung [7]. The theory currently invoked to explain these deleterious effects points to capillary stress failure due to alveolar overdistension and cyclic opening and closing of atelectatic alveoli during mechanical ventilation. Various protective ventilatory strategies have been developed in attempts to avoid the development of ventilator-induced lung injury [8-11].

Pathophysiology of permeability oedema: injury to the alveolar–capillary barrier

In the acute phase of ALI and ARDS, the first lesions consist of interstitial oedema, followed by severe alveolarepithelial damage [12]. Endothelial injury and the consequent increased vascular permeability lead to interstitial oedema, while the gathering of neutrophils, macrophages and erythrocytes and the influx of oedema fluid into the air spaces induce alveolar epithelial damage [13].

The normal alveolar epithelium is composed of two types of cells. Flat type I cells cover 90% of the alveolar surface area and are easily injured. Type II cells make up the remaining 10%. Alveolar type II cells are more resistant to injury, and their functions include surfactant production and ion transport. In ALI and ARDS, the alveolar epithelium usually exhibits extensive necrosis of alveolar type I cells, leaving a denuded, but mainly intact, basement membrane with overlying hyaline membranes. The loss of alveolar epithelial integrity thus contributes to alveolar flooding through (1) the increase in permeability of the alveolar–capillary barrier, (2) the impairment of the removal of oedema fluid from the alveolar space as a consequence of injury to type II cells [14, 15], and (3) the reduction in the production and turnover of surfactant [16]. Alveolar type II cells may then proliferate to cover the denuded basement membrane and may differentiate into type I cells, restoring the normal alveolar architecture and increasing the fluid-transport capacity of the alveolar epithelium [17]. This proliferation is controlled by epithelial growth factors, including keratinocyte and hepatocyte growth factors.

Inflammation increases leucocyte production, which causes further cell damage through the production of free radicals, endotoxin and proinflammatory cytokines (tumour necrosis factor (TNF)-α and interleukin (IL)-1β, IL-6 and IL-8) [18]. IL-8 has been identified as a powerful neutrophil chemoattractant [19]. Because of the capillary leak, direct contact between factors contained in the bronchoalveolar lavage fluid and the endothelium can occur. Inflammatory cytokines may thus lead to major changes in endothelial cells [20] and produce diffuse transmural alveolar

wall damage. This phenomenon may be responsible for the amplification of ALI and for its dissemination [11], contributing in this way to multiorgan failure [21].

The factors associated with the development of pulmonary fibrosis or restoration of the normal pulmonary architecture after ALI and ARDS remain unclear. Efficient alveolar epithelial repair seems to suppress fibroblast proliferation and matrix deposition in animal models [22]. Restoration of the alveolar epithelium in the early phase of ALI and ARDS may therefore be a means not only of speeding recovery by enhancing alveolar liquid clearance, but also of preventing the development of pulmonary fibrosis [23]. The degree of alveolar epithelial injury has been shown to be an important predictor of outcome [24].

Resolution of permeability oedema

Alveolar oedema is resolved by the active transport of sodium from the distal air spaces into the lung interstitium. This transport uses sodium channels [25] and sodium/potassium adenosine triphosphatase (Na^+/K^+-ATPase) pumps [25], which are located mostly in type II, but also in type I cells [26]. Active transport of chloride may also be involved [25, 27]. Water follows passively, probably through transcellular water channels (aquaporins) located primarily on type I cells [28, 29].

In clinical studies, clearance of alveolar fluid can occur surprisingly early and is often apparent within the first few hours after intubation and the initiation of mechanical ventilation [30, 31]. Measurements of alveolar fluid clearance from 65 patients with severe hydrostatic pulmonary oedema [32] showed that 75% of patients had intact alveolar fluid clearance and the mean clearance was 13%/h. In contrast, a study conducted in 79 ALI and ARDS patients found that 56% of them presented impaired alveolar fluid clearance (<3%/h), which was associated with poorer oxygenation and higher mortality than in the other patients [30]. In the same study, the mean alveolar fluid clearance was 6%/h. This difference is probably due to the preservation of an intact and functional alveolar–epithelial barrier in the majority of patients with hydrostatic oedema. In ALI and ARDS, female patients, nonsmokers and patients without sepsis were more likely to have maximal alveolar fluid clearance [30]. The explanation that seems most plausible is that sepsis was associated with more severe and lasting injury to the alveolar–capillary barrier than other causes of lung injury, such as aspiration of gastric contents or primary pneumonia.

In the same study, levels of endogenous and exogenous catecholamines did not correlate with alveolar fluid clearance in ALI and ARDS patients [30]. This is at odds with observations in experimental studies, which revealed an up-regulation of alveolar fluid clearance caused by endogenous epinephrine [33, 34] and by a variety of exogenous β2-agonists, including terbutaline, salmeterol, epinephrine and dobutamine, and by the β1- and β2-agonist isoproterenol [35–40]. Possible explanations are the inability of the injured alveolar epithelium to respond to catecholamine stimulation [34] and the β-agonist receptor down-regulation caused by the presence of high levels of catecholamines over a prolonged length of time. Dopamine and glucocorticoids have also been shown to increase alveolar fluid

clearance experimentally [41–43], an observation that could not be clinically reproduced in ALI and ARDS patients [30].

An additional mechanism that might be important in determining the rate of alveolar fluid clearance is alveolar epithelial type II cell hyperplasia [17, 44]. This process, however, does not become significant for 1 or 2 days [23]. Being faster than proliferation, alveolar type II epithelial cell spreading and migration may be primarily responsible for efficient epithelial wound repair [45]. Hence, it seems reasonable to speculate that in vivo cell spreading and migration are the primary mechanisms during the early phase of alveolar epithelial repair, followed by cell proliferation leading to alveolar type II hyperplasia.

Besides water, a considerable quantity of both soluble and insoluble protein needs to be removed from the air spaces. Soluble protein appears to be removed primarily by diffusion between alveolar epithelial cells. Insoluble protein may be removed by endocytosis and transcytosis effected by alveolar epithelial cells and by phagocytosis effected by macrophages [46]. Apoptosis (programmed cell death) may be important in the clearance of neutrophils from the injured lung. A clinical study of ALI and ARDS did not confirm this, perhaps because of the presence of anti-apoptotic factors [47]. Nevertheless, high concentrations of the markers of apoptosis are present in the pulmonary oedema fluid of ALI and ARDS patients [30], and exposure in vitro to bronchoalveolar lavage fluids from these patients can promote epithelial cell apoptosis [47, 48].

Treatment of permeability oedema

Fluid and haemodynamic management

The rationale for restricting fluids in patients with ALI and ARDS is to decrease pulmonary oedema. Studies in animals with ALI indicated that the degree of oedema was reduced if pulmonary arterial occlusion pressure (PAOP) was lowered [49]. Some clinical studies have supported this hypothesis [50, 51]. Unlike PAOP, which translates left atrial pressure, pulmonary capillary pressure is the mean pressure in the sites where fluid leakage occurs [52, 53], and its importance is increased in the presence of increased permeability of the alveolar–capillary barrier. High pulmonary capillary pressures have been shown to worsen transvascular fluid filtration in dog lungs with increased vascular permeability after acid aspiration [53], and indirect evidence exists of decreased pulmonary transvascular albumin flux after capillary pressure decrease in ALI [54]. Recent data point to the presence of high pulmonary capillary pressures throughout the course of ALI and ARDS [55]. However, pulmonary capillary pressures are not usually assessed in clinical practice. Furthermore, the lack of any consistent relationship between the pulmonary capillary pressure and PAOP is well documented [56, 57]. PAOP cannot, therefore, be used to predict pulmonary capillary pressure in ALI and ARDS. Direct assessment of pulmonary capillary pressures could, therefore, be beneficial in clinical practice to avoid the risk of worsening lung oedema in the presence of increased permeability, even if some evidence suggests that directed fluid loading

(optimised preload/cardiac output ratio) in ALI does not result in a significant increase in pulmonary capillary pressure as opposed to filling pressures (pulmonary arterial occlusion pressure and central venous pressure) [57].

The NIH ARDSnet has designed and is presently carrying out a randomised trial of fluid management comparing restricted-fluid with liberal-fluid management, based on monitoring haemodynamics with either a pulmonary-artery catheter or a central venous catheter [58]. Results obtained in this trial are expected to improve our present knowledge on how pulmonary oedema might be avoided in ALI and ARDS. Until these results are available, standard clinical management includes maintenance of the intravascular volume at the lowest level that is consistent with adequate systemic perfusion as assessed by metabolic acid–base balance and renal function. If the restoration of intravascular volume is not enough to maintain systemic perfusion, as is the case in patients with septic shock, treatment with vasopressors is indicated.

Acceleration of resolution

The rapid removal of alveolar fluid from the alveolar space is associated with improved oxygenation, shorter duration of mechanical ventilation and increased likelihood of survival in ALI and ARDS [24, 30]. Even when mild to moderate alveolar epithelial injury occurs, the capacity of the alveolar epithelium to transport salt and water is often preserved [59]. Although enhancement of the fluid transport capacity of the distal pulmonary epithelium is possible, this up-regulation may not be sufficient to counterbalance alveolar flooding. Therefore, efforts to attenuate injury to the alveolar–capillary barrier [14] are as important as treatments that might enhance the reabsorptive capacity of the alveolar epithelium.

The alveolar epithelial repair process probably begins in the very early phase of ALI and ARDS, since during the first 12 h after intubation the epithelial repair activity of the pulmonary oedema fluid is higher than that of the oedema fluid obtained more than 12 h after intubation [60]. Alveolar epithelial repair activity induced by pulmonary oedema fluid from patients with ALI and ARDS is also markedly increased over that induced by plasma obtained from the same patients or by pulmonary oedema fluid from patients with hydrostatic oedema [60]. These results indicate that biologically active mediators capable of enhancing alveolar epithelial repair in vitro are released into the alveolar space in patients with ALI and ARDS. Some data point to a trend towards longer survival and shorter duration of mechanical ventilation in patients with increased alveolar-epithelial wound repair activity induced by oedema fluid [61]. The alveolar-epithelial repair activity of pulmonary oedema fluid in vitro may have thus some prognostic value, which needs to be confirmed by further studies.

Catecholamine-dependent mechanisms

Beta2-agonists are attractive choices as therapeutic agents, because they are already in widespread clinical use and have minimal side effects [62]. Treatment with

β2-agonists may increase alveolar fluid clearance, increase the secretion of surfactant and perhaps exert an anti-inflammatory effect [63, 64]. In addition to endogenous up-regulation, there is growing evidence that alveolar fluid clearance can be further stimulated by exogenous β-adrenergic therapy in the presence of lung injury [36, 39]. However, in certain circumstances the epithelium may not respond to β2-agonist stimulation because of extensive injury and loss of alveolar type II cells or because of a reactive effect of the inflammatory environment on the normal ability of type II cells to increase alveolar fluid clearance. This may justify the absence of correlation between the levels of endogenous and exogenous catecholamines and alveolar fluid clearance in ALI and ARDS patients [30].

Cytokines and growth factors

Interleukin-1β (IL-1β) is a proinflammatory cytokine that also seems to mediate a major fraction of alveolar epithelial repair in vitro. Concentrations of IL-1β showing significant alveolar epithelial repair in vitro are in a similar range to the concentrations of IL-1β found in a pulmonary oedema fluid from patients with ALI and ARDS, indicating that IL-1β may contribute to repair of the alveolar epithelium in early ALI and ARDS [65].

Recent animal experiments suggest that keratinocyte growth factor (KGF) and hepatocyte growth factor (HGF) are major mitogens for alveolar epithelial type II cells and may thus have a significant role as new prophylactic or therapeutic agents in lung injury. KGF is mainly produced by fibroblasts and has been shown to induce alveolar type II proliferation in vitro [66] and in vivo [67]. Studies in different lung injury models show a protective effect of KGF when it is given before the induction of lung injury [68, 69]. The mechanism of protection is thought to be due to an increase in alveolar fluid transport secondary to increased numbers of alveolar type II cells even though other mechanisms (including cytoprotection [70], antioxidant effect [71], increased release of surface-active material [72] and, perhaps, reduction of lung endothelial injury [73]) may have additive roles. Interestingly, the combination of KGF and β2-agonist treatment results in additive up-regulation of alveolar fluid clearance [44]. This suggests that there may be mechanisms for providing both short-term (β2-agonists) and long-term (growth factor) up-regulation of alveolar fluid transport that might hasten the resolution of clinical pulmonary oedema. HGF is another potent mitogen for alveolar type II cells in vivo and in vitro that is up-regulated by IL-1β and other inflammatory cytokines in lung fibroblasts [74]. HGF was found in elevated concentrations in pulmonary oedema fluid from patients with ALI and ARDS, signalling a potential role for it in alveolar epithelial repair [75].

Gene therapy

Alveolar oedema clearance seems to correlate with Na^+/K^+-ATPase activity in both normal and acutely injured animal lungs [36, 76]. Overexpression of the Na^+/K^+-ATPase gene in the alveolar epithelium could thus provide another potential

approach to increasing sodium transport and alveolar fluid reabsorption. The expression and function of the sodium pump in the adult rat lung was increased after overexpression of its β1- or α2-subunits [77]. Gene transfer technology [78] or transgenic overexpression [79] has also been used to overexpress the β2-adrenergic receptor. This method has been shown to stimulate liquid clearance from the normal lung by increasing sensitivity to endogenous catecholamines in rats and mice [78, 79]. Overexpression of β-receptors in the alveolar epithelium may become a clinical therapeutic alternative to deal with the down-regulation produced by prolonged exposure to catecholamines.

References

1. Lumb AB (2000) Nunn's Applied Respiratory Physiology. Butterworth-Heinemann, Oxford Auckland Boston
2. Weibel ER, Federspiel WJ, Fryder-Doffey F et al (1993) Morphometric model for pulmonary diffusing capacity. I. Membrane diffusing capacity. Resp Physiol 93:125-149
3. Aberle DR, Wiener-Kronish JP, Webb WR et al (1988) Hydrostatic versus increased permeability pulmonary edema: diagnosis based on radiographic criteria in critically ill patients. Radiology 168:73-79
4. Wiener-Kronish JP, Matthay MA (1988) Pleural effusions associated with hydrostatic and increased permeability pulmonary edema. Chest 93:852-858
5. Gattinoni L, Bombino M, Pelosi P et al (1994) Lung structure and function in different stages of severe adult respiratory distress syndrome. JAMA 271:1772-1779
6. Dreyfuss D, Saumon G (1993) Role of tidal volume, FRC and end-inspiratory volume in the development of pulmonary edema following mechanical ventilation. Am J Respir Crit Care Med 148:1194-1203
7. Corbridge TC, Wood LD, Crawford GP et al (1990) Adverse effects of large tidal volume and low PEEP in canine acid aspiration. Am Rev Respir Dis 142:311-315
8. The Acute Respiratory Distress Syndrome Network (2000) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 342:1301-1308
9. Amato MBP, Barbas CSV, Medeiros DM et al (1998) Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 338:347-354
10. Brochard L, Roudot-Thoraval F, Roupie E et al (1998) Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trail Group on Tidal Volume reduction in ARDS. Am J Respir Crit Care Med 158:1831-1838
11. Ranieri VM, Suter PM, Tortorella C et al (1999) Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. JAMA 282:54-61
12. Bachofen M, Weibel ER (1977) Alterations of the gas exchange apparatus in adult respiratory insufficiency associated with septicemia. Am Rev Respir Dis 116:589-615
13. Pugin J, Verghese G, Widmer MC et al (1999) The alveolar space is the site of intense inflammatory and profibrotic reactions in the early phase of acute respiratory distress syndrome. Crit Care Med 27:304-312
14. Modelska K, Pittet JF, Folkesson HG et al (1999) Acid-induced lung injury. Protective

effect of anti-interleukin-8 pretreatment on alveolar epithelial barrier function in rabbits. Am J Respir Crit Care Med 160:1450-1456
15. Sznajder JI (1999) Strategies to increase alveolar epithelial fluid removal in the injured lung. Am J Respir Crit Care Med 160:1441-1442
16. Greene KE, Wright JR, Steinberg KP et al (1999) Serial changes in surfactant-associated proteins in lung and serum before and after onset of ARDS. Am J Respir Crit Care Med 160:1843-1850
17. Folkesson HG, Nitenberg G, Oliver BL et al (1998) Upregulation of alveolar epithelial fluid transport after subacute lung injury in rats from bleomycin. Am J Physiol 275:L478-L490
18. Meduri GU, Headley S, Kohler G et al (1995) Persistent elevation of inflammatory cytokines predicts a poor outcome in ARDS; plasma IL-1 and IL-6 levels are consistent and efficient predictors of outcome over time. Chest 107:1062-1073
19. Donnelly SC, Strieter RM, Kunkel SL et al (1993) Interleukin-8 and development of adult respiratory distress syndrome in at-risk patient groups. Lancet 341:643-647
20. Hamacher J, Lucas R, Lijnen HR et al (2002) Tumor necrosis factor-alpha and angiostatin are mediators of endothelial cytotoxicity in bronchoalveolar lavages of patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 166:651-656
21. Ranieri VM, Giunta F, Suter PM et al (2000) Mechanical ventilation as a mediator of multisystem organ failure in acute respiratory distress syndrome. JAMA 284:43-44
22. Adamson IY, Young L and Bowden DH (1988) Relationship of alveolar epithelial injury and repair to the induction of pulmonary fibrosis. Am J Pathol 130:377-383
23. Berthiaume Y, Lesur O, Dagenais A (1999) Treatment of adult respiratory distress syndrome: plea for rescue therapy of the alveolar epithelium. Thorax 54:150-160
24. Matthay MA and Wiener-Kronish JP (1990) Intact epithelial barrier function is critical for the resolution of alveolar edema in humans. Am Rev Respir Dis 142:1250-1257
25. Matalon S, Benos DJ, Jackson RM (1996) Biophysical and molecular properties of amiloride-inhibitable Na+ channels in alveolar epithelial cells. Am J Physiol 271:L1-L22
26. Johnson MD, Widdicombe JH, Allen L et al (2002) Alveolar epithelial type I cells contain transport proteins and transport sodium, supporting an active role for type I cells in regulation of lung liquid homeostasis. Proc Natl Acad Sci USA 99:1966-1971
27. Widdicombe JH (2000) How does cAMP increase active Na absorption across alveolar epithelium? Am J Physiol Lung Cell Mol Physiol 278:L231-L232
28. Dobbs LG, Gonzalez R, Matthay MA et al (1998) Highly water-permeable type I alveolar epithelial cells confer high water permeability between the airspace and vasculature in rat lung. Proc Natl Acad Sci USA 95:2991-2996
29. Matthay MA, Folkesson HG and Verkman AS (1996) Salt and water transport across alveolar and distal airway epithelia in the adult lung. Am J Physiol 270:L487-L503
30. Ware LB, Matthay MA (2001) Alveolar fluid clearance is impaired in the majority of patients with acute lung injury and the acute respiratory distress syndrome. Am J Respir Crit Care Med 163:1376-1383
31. Ware LB, Golden JA, Finkbeiner WE et al (1999) Alveolar epithelial fluid transport capacity in reperfusion lung injury after lung transplantation. Am J Respir Crit Care Med 159:980-988
32. Verghese GM, Ware LB, Matthay BA et al (1999) Alveolar epithelial fluid transport and the resolution of clinically severe hydrostatic pulmonary edema. J Appl Physiol 87:1301-1312
33. Lane SM, Maender KC, Awender NE et al (1998) Adrenal epinephrine increases alveolar liquid clearance in a canine model of neurogenic pulmonary edema. Am J Respir Crit Care Med 158:760-768

34. Modelska K, Matthay MA, Brown LA et al (1999) Inhibition of beta-adrenergic-dependent alveolar epithelial clearance by oxidant mechanisms after hemorrhagic shock. Am J Physiol 276:L844-L857
35. Berthiaume Y, Broaddus VC, Gropper MA et al (1988) Alveolar liquid and protein clearance from normal dog lungs. J Appl Physiol 65:585-593
36. Lasnier JM, Wangensteen OD, Schmitz LS et al (1996) Terbutaline stimulates alveolar fluid resorption in hyperoxic lung injury. J Appl Physiol 81:1723-1729
37. Maron MB (1998) Dose-response relationship between plasma epinephrine concentration and alveolar liquid clearance in dogs. J Appl Physiol 85:1702-1707
38. Norlin A, Finley N, Abedinpour P et al (1998) Alveolar liquid clearance in the anesthetized ventilated guinea pig. Am J Physiol 274:L235-L243
39. Sakuma T, Folkesson HG, Suzuki S et al (1997) Beta-adrenergic agonist stimulated alveolar fluid clearance in ex vivo human and rat lungs. Am J Respir Crit Care Med 155:506-512
40. Tibayan FA, Chesnutt AN, Folkesson HG et al (1997) Dobutamine increases alveolar liquid clearance in ventilated rats by beta-2 receptor stimulation. Am J Respir Crit Care Med 156:438-444
41. Barnard ML, Ridge KM, Saldias F et al (1999) Stimulation of the dopamine 1 receptor increases lung edema clearance. Am J Respir Crit Care Med 160:982-986
42. Folkesson HG, Norlin A, Wang Y et al (2000) Dexamethasone and thyroid hormone pretreatment upregulate alveolar epithelial fluid clearance in adult rats. J Appl Physiol 88:416-424
43. Saldias FJ, Lecuona E, Comellas AP et al (1999) Dopamine restores lung ability to clear edema in rats exposed to hyperoxia. Am J Respir Crit Care Med 159:626-633
44. Wang Y, Folkesson HG, Jayr C et al (1999) Alveolar epithelial fluid transport can be simultaneously upregulated by both KGF and beta-agonist therapy. J Appl Physiol 87:1852-1860
45. Geiser T, Jarreau PH, Atabai K et al (2000) Interleukin-1beta augments in vitro alveolar epithelial repair. Am J Physiol Lung Cell Mol Physiol 279:L1184-L1190
46. Folkesson HG, Matthay MA, Westrom BR et al (1996) Alveolar epithelial clearance of protein. J Appl Physiol 80:1431-1445
47. Matute-Bello G, Liles WC, Radella F et al (1997) Neutrophil apoptosis in the acute respiratory distress syndrome. Am J Respir Crit Care Med 156:1969-1977
48. Hashimoto S, Kobayashi A, Kooguchi K et al (2000) Upregulation of two death pathways of perforin/granzyme and FasL/Fas in septic acute respiratory distress syndrome. Am J Respir Crit Care Med 161:237-243
49. Prewitt RM, McCarthy J and Wood LD (1981) Treatment of acute low pressure pulmonary edema in dogs: relative effects of hydrostatic and oncotic pressure, nitroprusside, and positive end-expiratory pressure. J Clin Invest 67:409-418
50. Humphrey H, Hall J, Sznajder I et al (1990) Improved survival in ARDS patients associated with a reduction in pulmonary capillary wedge pressure. Chest 97:1176-1180
51. Mitchell JP, Schuller D, Calandrino FS et al (1992) Improved outcome based on fluid management in critically ill patients requiring pulmonary artery catheterization. Am Rev Respir Dis 145:990-998
52. Cope DK, Grimbert F, Downey JM et al (1992) Pulmonary capillary pressure: a review. Crit Care Med 20:1043-1056
53. Grimbert F (1988) Effective pulmonary capillary pressure. Eur Respir J 1:297-301
54. Benzing A, Bräutigam P, Geiger K et al (1995) Inhaled nitric oxide reduces pulmonary transvascular albumin flux in patients with acute lung injury. Anesthesiology 83:1153-1161

55. Nunes S, Ruokonen E, Takala J (2003) Pulmonary capillary pressures during the acute respiratory distress syndrome. Intensive Care Med 29:2174-2179
56. Fang K, Krahmer RL, Rypins EB et al (1996) Starling resistor effects on pulmonary artery occlusion pressure in endotoxin shock provide inaccuracies in left ventricular compliance assessments. Crit Care Med 24:1618-1625
57. Matejovic M, Krouzecky A, Rokyta R et al (2004) Fluid challenge in patients at risk for fluid loading-induced pulmonary edema. Acta Anaesthesiol Scand 48:69-73
58. Prospective, Randomized, Multi-Center Trial of Pulmonary Artery Catheter (PAC) vs. Central Venous Catheter (CVC) for Management of Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS) and Prospective, Randomized, Multi-Center Trial of "Fluid Conservative" vs. "Fluid Liberal" Management of Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS). http://www.ardsnet.org/studies.php
59. Wiener-Kronish JP, Albertine KH et al (1991) Differential responses of the endothelial and epithelial barriers of the lung in sheep to *Escherichia coli* endotoxin. J Clin Invest 88:864-875
60. Geiser T, Atabai K, Jarreau PH et al (2001) Pulmonary edema fluid from patients with acute lung injury augments in vitro alveolar epithelial repair by an IL-1beta-dependent mechanism. Am J Respir Crit Care Med 163:1384-1388
61. Geiser T (2003) Mechanisms of alveolar epithelial repair in acute lung injury—a translational approach. Swiss Med Weekly 133:586-590
62. Wright PE, Carmichael LC, Bernard GR (1994) Effects of bronchodilators on lung mechanics in the acute respiratory distress syndrome (ARDS). Chest 106:1517-1523
63. Barnard JW, Seibert AF, Prasad VR et al (1994) Reversal of pulmonary capillary ischemia-reperfusion injury by rolipram, a cAMP phosphodiesterase inhibitor. J Appl Physiol 77:774-781
64. Masclans JR, Barbera JA, MacNee W et al (1996) Salbutamol reduces pulmonary neutrophil sequestration of platelet-activating factor in humans. Am J Respir Crit Care Med 154:529-532
65. Pugin J, Ricou B, Steinberg KP et al (1996) Proinflammatory activity in bronchoalveolar lavage fluids from patients with ARDS, a prominent role for interleukin-1. Am J Respir Crit Care Med 153:1850-1856
66. Panos RJ, Rubin JS, Csaky KG et al (1993) Keratinocyte growth factor and hepatocyte growth factor/scatter factor are heparin-binding growth factors for alveolar type II cells in fibroblast-conditioned medium. J Clin Invest 92:969-977
67. Ulich TR, Yi ES, Longmuir K et al (1994) Keratinocyte growth factor is a growth factor for type II pneumocytes in vivo. J Clin Invest 93:1298-1306
68. Barazzone C, Donati YR, Rochat AF et al (1999) Keratinocyte growth factor protects alveolar epithelium and endothelium from oxygen-induced injury in mice. Am J Pathol 154:1479-1487
69. Deterding RR, Havill AM, Yano T et al (1997) Prevention of bleomycin-induced lung injury in rats by keratinocyte growth factor. Proc Assoc Am Physicians 109:254-268
70. Yano T, Deterding RR, Simonet WS et al (1996) Keratinocyte growth factor reduces lung damage due to acid instillation in rats. Am J Respir Cell Mol Biol 15:433-442
71. Waters CM, Savla U, Panos RJ (1997) KGF prevents hydrogen peroxide-induced increases in airway epithelial cell permeability. Am J Physiol 272:L681-L689
72. Xu X, McCormick-Shannon K, Voelker DR et al (1998) KGF increases SP-A and SP-D mRNA levels and secretion in cultured rat alveolar type II cells. Am J Respir Cell Mol Biol 18:168-178

73. Viget NB, Guery BP, Ader F et al (2000) Keratinocyte growth factor protects against *Pseudomonas aeruginosa*-induced lung injury. Am J Physiol Lung Cell Mol Physiol 279:L1199-L1209
74. Ohmichi H, Matsumoto K, Nakamura T (1996) In vivo mitogenic action of HGF on lung epithelial cells: pulmotrophic role in lung regeneration. Am J Physiol 270:L1031-L1039
75. Verghese GM, McCormick-Shannon K, Mason RJ et al (1998) Hepatocyte growth factor and keratinocyte growth factor in the pulmonary edema fluid of patients with acute lung injury. Biologic and clinical significance. Am J Respir Crit Care Med 158:386-394
76. Barnard ML, Olivera WG, Rutschman DM et al (1997) Dopamine stimulates sodium transport and liquid clearance in rat lung epithelium. Am J Respir Crit Care Med 156:709-714
77. Factor P, Saldias F, Ridge K et al (1998) Augmentation of lung liquid clearance via adenovirus-mediated transfer of a Na,K-ATPase beta1 subunit gene. J Clin Invest 102:1421-1430
78. Dumasius V, Sznajder JI, Azzam ZS et al (2001) Beta(2)-adrenergic receptor overexpression increases alveolar fluid clearance and responsiveness to endogenous catecholamines in rats. Circ Res 89:907-914
79. McGraw DW, Fukuda N, James PF et al (2001) Targeted transgenic expression of beta(2)-adrenergic receptors to type II cells increases alveolar fluid clearance. Am J Physiol Lung Cell Mol Physiol 281:L895-L903

Chapter 32

Grading severity of respiratory dysfunction, clinical correlates and indications for mechanical ventilation

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Definitions and aetiology

In principle, we distinguish two different forms of acute respiratory dysfunctions, which are characterised either by ventilatory (muscle) failure or by disturbances of pulmonary gas exchange with a mismatch of ventilation and perfusion. Aetiologically, disorders of ventilation are based on fatigue of the ventilatory pump, which can occur both acutely and chronically and yields hypercapnic respiratory failure. Acute ventilatory disorders can be found with exacerbation of a pre-existing chronic obstructive pulmonary disease, in the weaning phase after mechanical ventilation or in respiratory failure after extubation. Examples of disorders associated with a chronic failure of ventilation are seen in neuromuscular disorders,deformities of the spine and afflictions of the chest wall.

Disturbances of pulmonary gas exchange leading to hypoxaemic insufficiency are caused by atelectasis, consolidation or infiltration of lung parenchyma with resultant hypoventilated or even atelectactic alveolar regions although they are still perfused.

The clinical appearance when pulmonary gas exchange is impaired is that of the entities of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). The differentiation between these two manifestations of acute respiratory insufficiency can be made by determining the grade of severity of impaired oxygenation, which is expressed as the ratio of arterial oxygen partial pressure to inspiratory oxygen fraction (PaO_2/FiO_2).

Further differentiation of the severity of lung damage can be carried out by the lung injury score proposed by Murray et al. in 1988 [1]. The components of this score consist in roentgenographic evidence of alveolar consolidation in none of the four quadrants or in all of them, a PaO_2/FiO_2 ratio ranging from less than 100 up to greater than 300, use of PEEP beginning above a level of 5 cmH_2O and ranging in increments of 3 cmH_2O up to greater than 15, and measured static compliance of the respiratory system ranging from less than 19 ml per cmH_2O up to greater than 80 ml per cmH_2O.

The lung injury score makes rough quantification of presence, severity and evolution of lung damage, and severe ARDS must be assumed with a score of greater than 2.5 [1].

Clinical presentation and pathophysiology

Acute respiratory distress syndrome/acute lung injury

ARDS was first described in 1967 by Asbaugh et al. [2].The current valid definition of ARDS is based upon the American European Consensus Conference on ARDS dating from 1994. Both ALI and ARDS are defined by their acute onset, impaired oxygenation, bilateral infiltrates seen on frontal chest radiograph and a PCWP <18mmHg and by the lack respectively of any clinical evidence of left atrial hypertension for differentiation from cardiogenic pulmonary oedema [3].

ALI and ARDS differ in the grade of oxygenation disturbance, with a PaO_2/FiO_2 ratio of <200 for ARDS and <300 for ALI.

The main risk factors for the development of acute respiratory failure are aspiration, pneumonia, near-drowning accidents, inhalation of toxic substances and contusions of the lungs as direct injuries to the lungs. Sepsis or severe inflammatory response syndrome, severe trauma not primarily affecting the chest, mass transfusion and extracorporeal circulation have indirect mechanisms that can lead to the development of ARDS.

Pathophysiologically, in ARDS increased permeability both of the capillary and the alveolar membrane is found, leading to exsudation of fluid into the interstitial and then into the alveolar spaces. These changes and, if present as a result of the ventilatory mode used, the impaired spontaneous breathing, lead to atelectasis in the dependent regions of the lung, explaining the reduced compliance and lung volume. The impaired autoregulation of pulmonary vessels yields enhancement of intrapulmonary shunt and increasing pulmonary-vascular resistance results in loading of the right heart.

If cardiac output cannot be kept constant, increased pre- and intracardial pressure may lead to heart failure and then to decreased systemic blood flow and impaired organ perfusion.

These changes determine the initial phases of ARDS. Later on, fibrotic alteration may follow as immigration of immune cells into the exsudates is implemented by the activity of inflammatory and anti-inflammatory mediators. All of these processes are flexible in the sequence of their chronological appearance and are reversible up to a certain period of disease. They do not appear either in a synchronous manner or in all regions of the lung.

Hypercapnic ventilatory dysfunction

In the case of exacerbated chronic obstructive pulmonary disease, impairment of the underlying disease leads to overdistension of the lungs, leading to flattening of the diaphragm and the physiological angle of the ribs. Subsequently, elongation and contractility of both the diaphragm and the intercostal muscles decreases. Patients try to compensate the resulting alveolar hypoventilation by enhancement of the breathing rate.

Ongoing enhancement of the breathing rate, decreasing tidal and increasing dead space ventilation leads to useless consumption of energy causing further

failure of the respiratory muscles and increasing hypercapnia. In addition, the inspiratory airway resistance and intrinsic PEEP rises and overdistension of the lung increases. In the case of abortive weaning after mechanical ventilation and respiratory failure after extubation as clinical manifestations of respiratory fatigue, the underlying mechanism appears to be similar.

In addition to the primary confinement of pulmonary gas exchange in acute cardiogenic lung oedema based on left ventricular insufficiency, additional fatigue of the respiratory muscles is a pivotal pathophysiological mechanism in acute respiratory dysfunction, particularly in elderly patients.

Indications for and modes of mechanical ventilation

Mechanical ventilation in acute respiratory dysfunctions is aimed either at reduction of increased work of breathing or at correction of severe dysfunction of pulmonary gas exchange.

Whereas temporary takeover of an increased work of breathing is the decisive factor in hypercapnic ventilatory failure, impaired gas exchange is the principal indication for mechanical ventilation in hypoxaemic insufficiency.

Even though our understanding of pathophysiological mechanisms and effects of both ARDS and given ventilatory modalities has expanded greatly, criteria that the physician could use to decide when to carry out intubation and mechanical ventilation have not improved to the same degree [4].

Clinical indications for the use of mechanical ventilation based upon definite threshold values of pCO_2 and pH or on different indices of arterial oxygenation are seen not to be applicable for all patients suffering from acute respiratory failure. There is no single value among those mentioned that by itself would necessarily indicate that intubation and mechanical ventilation were indicated, so that the decision for the initiation of mechanical ventilatory support is still at the clinician's discretion [4].

Indications for invasive mechanical ventilation have not yet been validated by clinical evidence. At present, few data are available on two of the present techniques of ventilatory support that have been investigated in large randomised clinical trials,i.e. noninvasive ventilation in acute exacerbation of chronic obstructive pulmonary disease and high-frequency ventilation [4].

Noninvasive ventilation is a level 1 recommendation in hypercapnic respiratory failure on a background of chronic obstructive pulmonary disease (COPD) or cardiogenic lung oedema and in immunodeficient patients suffering from pulmonary infiltration and fever.

As mentioned in the following comments, in many cases of acute ventilatory failure and in immunodeficient patients suffering from acute hypoxaemic failure, intubation should be avoided and noninvasive ventilatory support should be initiated as this has proved to be beneficial in terms of patient outcome.

Noninvasive positive-pressure ventilation

Noninvasive positive pressure ventilation in hypercapnic respiratory failure

At present, exacerbation of chronic pulmonary disease, acute cardiogenic lung oedema and weaning or respiratory failure after extubation are the most important indications for noninvasive positive-pressure ventilation (NIPPV) in intensive care medicine. The last has been called in question by recent data, as mentioned below [5].

Neuromuscular disorders, disturbances of chest wall mechanics, and chronic obstructive pulmonary disease as an entity primarily of hypercapnic respiratory dysfunction are considered to be definite indications for noninvasive ventilatory modes, as an improvement in outcome and prognosis have been shown for this patient subgroup in long-term studies [6].

NIPPV in exacerbated COPD

In case of acute deterioration of a chronic respiratory dysfunction, NIPPV seems to be the main therapeutic option [7]. The need for conventional mechanical ventilation in patients suffering from exacerbated COPD is associated with a high mortality owing to the complicated weaning phase and respirator-associated infections [8,9].

In a recently published meta-analysis by Antonelli et al. a significant benefit of applying noninvasive ventilatory modes was shown in terms of mortality, ventilator-free-days and duration of stay in hospital [10]. NIPPV leads to relief of the respiratory muscles and improves arterial blood gases, subjective dyspnoea and the breathing pattern. With external application of positive end-expiratory pressure, intrinsic PEEP decreases and—compared with conventional invasive mechanical ventilation—vital functions, rate of treatment complications, duration of stay in hospital, in-hospital-mortality and frequency of endotracheal intubation are reduced [11].

NIPPV in the weaning phase and in respiratory failure after extubation

The majority of studies conducted to examine NIPPV have assessed its role in averting the need for primary intubation in patients suffering from acute respiratory failure, and few have assessed the use of noninvasive ventilatory modes in patients with respiratory failure after extubation.

Thus, the role of NIPPV in the weaning phase and in respiratory failure after extubation remains controversial at present, and existing data provide inconsistent information concerning the clinical impact and possible beneficial influence in terms of patients outcome. One the one hand, there are some indications that extubation and continuation of mechanical ventilatory support with NIPPV might reduce mortality and duration of mechanical ventilation and of stay in the ICU, at least in patients with COPD [12, 13].

Comparable data documenting a further decrease in the rate of reintubation and tracheotomy in patients with persistent weaning failure when NIPPV was applied have been published by Ferrer et al. [14].

Early use of NIPPV was found to significantly reduce the frequency of reintubation in patients at high risk of a repeated ventilatory dysfunction [15, 16].

Comparable data are available for patients in whom respiratory failure is already recurrent. In 2001, Antonelli et al. showed in a multicentre study that acute respiratory insufficiency following extubation after solid organ transplantation can be overcome with CPAP or NIPPV [17].

One the other hand, in a recently published study by Esteban et al., with a total of 221 patients in a multicentre randomised trial, noninvasive ventilation was found not to be effective in averting the need for reintubation or reducing mortality in patients developing respiratory failure after extubation. In addition, NIPPV did not improve survival; on the contrary, the death rate in the ICU was higher among patients assigned to the NIPPV group then among the standard therapy group [5].

These data are confirmed by a comparable single-centre study by Keenan et al., who found that the use of NIPPV did not significantly alter the need for reintubation, even though no differences in the rate of death in the ICU or in hospital overall were detected [18].

NIPPV in hypoxaemic respiratory failure

In cardiogenic lung oedema, NIPPV is known to reduce pre- and afterload of the left heart owing to the increased intrathoracic pressure. Whereas this pressure increase yields a decrease of cardiac output in normal subjects, in patients with left ventricular dysfunction stroke volume and cardiac index are enhanced, with a concomitant diminution of left ventricular and atrial dimensions.

Studies of patients with cardiogenic pulmonary oedema treated with ventilatory support of continuous positive airway pressure at 10 cmH_2O revealed lower mortality and a lower rate of endotracheal intubation than in treated with drug therapy alone [19]. The benefit of applying NIPPV in this patient subgroup was shown in several later randomised and controlled studies [20, 21], in which pressure support ventilation appeared to be the most reasonable breathing pattern. Overall, there is impressive confirmation that there is a place for NIPPV in the treatment of patients in acute respiratory failure, but careful selection of patients remains of pivotal impact in the achievement of success.

Thus, noninvasive ventilatory modes applied in a discontinuous manner appear to be successful both in acute cardiogenic lung oedema that shows a rapid response to medicamentous therapy and in exacerbation of COPD when it leads to temporary relief for respiratory muscles. The lack of any beneficial effect of NIPPV in pneumonia and in ARDS may be explained by derecruitment of reopened alveolar regions when NIPPV is implemented as the selected form of mechanical ventilatory support.

Contraindications for the use of NIPPV

Contraindications for the use of noninvasive ventilatory strategies consist in coma or uncontrollable discomposure, patient noncompliance, acute life-threatening

hypoxia, cardiac or respiratory arrest, haemodynamic instability, increased risk of regurgitation and aspiration, upper airway obstruction and irremediable congestion of upper airway secretions [22].

Invasive mechanical ventilation

The use of NIPPV in nonhypercapnic hypoxaemic respiratory dysfunction remains controversial. The rate of failures using noninvasive ventilation modes is greater than 50% for patients suffering from moderate to severe adult RDS [23].

In concomitant or beginning multiorgan dysfunction with impending or current circulatory failure and a large intrapulmonary shunt fraction caused by the collapse of major alveolar regions, endotracheal intubation is unavoidable, as levels of in- and expiratory pressure that cannot be applied via a face-mask are needed.

On the other hand, acute respiratory dysfunction in patients suffering from haematological malignancies has a mortality rate of over 75% when endotracheal intubation and mechanical ventilation are performed [24]. Early application of noninvasive ventilatory support is feasible to reduce the rate of intubation to about 40% and the in-hospital-mortality to about 38% [25].

For ARDS overall, no significant benefit of using noninvasive ventilatory modes has been revealed [11].

The different forms of invasive mechanical ventilation are divided into total and partial ventilatory mechanical support, depending on the proportion of the overall ventilation attributed by the respirator. Among the modes for partial ventilatory support, spontaneous breathing is at least partly maintained. Either spontaneous breathing and mechanical ventilation alternate, or each inspiratory effort is supported by the respirator.

Controlled versus assisted mechanical ventilation

Traditionally, in acute respiratory failure controlled mechanical ventilation is provided to ensure full alveolar ventilation, to improve gas exchange and to perform the work of breathing until the underlying respiratory dysfunction has been improved and weaning from mechanical ventilation can be begun. Although partial ventilatory support modes were developed for weaning from mechanical ventilation, they are nowadays increasingly being applied as primary modalities of ventilation, even for patients in the acute phase of pulmonary dysfunction.

Ventilatory modes in ALI/ARDS

Owing to the mismatch between ventilation and perfusion in ARDS and ALI, alveolar recruitment and maintenance of reopened, previously collapsed, consolidated or infiltrated alveolar regions by application of continuous positive airway pressure during the entire respiratory cycle displays the crucial therapeutic step. Based on the knowledge of ventilator-associated lung injury and the roentgenographic observation that in ALI and ARDS only small regions of the lung are

normally ventilated (baby lung) questions about what ventilation mode is preferable for this patient group have arisen. Since the Low V_T ARDS Network Study comparing tidal volumes of 12 ml per kg body weight and 6 ml per kg showed a significant decrease in lethality from 40% to 30% in the group ventilated with low tidal volumes, the so-called protective ventilatory strategy may be considered proven [26].

Since in the 1970s PEEP was shown to be feasible to increase end-expiratory lung volume and thus to improve oxygenation by augmentation of FRC, maintenance of PEEP has been a substantial part of the ventilatory therapy in ARDS.

Concerning the question about selection of the optimal extent of PEEP, data from a recently published study from the ARDS Network Study Group suggest that in patients with ALI and ARDS who receive mechanical ventilation with a tidal volume goal of 6 ml per kg of predicted body weight and an end-inspiratory plateau pressure limit of 30 cmH_2O, clinical outcomes are similar whether lower (mean±SD PEEP values on days 1–4 8.3±3.2 cmH_2O) or higher (mean±SD PEEP values on days 1–4 13.2±3.5 cmH_2O) PEEP levels are used. Raising PEEP to levels that exceed those used in the lower-PEEP strategy does not improve clinical outcome and has no influence on mortality rates or the numbers of ventilator-free days, ICU-free days, or organ-failure-free days [27]. In addition, although in Europe pressure-controlled ventilatory modes are preferred, data that would prove a significant benefit over volume-controlled ventilatory modes are lacking.

It can be regarded as fact that maintenance of spontaneous breathing during mechanical ventilatory support leads to better pulmonary gas exchange than controlled mechanical ventilation. During spontaneous breathing, the posterior muscular sections of the diaphragm move more than the anterior tendon plate and spontaneous ventilation is directed preferentially to the dependent, well-perfused regions of the lung. In patients with ARDS we have been able to show that spontaneous breathing of 10–30% of the total minute volume during APRV/BIPAP with equal airway pressure limits or minute volume accounts for an improvement in the match between ventilation and perfusion and arterial oxygenation (Figs. 1, 2) [28]. This increase in arterial oxygenation may be due to the recruitment of previously nonventilated lung areas.

Although pressure support ventilation has also been performed in patients with ARDS, intrapulmonary shunt, ventilation–perfusion match and gas exchange are not significantly better than with controlled mechanical ventilation. Obviously, the spontaneous contribution to mechanically assisted breathing was not sufficient to counteract ventilation–perfusion mismatch of positive pressure insufflations, which may be due to early termination of the inspiratory part of the breathing cycle by the end-inspiratory decrease in gas flow during PSV, thus leading to reduced alveolar ventilation in areas with a slow time constant [29, 30].

We found concordant results in a later study of patients with multiple trauma and at high risk of ARDS, in which maintenance of spontaneous breathing with BIPAP/APRV led to lower venous admixture and improved arterial oxygenation than in patients ventilated in controlled mechanical mode with a subsequent weaning period (Figs. 3, 4) [31].

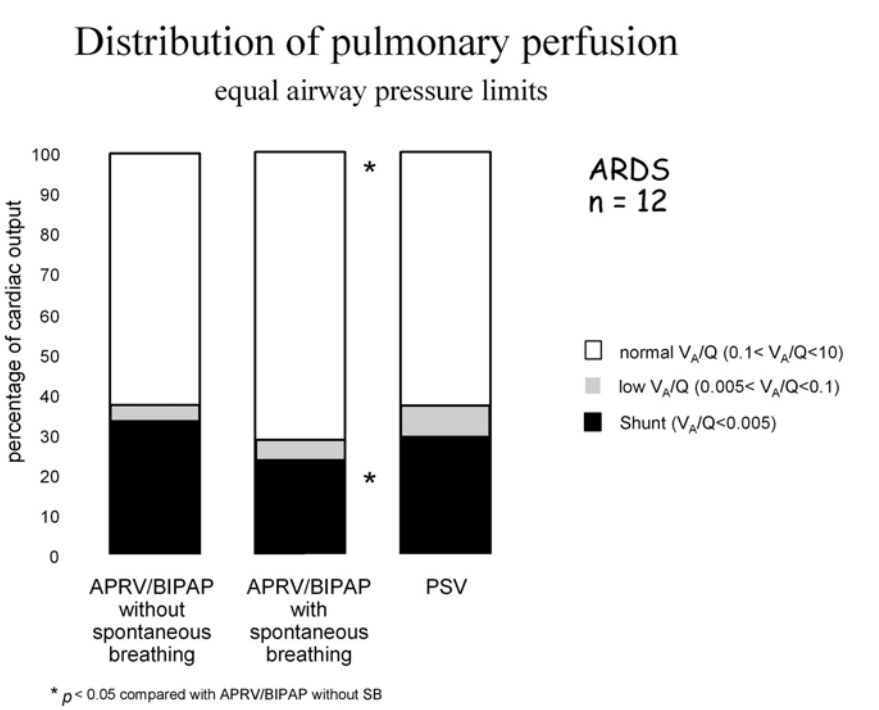

Fig. 1. Spontaneous breathing during APRV with equal airway pressure limits or E accounted for a decrease (P<0.05) in the blood flow to shunt units (VA/Q < 0.005) and an increase (P<0.05) in the fraction of cardiac output to units with a normal A/Q ratio (0.1 < VA/Q < 10). Pulmonary blood flow distribution to shunt and normal A/ units remained essentially unchanged during PSV, compared with APRV without spontaneous breathing in both groups. Dead space (VA/Q> 100) was lowest with spontaneous breathing during APRV (P<0.05). Assisted inspiration with PSV produced no significant difference in dead space compared with APRV without spontaneous breathing (APRV/BIPAP = airway pressure release ventilation/biphasic positive airway pressure; PSV=pressure support ventilation; dead space = V A/Q > 100; high VA/Q = 10 < V A/Q < 100; low VA/Q = 0.005 < V A/Q < 0.1; normal VA/Q = 0.1 < A/Q < 10; shunt = VA/Q < 0.005) [28]

In our opinion, these data show that maintained spontaneous breathing is feasible as a way of counteracting the progressive deterioration in pulmonary gas exchange even in patients requiring ventilatory support. In a recently published study we were able to show that besides pulmonary effects such as improved gas exchange, improved ventilation–perfusion distribution and arterial oxygenation spontaneous breathing during APRV lead to better renal perfusion and function in patients with ALI than did APRV without spontaneous breathing even when the same minute volume or the same airway pressure limits were applied (Fig. 5) [32].

Moreover, maintenance of spontaneous breathing during APRV in patients at high risk of ARDS improves cardiopulmonary function and results in a significantly shorter duration of ventilatory support and ICU stay [31].

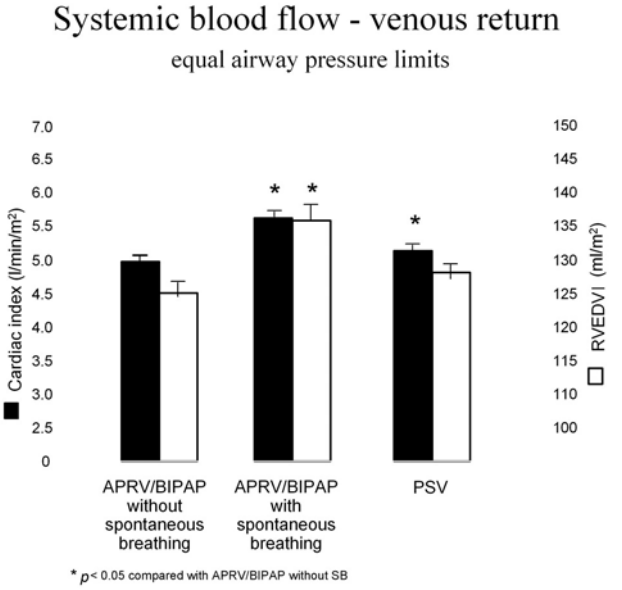

Fig. 2. Spontaneous breathing during APRV/BIPAP increased RVEDVI and CI ($P<0.05$). Assisted inspiration with PSV increased RVEDVI and CI ($P<0.05$) when compared with APRV/BIPAP without spontaneous breathing, but not when the high Paw level was increased to maintain VE constant (*APRV/BIPAP* airway pressure release ventilation/biphasic intermittent positive airway pressure, *PSV* pressure support ventilation, *CI* cardiac index, *RVEDVI* right ventricular end-diastolic volume index) [28]

Conclusions

Thus, despite greatly increased knowledge about pathophysiology of acute respiratory dysfunctions and treatment modalities, the clinician is still the one left in the hot seat to decide when, whether and how to use the various ventilation modes currently available. Noninvasive ventilation strategies have to be considered as therapeutic alternatives at all times for certain patient subgroups, as beneficial outcomes of these have been shown.

Apart from that, the maintenance of spontaneous breathing should be standard practice from the very beginning of ventilatory support even in patients with severe pulmonary dysfunction, as should continuous adaptation of ventilatory support to each patient's individual needs.

We hope that scientific research and experimental studies will continue and yield still further knowledge relating to the optimum treatment strategies in respiratory dysfunction.

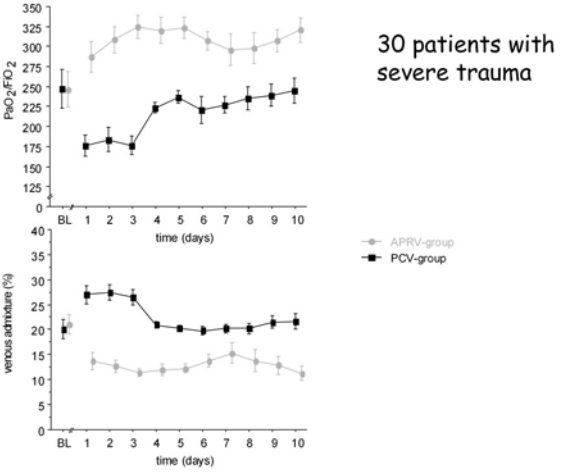

Fig. 3. PaO_2/FIO_2 ratio and venous admixture at baseline (*BL*) and for 10 days in patients immediately breathing spontaneously with APRV (APRV group; *open circles*) or ventilated with a pressure-controlled, time-cycled mechanical mode for 72 h and then weaned with APRV (PCV group; *closed squares*). Values are mean ± SEM; $P<0.05$ between groups, $^*P<0.05$ between groups at the same time point, $P<0.05$ compared with days 1, 2, or 3 within the same group (*APRV* airway pressure release ventilation, *PCV* pressure-controlled ventilation) [31]

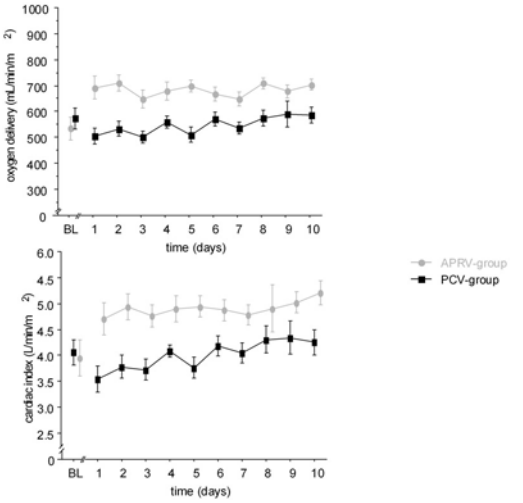

Fig. 4. DO_2 and CI at baseline (*BL*) and for 10 days in patients immediately breathing spontaneously with APRV (APRV group; *open circles*) or ventilated with a pressure-controlled, time-cycled mechanical mode for 72 h and then weaned with APRV (PCV group; *closed squares*). Values are mean±SEM. $P<0.05$ between groups, $^*P<0.05$ between groups at the same time point, $P<0.05$ compared with days 1, 2 or 3 within the same group (*APRV* airway pressure release ventilation, *PCV* pressure-controlled ventilation, DO_2 oxygen delivery; *CI* cardiac index) [31]

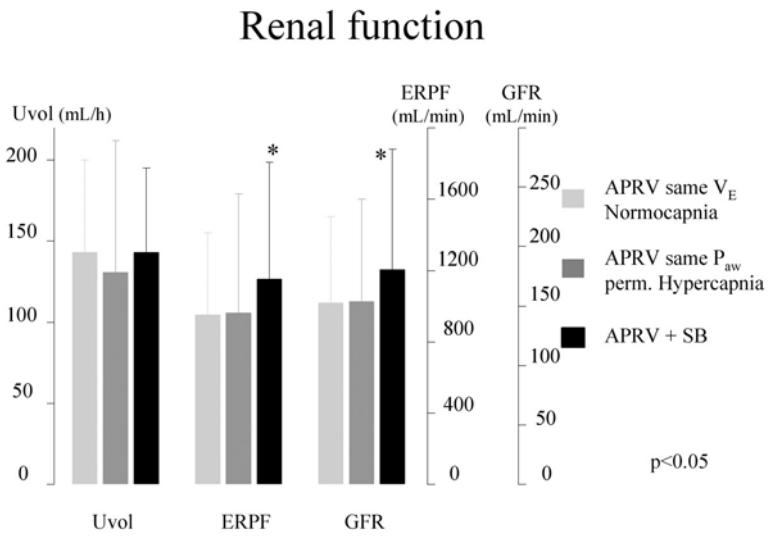

Fig. 5. Effective renal blood flow (*ERBF*), GFR and urine volume were highest in the presence of spontaneous breathing ($P<0.05$) (*APRV* airway pressure release ventilation; *ERBF* effective renal blood flow; *GFR* glomerular filtration rate; V_E minute ventilation; *SB* spontaneous breathing, *Paw*=airway pressure) [32]

References

1. Murray JF, Matthay JM, Flick MR (1988) An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis 138:720-723
2. Ashbaugh DG, Bigelow DB, Petty TL et al (1967) Acute respiratory distress in adults. Lancet 7511:319-323
3. Bernard GR, Artigas A, Brigham KL et al (1994) Report of the American-European Consensus Conference on Acute Respiratory Distress Syndrome: definitions, mechanisms, relevant outcomes, and clinical trial coordination. Consensus Committee. J Crit Care 9:72-81
4. Pierson DJ (2002) Indications for mechanical ventilation in adults with acute respiratory failure. Respir Care 47:249-262
5. Esteban A, Frutos-Vivar F, Ferguson ND et al (2004) Noninvasive positive-pressure ventilation for respiratory failure after extubation. N Engl J Med 350:2452-2460
6. Simnods A, Elliott MW (1995) Outcome of domiciliary nasal intermittent positive pressure ventilation in restrictive and obstructive disorders. Thorax 50:604-609
7. Kahler CM, Hogl B, Habeler R et al (2002) Management of acute respiratory deterioration in a pregnant patient with severe kyphoscoliosis by non-invasive pressure ventilation. Wien Klin Wochenschr 114:874-877
8. Vallverdu I, Calaf N, Subirana M et al (1998) Clinical characteristics, respiratory functional parameters, and outcome of a two-hour T-piece trial in patients weaning from mechanical ventilation. Am J Respir Crit Care Med 156:1855-1862

9. Girou E, Schortgen F, Delclaux C et al (2000) Association of non-invasive ventilation with nososcomial infections and survival in critically ill patients. JAMA 284:2361-2367
10. Antonelli M, Conti G, Rocco M et al (1998) A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure. N Engl J Med 12:101-111
11. Peter JV, Moran JL, Phillips-Hughes J et al (2002) Noninvasive ventilation in acute respiratory failure—a meta-analysis update. Crit Care Med 30:555-562
12. Nava S, Ambrosino N, Clini E et al (1998) Noninvasive mechanical ventilation in the weaning of patients with respiratory failure due to chronic obstructive pulmonary disease. Ann Intern Med 128:721-728
13. Girault C, Daudenthum I, Chevron V et al (1999) Nonivasive ventilation as a systemic extubation and weaning technique in acute-on-chronic respiratory failure: a prospective, randomized controlled study. Am J Respir Crit Care Med 160:86-92
14. Ferrer M, Esquinas A, Arancibia F et al (2003) Noninvasive ventilation during persistent weaning failure: a randomized controlled trial. Am J Respir Crit Care Med 168:70-76
15. Carlucci A, Gregoretti C, Squadrone V et al (2001) Preventive use of noninvasive mechanical ventilation to avoid post-extubation respiratory failure: a randomised controlled study. Eur Respir J 18:306
16. Hilbert G, Gruson D, Vargas F et al (1998) Noninvasive pressure support ventilation in COPD patients with postextubation hypercapnic respiratory insufficiency. Eur Respir J 11:1349-1353
17. Antonelli M, Conti G, Bufi M et al (2000) Noninvasive ventilation for treatment of acute respiratory failure in patients undergoing solid organ transplantation: a randomized trial JAMA 283:235-241
18. Keenan SP, Powers C, McCormack DG et al (2002) Noninvasive pressure support ventilation for postextubation respiratory distress. JAMA 287:3238-3244
19. Pang D, Keenan SP, Cook DJ et al (1998) The effect of positive pressure airway support on mortality and the need for intubation in cardiogenic pulmonary edema: a systematic review. Chest 114:1185-1192
20. Masip J, Betbese AJ, Paez J et al (2000) Non-invasive pressure support ventilation versus conventional oxygen therapy in acute cardiogenic pulmonary oedema: a randomised trial. Lancet 356:2126-2132
21. Hoffman B, Welte T (1999) The use of non-invasive pressure support ventilation for severe respiratory insufficiency due to pulmonary oedema. Intensive Care Med 25:15-20
22. Burchardi H, Kuhlen R, Schönhofer B et al (2002) Nicht-invasive Beatmung. Konsensus-Statement zu Indikation, Möglichkeiten und Durchführung bei der akuten respiratorischen Insuffizienz. Anästhesist 51:33-41
23. Antonelli M, Conti G, Moro ML et al (2001) Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multi-center study. Intensive Care Med 28:1718-1728
24. Ewig S, Torres A, Riquelme R et al (1998) Pulmonary complications in patients with hematological malignancies treated at a respiratory ICU. Eur Respir J 12:116-122
25. Hilbert G, Gruson D, Vargas F et al (2001) Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever and acute respiratory failure. N Engl J Med 344:481-487
26. The Acute Respiratory Distress Syndrome Network (2000) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 342:1301-1308

27. The National Heart, Lung, and Blood Institute ARDS Clinical Trials Network (2004) Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med 351:327-336
28. Putensen C, Mutz N, Putensen-Himmer G et al (1999) Spontaneous breathing during ventilatory support improves ventilation-perfusion distributions in patients with acute respiratory distress syndrome. Am J Respir Care Med 159:1241-1248
29. Putensen C, Hering R, Wrigge H (2002) Controlled versus assisted mechanical ventilation. Curr Opin Crit Care 8:51-57
30. Marini JJ, Crooke PS III, Truwit JD (1989) Determinants and limits of pressure-support ventilation: a mathematical model of pressure control. J Appl Physiol 67:1081-1092
31. Putensen C, Zech S, Wrigge H et al (2001) Long-term effects of spontaneous breathing during ventilatory support in patients with acute lung injury. Am J Respir Crit Care Med 164:43-49
32. Hering R, Peters D, Zinserling J et al (2002) Effects of spontaneous breathing during airway pressure release ventilation on renal perfusion and function in patients with acute lung injury. Intensive Care Med 28:1426-1433

Chapter 33

Weaning as a cardiac stress test

B. Lamia, J.-L. Teboul

Mechanical ventilation (MV) can have deleterious haemodynamic effects in patients with normal cardiac function, because of the reduction in venous return induced by positive intrathoracic pressure [1]. However, MV could be also have beneficial effects on the cardiovascular system in patients suffering from left heart disease [2]. Accordingly, MV is used routinely as a therapy for acute heart failure, even with a noninvasive mode [3]. Conversely, the cardiovascular consequences of an abrupt transfer from MV to spontaneous breathing (SB) could be responsible for weaning failure in patients with left heart disease.

Physiological consequences of transfer from MV to SB and potential adverse effects on cardiac function

Increase in work of breathing

Because of the respiratory muscles' activity, SB results in an increase in global oxygen (O_2) demand [4, 5]. This in turn results in increases in cardiac work and myocardial O_2 demand, with the risk of onset of myocardial ischaemia in patients with coronary artery disease. On the other hand, the increased O_2 demand of the respiratory muscles may lead to blood flow redistribution towards the respiratory muscles, with the risk of hypoperfusion of critical organs [6–10].

Negative intrathoracic pressure

Weaning from MV results in negative intrathoracic pressure [11]. This leads to an increase in the systemic venous return pressure gradient and a decrease in the left ventricular (LV) ejection pressure gradient [1, 12]. The increase in systemic venous return pressure gradient can be responsible for an increase in central blood volume [13], with a subsequent risk of pulmonary oedema formation. During spontaneous inspiration, the pressure surrounding the left ventricle decreases while the pressure surrounding the extrathoracic arterial compartment remains constant. Consequently, the left ventricle needs to generate a higher pressure, i.e. transmural pressure, before blood can leave the thorax. This condition is sensed by the left ventricle as an increased afterload [2].

Increase in sympathetic tone

The catecholamine discharge induced by weaning from MV [11, 14] is related to emotional stress consequent on the sudden transfer from MV to SB. It results in tachycardia, an increase in global O_2 demand [14] and increases in systemic venous return and arterial hypertension.

Main cardiovascular causes of weaning failure

Myocardial ischaemia

Mechanisms

Weaning from MV can result in an imbalance between myocardial O_2 supply and demand and may thus induce myocardial ischaemia that prevents successful weaning, especially in patients with coronary artery disease [15].

Myocardial O_2 delivery might be potentially reduced during weaning because of the onset of the following phenomena:

- The weaning-induced decrease in PaO_2, which can be secondary to (1) worsening of heterogeneity of ventilation/perfusion ratios in patients with chronic obstructive pulmonary disease (COPD) [16], (2) onset of weaning-induced pulmonary oedema, as described below, and (3) decrease in PvO_2 related to excessive increase in global O_2 demand [17]. The decreased PaO_2 combined with respiratory acidosis may lead to low values of SaO_2, which can significantly lower the amount of O_2 delivered to the myocardium.
- The decrease in diastolic arterial pressure related to the decrease in intrathoracic pressure during inspiration, which may be significant in patients with marked inspiratory efforts due to difficulty in weaning. As diastolic arterial pressure is the inflow pressure for coronary perfusion, a decrease in coronary blood flow could occur. In addition, tachycardia induced by excessive catecholamine release in difficult weaning can shorten the coronary perfusion time by reducing the duration of diastole.

On the other hand, myocardial O_2 demand might be potentially increased during weaning because of the onset of the following phenomena:

- The increased work of breathing results in an increased O2 cost of breathing [4], which leads to increased cardiac work to ensure adequate O_2 delivery to the respiratory muscles. This results in increased myocardial O_2 demand.
- The potential increase in LV afterload during weaning may lead to increased systolic LV wall stress and hence myocardial O_2 demand.
- The excessive catecholamine release associated with difficult weaning [11, 14] may also result in increased myocardial O_2 demand related to tachycardia.

Clinical studies

A potential role of weaning-induced myocardial ischemia has been suggested to account for weaning failure in patients with previous coronary artery disease.

In a series of 12 patients ventilated for acute myocardial infarction and pulmonary oedema, Rasanen et al. [18] observed some clinical and electrical aspects of myocardial ischaemia in 5 of them on transfer from MV to SB.

In a series of 15 patients with COPD and coronary artery disease who failed to wean because of the occurrence of pulmonary oedema, segmental wall motion abnormalities suggesting the onset of myocardial ischaemia were detected with technetium-99 angioscintigraphy in 3 [11].

For further evaluation of the possibility that myocardial ischaemia may occur during weaning, Hurford et al. [19] performed a study using thallium-201 myocardial scintigraphy in ventilator-dependent patients who were able to breathe spontaneously for at least 10 min. During spontaneous ventilation, 8 of the 15 patients exhibited decreased myocardial thallium uptake with redistribution of the label on delayed images, indicating decreased myocardial perfusion during SB [19].

Chatila et al. [20] examined the rate of occurrence of ST segment abnormalities during weaning in a population of 93 patients (49 had known coronary artery disease). Only 6% of the patients exhibited ST segment abnormalities during the weaning period. Such abnormalities were associated with the highest rate of weaning failure [20]. Similar results were found by the same group of investigators in a group of 83 patients suffering from coronary artery disease [21].

Cardiogenic pulmonary oedema

A marked rise in pulmonary artery occlusion pressure (PAOP) has been observed during weaning in patients with pre-existing left heart disease [11, 17, 18, 22]. There are several mechanisms that might explain this abnormality.

Increase in LV afterload induced by weaning

The fall in intrathoracic pressure during spontaneous inspiration first decreases the driving pressure for LV ejection, while the pressure in the extrathoracic vessels relative to the atmospheric pressure remains unchanged. In order to eject the same volume of blood from the thorax, the left ventricle needs to generate an intraventricular pressure that is stronger than the juxtacardiac pressure (increase of transmural pressure). In other words, lowering intrathoracic pressure would be equivalent to raising the arterial pressure by a similar amount, and both conditions would be sensed as an increased afterload on the left ventricle [2, 12]. In a series of patients with COPD and without pre-existing LV disease, a weaning-induced increase in LV afterload was suggested by the occurrence of a decrease in LV ejection fraction during transfer from MV to SB [23].

It is likely that this mechanism is involved in the marked rise of PAOP observed in some patients who fail to wean [11, 17, 18, 22].

Influence of increased sympathetic tone

Independently of any change in intrathoracic pressure, an increase in LV afterload may occur during weaning because of the systemic hypertension related to a marked catecholamine discharge [24].

Weaning-induced increase in LV preload

The fall in intrathoracic pressure during spontaneous inspiration is responsible for the widening of the systemic venous return pressure gradient, owing to the decrease in right atrial pressure while the peripheral venous pressure remains unchanged relative to the atmospheric pressure. The resulting increase in right ventricular (RV) preload leads to increased RV stroke volume, pulmonary venous return and LV preload, provided the right ventricle is preload dependent. This necessarily induces an increase in LV filling pressures, particularly in the case of pre-existing cardiac disease. Indeed, in the presence of dilated cardiomyopathy a further increase in LV ventricular end-diastolic volume will result in a marked increase in LV filling pressure. In the presence of reduced LV ventricular compliance, the increase in LV end-diastolic volume induced by weaning will result in a marked increase in ventricular LV filling pressure. These mechanisms probably explain, in part, the rise in PAOP observed during weaning in patients with pre-existing cardiac disease, in whom an increase in LV end-diastolic volume was actually measured during weaning from ventilation [11].

Reduction of LV compliance secondary to weaning

The transfer from MV to SB can reduce LV compliance and induce an increase in PAOP, provided that pulmonary venous return is maintained or increased. This phenomenon can result either from the onset of myocardial ischemia or from biventricular interdependence, a mechanism that can occur during weaning especially when RV impedance increases secondary to an increase in pulmonary artery pressure [25]. This latter phenomenon can occur as a consequence of (1) weaning-related worsening of hypoxaemia, (2) weaning-related respiratory acidosis, (3) weaning-induced increase in PAOP or (4) weaning-induced compression of alveolar vessels related to dynamic pulmonary hyperinflation created by tachypnoea. The resulting increase in RV afterload associated with the simultaneous increase in systemic venous return and RV filling may lead to a marked enlargement of the right ventricle during the transfer from MV to SB. This may decrease the ability of the left ventricle to fill during diastole and hence result in a marked increase in PAOP. This phenomenon is likely to occur in patients with pre-existing RV disease and has been considered responsible for weaning-induced pulmonary oedema in COPD patients [11].

In summary, numerous mechanisms can contribute to an increase in PAOP during the transfer from MV to SB. However, in the absence of left heart disease the rise of PAOP is limited [5, 26]. By contrast, marked increases in PAOP have been reported to occur in patients suffering from left heart disease who failed to wean because of the onset of cardiogenic pulmonary oedema [11, 17, 18, 22].

How to recognize the cardiac origin of weaning failure

The diagnosis of weaning-induced cardiac dysfunction can be considered in high-risk (COPD and chronic left heart disease) patients after the classic causes of weaning failure have been rejected. To establish this diagnosis, it is reasonable to perform a weaning test over a 1-h period of SB using either a T-piece or pressure support with low levels of insufflation pressure (7–10 cmH_2O).

Weaning-induced myocardial ischaemia can be detected by ST segment monitoring [15, 16, 20, 21].

Weaning-induced pulmonary oedema can require pulmonary artery catheterisation providing evidence of the increase in PAOP during the weaning test [1, 17]. The decrease in SvO_2 during the test may also detect weaning failure of cardiovascular origin [17]. The PiCCO system, by demonstrating an increase in extravascular lung water during weaning, could be helpful in detecting weaning-induced pulmonary oedema, but its clinical utility for this purpose has not been yet fully established.

How to treat weaning-induced cardiac dysfunction

There are no formal recommendations on therapy. The treatment must be adjusted according to the mechanism that is the most likely to have occurred and requires individual pathophysiological analysis. Diuretics can be considered when an increase in LV preload is assumed to be the predominant mechanism [11]. Treatment with nitrates seems logical when weaning-induced pulmonary oedema is thought to be related to a marked increase in LV preload and/or myocardial ischaemia. Systemic vasodilating agents might be considered when the predominant mechanism is assumed to be augmentation of LV afterload. In this regard, phosphodiesterase inhibitors have been shown to be efficacious in allowing successful weaning in patients exhibiting weaning-induced pulmonary oedema [22, 27].

Conclusion

The possibility of weaning failure of cardiac origin must be considered in patients suffering from previous left heart disease, in particular when they have associated airway obstruction and/or right heart disease. Among the complex pathophysiological mechanisms, myocardial ischaemia and augmentation of LV afterload must be emphasised. Detection of such phenomena may allow successful weaning after adjustment of the most appropriate therapy.

References

1. Morgan BC, Martin WE, Hornberger JF et al (1966) Hemodynamic effects of intermittent positive pressure respiration. Anesthesiology 27:584-590
2. Pinsky MR (1989) Effects of changing intrathoracic pressure in the normal and failing heart. In: Scharf SM, Cassidy SS (eds) Heart–lung interactions in health and disease. Marcel Dekker, New York, pp 839-876
3. International Consensus Conferences in Intensive Care Medicine (2000) Noninvasive positive pressure ventilation in acute respiratory failure. Am J Respir Crit Care Med 163:283-291
4. Field S, Kelly SM, Macklem PT (1982) The oxygen cost of breathing in patients with cardiorespiratory disease. Am Rev Respir Dis 126:9-13
5. De Backer D, Haddad PE, Preiser JC et al (2000) Hemodynamic responses to successful weaning from mechanical ventilation after cardiovascular surgery. Intensive Care Med 26:1201-1206
6. Viires N, Sillye G, Aubier M et al (1983) Regional blood flow distribution in dog during induced hypotension and low cardiac output. Spontaneous breathing versus artificial ventilation. J Clin Invest 72:935-947
7. Mohsenifar Z, Hay A, Hay J et al (1983) Gastric intramural pH as a predictor of success or failure in weaning patients from mechanical ventilation. Ann Intern Med 119:794-798
8. Bocquillon N, Mathieu D, Nevière R et al (1999) Gastric mucosal pH and blood flow during weaning from mechanical ventilation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 160:1555-1561
9. Uusaro A, Chittock DR, Russell JA et al (2000) Stress test and gastric-arterial PCO_2 measurement improve prediction of successful extubation. Crit Care Med 28:2313-2319
10. Hurtado FJ, Beron M, Oliviera W et al (2001) Gastric intramucosal pH and intraluminal PCO_2 during weaning from mechanical ventilation. Crit Care Med 29:70-76
11. Lemaire F, Teboul JL, Cinotti L et al (1988) Acute left ventricular dysfunction during unsuccessful weaning from mechanical ventilation. Anesthesiology 69:171-179
12. Buda AJ, Pinsky MR, Ingels NB et al (1979) Effect of intrathoracic pressure on left ventricular performance. N Engl J Med 301:453-459
13. Schmidt H, Rohr D, Bauer H et al (1997) Changes in intrathoracic fluid volumes during weaning from mechanical ventilation in patients after coronary artery bypass grafting. J Crit Care 12:22-27
14. Oh TE, Bhatt S, Lin ES et al (1991) Plasma catecholamines and oxygen consumption during weaning from mechanical ventilation. Intensive Care Med 17:199-203
15. Hurford WE, Favorito F (1995) Association of myocardial ischemia with failure to wean from mechanical ventilation. Crit Care Med 23:1475-1480
16. Torres A, Reyes A, Roca J et al (1989) Ventilation-perfusion mismatching in chronic obstructive pulmonary disease during ventilator weaning. Am Rev Respir Dis 140:1246-1250
17. Jubran A, Mathru M, Dries D et al (1998) Continuous recordings of mixed venous oxygen saturation during weaning from mechanical ventilation and the ramifications thereof. Am J Respir Crit Care Med 158:1763-1769
18. Rasanen J, Nikki P, Heikkila J et al (1984) Acute myocardial infarction complicated by respiratory failure. The effects of mechanical ventilation. Chest 85:21-28
19. Hurford WE, Lynch KE, Strauss RN et al (1991) Myocardial perfusion as assessed by thallium-201 scintigraphy during the discontinuation of mechanical ventilation in ventilator-dependent patients. Anesthesiology 74:1007-1016

20. Chatila W, Ani S, Cuaglianone D et al (1996) Cardiac ischemia during weaning from mechanical ventilation. Chest 109: 577-583
21. Srivastava S, Chatila W, Amoateng-Adjepong Y et al (1999) Myocardial ischemia and weaning failure in patients with coronary artery disease: an update. Crit Care Med 27:2109-2112
22. Paulus S, Lehot JJ, Bastien O et al (1994) Enoximone and acute left ventricular failure during weaning from mechanical ventilation after cardiac surgery. Crit Care Med 22:74-80
23. Richard C, Teboul JL, Archambaud F et al (1994) Left ventricular function during weaning of patients with chronic obstructive pulmonary disease. Intensive Care Med 20:181-186
24. Dryden CM, Smith DC, McLintic AJ et al (1993) The effect of preoperative beta-blocker therapy on cardiovascular responses to weaning from mechanical ventilation and extubation after coronary artery bypass grafting. J Cardiothorac Vasc Anesth 7:547-550
25. Teboul JL, Lemaire F (1996) Left ventricular function during acute respiratory failure of chronic obstructive pulmonary disease. In: Derenne JP, Whitelaw WA, Similowski T (eds) Acute respiratory failure in chronic obstructive pulmonary disease. Marcel Dekker, New York, pp 429-451
26. Teboul JL, Abrouk F, Lemaire F (1988) Right ventricular function in COPD patients during weaning from mechanical ventilation. Intensive Care Med 14:483-485
27. Valtier B, Teboul JL, Lemaire F (1990) Left ventricular dysfunction while weaning from mechanical ventilation. Contribution of enoximone. Arch Mal Coeur Vaiss 83:83-86

Chapter 34

Respiratory management in obese patients

P. Pelosi, T. Luecke, P. Caironi

Obesity is a metabolic disease in which adipose tissue accounts for a greater proportion of body mass tissue than normal. Up to 35% of the population in North America and 15-20% in Europe can be considered obese [1]. Many aetiological factors can be implicated in obesity, including genetic, environmental, socioeconomic and individual factors such as age and sex. In the absence of further pathologic conditions, adipose tissue represents 15–18% of body weight in males, and about 25% in females.

Recently, new surgical techniques have been developed for the treatment of obesity, such as ileojejunal bypass and gastric binding, and laparoscopic surgery has also been more widely applied in obese patients. Since these patients are characterised by various systemic physiopathological alterations, the perioperative management can present some problems, most of which are related to respiratory alterations [2].

In this review we will discuss (1) the influence of body mass on the respiratory function and on the ventilatory management in the perioperative period; and (2) the possible role of intensive care in reducing pulmonary complications and, probably, morbidity in the postoperative period.

Definition of obesity

In clinical practice, several criteria of the obese condition have been proposed [3]:

1) Height / weight tables
2) The ratio between the actual and 'ideal' weight of the patient. The ideal weight in kilograms is computed by subtracting 100 (in men) and 105 (in women) from the patient's height in centimetres. A person weighting greater than 120% of this ideal weight can be considered obese, and those weighing over 200% of their ideal weight, as pathologically obese.
3) The Body Mass Index (BMI, or Quetelet's index). This index is the ratio between the weight, expressed in kilograms, and the square of the height, expressed in meters. On the base of BMI, it is possible to divide the population into several classes: (a) underweight, with BMI (kg/m^2) lower than 20, (b) of normal weight, with BMI between 20 and 25, (c) overweight, with BMI between 25 and 30, (d) obese, with BMI between 30 and 40, and (e) morbidly obese, with BMI greater than 40 [1]. BMI is commonly used when dealing with

obesity, because it is easily calculated and there is a good correlation between BMI and the risk of death.

Respiratory function in the preoperative period

Simple obesity, meaning that uncomplicated by upper or lower airway obstruction leading to hypoventilation syndrome, generally produces only mild effects on respiratory function [4, 5]. The ranges of forced vital capacity (FVC), functional residual capacity (FRC) and total lung capacity (TLC) are within the normal values in most moderately obese patients, though the FVC is actually reduced by approximately 25%. Moreover, gas exchange and respiratory mechanics are not particularly affected.

In morbid obesity, in contrast, respiratory function is characterised by alterations of both static and dynamic pulmonary volumes, respiratory mechanics and gas exchange, even in resting conditions. A very obese patient appears to have reduced FVC, FRC and TLC, with a decreased expiratory reserve volume, meaning a typically restrictive pattern [6].

Concerning respiratory mechanics, an obese patient is characterised by decreased compliance of the respiratory system – compliance has been found to be 35% lower than expected values [7] – because of a reduction in either lung or chest wall compliance [8]. These alterations are directly due to the increased amount and to the distribution of adipose tissue, and their importance in determining the inefficiency of respiratory function parallels the increase in abdominal mass. Moreover, these patients are also characterised by increased respiratory resistances [6], but this increase is not likely to be due to airway obstruction so much as to the reduced lung volume: in fact, the specific resistances (i.e. the resistances related to the lung volume) are relatively normal. Anyway, while a minority of these patients can have some degree of flow limitation, this finding is not specific to obesity. Because of the reduced compliance of the respiratory system and the increased airway resistances, the work of breathing is greater in obese than in normal patients [5]. When the inefficiency of respiratory function is not paralleled by an increase in ventilation, the simultaneously increased work of breathing means that a hypercapnic syndrome associated with moderate hypoxaemia can occur.

One important task should be to define the role of preoperative pulmonary function tests in predicting postoperative pulmonary complications. In general, pulmonary function tests have been reported as not particularly sensitive in predicting postoperative pulmonary complications [9]. Recently we performed preoperative pulmonary functional tests in 58 morbidly obese patients (BMI 40) undergoing abdominal surgery, with the aim of identifying any preoperative pulmonary functional test that was better than the others for predicting postoperative pulmonary complications. We found that 14 patients had flow limitation detected by the application of negative expiratory pressure during expiration [10]. In addition, we found that FEV1, FVC and FEV1/FVC were all only partially lower in patients with flow limitation than in those without flow limitation, while the inspiratory capacity

was markedly lower in the patients with flow limitation. No difference in end-expiratory volume was detected between patients with and without flow limitation. More interestingly, patients with both flow limitation and reduced inspiratory capacity were characterised by higher rates of respiratory complications (35% vs 12%) and of alterations seen on chest X-ray after 24 h (55% vs 10%) and by a longer stay in the ICU (6.4 vs 1.2 days) in the postoperative period. Several studies have reported that, at least in COPD patients, the results of the commonly used pulmonary functional tests, i.e. FEV1, FVC, FEV1/FVC, are not related to the exercise capability, while the inspiratory capacity is [11]. Moreover, we should expect that the presence of PEEPi is a major determinant of respiratory failure in the postoperative period, promoting an increase in the work of breathing, rapid shallow breathing and consequent reductions in the lung volume and atelectasis. This is explained by the fact that patients with increased intrinsic PEEP are more likely to have a reduced inspiratory capacity, owing to the increased end-expiratory volume, than those with changed expiratory functional parameters. In other words, the inspiratory capacity is more representative than expiratory parameters as a means of detecting the presence of PEEPi, which is probably the major determinant of respiratory failure in the postoperative period. Thus, we propose that morbidly obese patients can be characterised by the presence or the absence of flow limitation. Those with flow limitation are more likely to have PEEPi, but neither flow limitation nor PEEPi is easily detected by common pulmonary functional tests. We suggest that more attention should be paid to the inspiratory capacity as an easily available parameter that can be used to detect the presence of flow limitation and PEEPi indirectly. Inspiratory capacity, being related to PEEPi, is likely to be very useful in attempts to predict which patients will experience postoperative pulmonary complications.

Respiratory function in the intraoperative period

Body mass is an important determinant of respiratory function during anaesthesia and paralysis, not only in morbidly obese, but also moderately obese, patients. Since obese patients are admitted with a respiratory condition that is already physiologically poor, the morphological and functional variations caused in the respiratory system by the induction and the maintenance of anaesthesia and paralysis are more pronounced than in normal subjects.

Lung volumes

There is a robust association between smaller lung volumes and higher body mass [12]. In morbidly obese patients, the FRC decreases after the induction of anaesthesia to approximately 50% of the pre-anaesthesia values [13]. Even in healthy subjects, the induction of anaesthesia and paralysis regularly leads to a decrease in FRC, and the magnitude of this reduction has been related to several individual factors, such as age, weight and height. However, the mechanisms leading to the

fall in FRC during anaesthesia are not completely understood. It is now accepted that its main causes could be: (a) atelectasis formation and (b) blood shift from abdomen to thorax [14]. Atelectasis can be due to changes in the shape and motion of the diaphragm or the rib cage or both [15], but it has mostly been ascribed to a decreased distribution of ventilation in the dependent lung regions during anaesthesia and mechanical ventilation, i.e. the paravertebral regions in the supine position [16]. The loss of diaphragmatic tone induced by anaesthetic agents makes movement of the diaphragm passively dependent [17]. Because of a gravitational pressure gradient in the abdomen owing to the presence of abdominal viscera, the distribution of ventilation is preferentially directed towards the nondependent lung regions. With a greater body mass, an increase in intra-abdominal pressure can occur [18]. The increased intra-abdominal pressure is mainly directed towards the most dependent lung regions with a more significant cephalad displacement. This results in a decreased movement of the dependent part of the diaphragm, where atelectasis is more likely to occur. When active, the ventilatory muscles counteract the intra-abdominal pressure load towards the dependent diaphragm, limiting the negative effects on the respiratory function. Therefore, the removal of ventilatory muscle tone by anaesthesia and muscle paralysis is likely to have an important role in determination of the reduction in FRC. This preferential alteration of the diaphragm favours greater development of atelectasis in the dependent lung regions than is seen in healthy subjects.

Respiratory mechanics

The alterations in respiratory mechanics during anaesthesia and paralysis are closely related to the body mass. The decrease in compliance of the respiratory system with increasing body mass is determined mainly by the reduction in lung compliance, rather than chest wall compliance [12]. The most important factor in the decreased lung compliance is probably the reduction in FRC, since the intrinsic mechanical characteristics of lung parenchyma – 'specific compliance' – are practically unchanged [19]. Respiratory resistances are also influenced by body mass, mainly because of increased lung resistances [12]. This is due to an increase in the airway resistance component, whereas the 'viscoelastic' component is only slightly affected by the body mass. However, the increase in airway resistance is mainly attributable, again, to the reduction in lung volume, the 'specific' resistances being relatively normal [19].

Gas exchange

Oxygenation decreases with increasing body mass [12]. In fact, the arterial hypoxaemia that characterises awake obese patients worsens during anaesthesia and paralysis [10]. As previously discussed, these patients differ from normal subjects in having a greater predisposition, with the induction of anaesthesia, to (1) pulmonary atelectasis and consequent shunt and (2) an alteration of the ventilation /

perfusion ratio. The lung bases are underventilated because of airway closure and atelectasis, thus producing pulmonary 'shunt' and hypoxaemia. Even in obese patients without hypoventilation syndrome, the physiological dead space is larger than in normal subjects during anaesthesia [20]. Again, the pronounced reduction in FRC and an altered ventilation-perfusion mismatch may have relevant roles in determining the increased physiological dead space.

Respiratory function and the prone position

During surgery, the prone position is commonly used to expose the dorsal surface of the body for specific surgical indications. In anaesthetised and paralysed subjects the prone position, ensuring free abdominal movements, is not associated with adverse effects on the respiratory function [21]. However, it has been stated in earlier discussions that anaesthesia and paralysis may have more pronounced negative effects on respiratory function in obese patients than in normal subjects. Thus, it is generally recommended that the prone position be avoided whenever possible, or at least used only with extreme caution, in obese patients. We have demonstrated that the prone position, in which the abdomen is free to move, increases FRC, lung compliance and oxygenation. Thus, contrary to common belief, the prone position does not seem to have any adverse effects on pulmonary function in obese patients [22]. The greater FRC in the prone position can be explained by a reduction in the cephalad displacement of the diaphragm and/or reopening of atelectatic segments. The prone position probably causes unloading of the abdominal viscera, thus reducing the pressure on the diaphragm. The increase in FRC is paralleled by an increase in lung compliance and oxygenation.

The mechanisms by which the prone position improves oxygenation have not been yet fully elucidated. Explanations proposed include a prone position-induced increase in FRC, a change in regional diaphragm movements with a consequent change in regional ventilation and a redistribution of perfusion along a gravitational gradient toward less atelectatic lung regions. However, as in normal subjects, we have found no significant correlation between changes in FRC and in oxygenation. Thus the increase in FRC alone may not fully explain the improved oxygenation in the prone position. In contrast, we found a good correlation between changes in chest wall compliance and variations in oxygenation: with the increasing reduction in chest wall compliance between supine and prone positions the improvement in oxygenation became more pronounced. These findings suggest that the changes in regional mechanical properties of the chest wall, as previously also reported in patients with respiratory failure [23], can have a relevant role in a more homogeneous distribution of ventilation and improvement in oxygenation.

Intubation of obese patients

A high degree of difficulty, requiring multiple attempts before endotracheal intubation is achieved, is experienced in a small number of patients. An overall

incidence of 1–4% of all subjects has been reported in whom it is impossible to view the vocal cords, and a lower percentage in whom intubation fails (around 0.05–0.35%) [24]. The highest incidence of intubation-related problems has been found in obstetric and obese patients. Many factors can indicate difficulty of endotracheal intubation, such as dental configuration, extension of the atlanto-occipital joint, maxillary length and height, and limited mandible movements. Morbidly obese patients may present additional risks factors, such as an increased amount of soft tissue in the upper airways (leading to an increase in the upper airway resistance), increased tongue size, large breasts (increasing the difficult of direct laryngoscopy because there is little room between the breasts and the mouth for the handle of a conventional laryngoscope) and increased neck circumference [25].

Moreover, as discussed above, obese patients characteristically cause more difficulty with oxygenation and mask ventilation. This is mainly due to a sharp decrease in lung volume with the induction of anaesthesia and to the reduced compliance and increased resistance [13, 18]. An additional difficulty in morbidly obese patients is the presence of an increased volume of gastric content, even after overnight fasting, which may favour pulmonary aspiration [26]. In view of all these considerations, we are of the opinion that an endotracheal tube should be positioned while such patients are awake [27, 28] and in reverse Trendelenburg position.

There are several reasons for choosing this option:

1) Patients maintain patency of the natural airways and spontaneous breathing.
2) FRC is not reduced by anaesthetics and muscle relaxants, so that oxygenation is preserved.
3) Muscle tone maintains upper airway structures in the usual position so that they are much more easily identified.
4) Mask ventilation is not necessary.
5) The reverse Trendelenburg position allows the maintenance of approximately physiological values of FRC, closing volumes and gas-exchange during the procedure. Moreover, this position improves the visual setting during intubation over that with the patient in the supine position.

Several techniques have been proposed for performance of an awake intubation: (1) blind nasal; (2) blind oral; (3) conventional direct laryngoscopy; (4) fibreoptic intubation.

One of the most popular methods of tracheal intubation of an awake patient is probably the use of the blind nasotracheal route. One advantage of this method is that it is not dependent on visualisation of the glottis, and it has a good chance of success in a wide range of patients of different ages and body sizes. Unfortunately, in about 20% of the patients it can cause upper airway bleeding that might compromise subsequent fibreoptic efforts, and it is very uncomfortable. Similar techniques are described for blind orotracheal intubation: under local anaesthesia a laryngeal mask airway is positioned and a tracheal tube can then be advanced, possibly with the support of a gum elastic guide. Of all these intubation techniques, conventional direct laryngoscopy is perhaps the most distressing for the patients and requires a high level of cooperation. Fibreoptic intubation can be performed by either the oral or nasal route, and the only major impediment is the presence of

a significant amount of blood or secretions, which can interfere with visualisation of the vocal cords [24]. Briefly, this technique requires insertion of a well-lubricated flexible fibreoptic laryngoscope into an endotracheal tube and then advanced through the nose or the mouth. Once the fibreoptic laryngoscope has been passed into the trachea the endotracheal tube can be railroaded over the fibroscope and properly positioned under direct vision with the tip above the tracheal carina. The fibreoptic laryngoscope can be withdrawn, the endotracheal tube connected to the breathing circuit and general anaesthesia induced. Numerous devices have been proposed to aid fibreoptic intubation through the mouth; all are designed to bring the tip of the instrument close to the laryngeal aperture without requiring much skill. The patient should always be in the reverse Trendelenburg position in order to avoid the possible negative effects of the supine position on respiratory function.

Our experience of fibreoptic intubation in morbidly obese patients (M. Croci and P. Pelosi) refers to 115 patients (29 male, age 34±8 years, BMI 47±5) receiving general anaesthesia for elective surgery (gastroplasty or jejunal bypass) in the Policlinico Hospital. The patients were intubated using a flexible fibreoptic laryngoscope (LF1 Olympus). We decided to use rather small endotracheal tubes (7 mm ID in female and 7.5 mm ID in male patients), although if the anaesthetist decides to place a larger tube it is possible to use a flexible, spiral-wound endotracheal tube. The average time needed for the performance of intubation was 65±30 s. No major complications such as hypoxaemia (defined as oxygen saturation lower than 90%), hypotension (defined as systolic pressure lower than 90 mmHg), aspiration of gastric content or failed intubation (defined as necessity for changing to a different technique) were observed. Unfortunately, this technique is described as 'unpleasant' by 17% of the patients. However, fibreoptic intubation attenuates or abolishes the hypertensive response usually observed during conventional laryngoscopy [28].

Fibreoptic intubation was performed under local anaesthesia and light sedation (benzodiazepines and opioids), which did not abolish consciousness (the patients were always able to breathe spontaneously and obey simple orders). However, comparative studies of conventional intubation techniques and fibreoptic laryngoscopy are, amazingly, lacking.

Recently, we conducted a prospective controlled trial to compare conventional intubation techniques with fibreoptic intubation in morbidly obese patients. The study was performed in three different hospitals: Policlinico Hospital, Milan (Drs. Croci and Pelosi); S. Orsola Policlinico Hospital, Bologna (Dr. Fusari); and Gemelli Policlinico Hospital, Rome (Dr. Sollazzi). We investigated 30 patients (4 male, age 40.3±11.8 years, BMI 48.8±6.8) divided into three groups of 10 patients each: (1) patients in group 1 underwent conventional intubation using propofol and a depolarising neuromuscular blocker (succinylcholine); (2) in group 2 patients underwent conventional intubation using propofol and a nondepolarising neuromuscular blocker (vecuronium bromide; and (3) in group 3 fibreoptic intubation as described above was performed. The main results are shown in Table 1.

Table 1. Comparison between fibreoptic intubation and conventional intubation techniques (succinylcholine and vecuronium) in morbidly obese patients[a] (*fibreoptic* patients who underwent fibreoptic intubation, *succinylcholine* patients who underwent conventional intubation with succinylcholine, *vecuronium* patients who underwent conventional intubation with vecuronium, *BMI* body mass index, *attempts 1* more than one intubation attempt, *PAmax–PAbasal* difference between maximal and baseline arterial pressure value, *HRmax–HRbasal* difference between maximal and basal heart rate, *n.s.* not significant)

	Group 1: fibreoptic	Group 2: succinylcholine	Group 3: vecuronium	*p*
No. of patients	10	10	10	
Sex (M/F)	2/8	0/10	2/8	n.s.
Age (years)	42.7±9.7	35.2±10.3	43.0±14.5	n.s.
BMI	48.4±7.0	49.7±7.6	48.3±6.4	n.s.
Time for intubation (s)	100.9±43.9	31.9±26.2	75.0±35.9	<0.01
Attempts >1	0/10	5/10	6/10	<0.01
$SatO_2$ <-90%	0/10	3/10	4/10	<0.01
PaO_2 <100 mmhg	0/10	3/10	6/10	<0.01
$PaCO_2$ >45 mmHg	0/10	5/10	6/10	<0.01
PA_{max}–PA_{basal} (mmHg)	14.9±3.0	52.0±23.2	43.5±26.9	<0.01
HR_{max}–HR_{basal} (b/min)	11.6±4.7	23.1±7.4	28.8±14.2	<0.01[a]

[a] Data expressed as mean±SD or as ratio of number of patients with events to total number of patients

We found that: (1) the time required for intubation was slightly longer in group 3 than in groups 1 and 2 (100.9±43.9 s vs 31.9±26.2 s and 75.0±35.9 s, respectively); (2) the number of attempts at intubations (more than one, and requiring a new complete sequence of intubation) was greater in groups 1 and 2 than in group 3 (5/10 and 6/10 vs 0/10, respectively); (3) the presence of at least one episode of arterial saturation lower than 90% during the induction procedure was more frequent in groups 1 and 2 than in group 3 (3/10 and 4/10 vs 0/10, respectively); (4) oxygenation levels lower than 100 mmHg just after intubation were more frequent in groups 1 and 2 than in group 3 (3/10 and 6/10 vs 0/10, respectively); (5) the frequency of $PaCO_2$ levels higher than 45 mmHg at the time of intubation was greater in groups 1 and 2 than in group 3 (5/10 and 6/10 vs 0/10, respectively); and (6) the ranges of arterial pressures and heart rate changes were wider in groups 1 and 2 than in group 3 (52.0±23.2 mmHg and 43.5±26.9 mmHg vs 14.9±3.0 mmHg, respectively, and 23.1±7.4 b/min and 28.8±14.2 b/min vs 11.6±4.7 b/min, respectively).

From this study, we conclude that for maintaining respiratory function fibreoptic intubation may effectively be superior to conventional intubation with depolarising or nondepolarising neuromuscular blockers.

Thus, awake fibreoptic intubation is a safe and useful technique in morbidly obese patients receiving general anaesthesia. However, more prospective controlled or randomised trials are warranted to define the specific role of awake fibreoptic intubation in morbidly obese patients more precisely.

More recently, the use of the videolaryngoscope has been proposed as an intubation technique that could be used in morbidly obese subjects. The videolaryngoscope is a conventional laryngoscope, with the one difference that it is

equipped with a fibreoptic at the its tip. This allows a better view of the larynx, with consequent improvement in the intubation technique. In general, a videolaryngoscope makes it possible to gain at least one or two points on the Cormack scale in the intubation view. Recently, a study has been conducted to evaluate the effectiveness of the videolaryngoscope technique in improving intubation in morbidly obese patients [29, 30]. In this study 80 morbidly obese patients were evaluated and randomised to a conventional or a videolaryngoscope technique. Use of the videolaryngoscope was found to reduce the time needed for intubation and to reduce the number of intubation attempts. Furthermore better oxygenation was maintained during intubation, with the videolaryngoscope technique. Some physicians are used to applying the Fast-Trach intubating laryngeal mask when they encounter difficulties with intubation. This is a laryngeal mask with a rigid handle, by way of which a special endotracheal tube can be placed. In most cases this is very easy, and the mask is associated with high success rates [31–33]. If 'blind' placement of the tube via the laryngeal mask proves not to be feasible the tube can be put on the fibrescope and 'directed' through the vocal cords by this means.

Another technical improvement that has been proposed for use during the intubation of morbidly obese patients is the use of CPAP during the preoxygenation period and induction of anaesthesia [34]. It has been shown that the use of CPAP (10 cmH_2O) was able to prevent atelectasis formation and prolong the duration of 'apnoea', i.e. the time required to reach a saturation of 90% after the induction of anaesthesia and paralysis with 100% oxygen. Thus, the combination of CPAP in the peri-intubation period and the use of a videolaryngoscope may prove to be the easiest and most comfortable alternative to fibreoptic intubation in morbidly obese patients.

How to ventilate obese patients

The increased intra-abdominal pressure in obese patients seems to play a relevant part in the reduction of FRC, which seems to be the prevalent phenomenon, resulting in a decrease of respiratory compliance and oxygenation. This suggests the occurrence of relevant collapse and lung-dependent atelectasis [21]. Different modalities of ventilation have been proposed to address the respiratory system alterations that occur in these patients:

1) High inspiratory oxygen fractions [2].
2) Ventilation using tidal volumes as great as 15–20 ml/kg ideal body weight [2].
3) Inclusion of large, manually or automatically performed, lung inflations (sighs) [35].
4) Application of a positive end-expiratory pressure (PEEP) after a recruitment manoeuvre [36, 37].

There have been no comparative studies to investigate whether one or more of these different ventilatory settings might give better results than the others.

As a consequence of respiratory modifications induced by general anaesthesia and paralysis, the main aim of mechanical ventilation in obese patients is to 'keep the lung open' during the entire respiratory cycle. This counteracts negative effects

induced by the increased body mass and the high intra-abdominal pressure (airway closure, atelectasis, impaired respiratory mechanics and oxygenation), which occur in the intraoperative period but can also persist for a few days in the postoperative period.

The use of low tidal volumes (and, as a consequence, low alveolar ventilation) and high inspired oxygen fraction (FiO2) should be avoided, since it has been clearly shown that this can lead to the formation of progressive reabsorption atelectasis [37].

The use of continuously high tidal volumes (> 13 ml/kg ideal body weight) seems to be ineffective to further improve oxygenation [38], while it can induce hypocapnia if the respiratory rate is not decreased. Moreover, the continuous use of high tidal volumes even during anaesthesia can be deleterious to the lung structure and to the haemodynamics.

To ventilate a lung that is showing a tendency to collapse we have to provide: (1) inspiratory pressure that is high enough to open the collapsed lung regions (recruitment pressure), and (2) a positive end-expiratory pressure (PEEP) high enough to keep the lung open at end-expiration.

An adequate opening pressure can be obtained by applying periodic large, manually performed lung inflations (recruitment manoeuvres) [36, 39, 40]. The application of periodic hyperinflations (sighs) may be also beneficial, providing inspiratory pressures high enough to reopen the lung and alveolar ventilation that is sufficient to avoid the formation of reabsorption atelectasis [41].

The role of PEEP in anaesthesia is still controversial: in fact, different studies have yielded differing results in terms of oxygenation response in different patient populations and clinical conditions [42-45]. This is probably due to the opposite effects induced by PEEP on oxygenation in different patients. PEEP can resolve atelectasis, if present, and prevent the collapse of small airways, improving ventilation-perfusion matching and oxygenation. On the other hand, increasing PEEP may lead to negative effects on the ventilation/perfusion ratio and pulmonary shunt if alveolar overstretching and cardiac output reduction or redistribution become the prevalent phenomena. The final effect of PEEP application on oxygenation depends on the balance between positive and negative effects in any given patients. We have found that applying 10 cmH_2O of PEEP during anaesthesia and paralysis induces improved oxygenation in morbidly obese patients, but not in normal subjects [36], and that the partitioned pressure–volume curves measured at PEEP 0 and 10 cmH_2O follow roughly the same pattern in normal subjects, while in obese patients the pressure–volume curves at 10 cmH_2O PEEP are shifted upward and to the left, suggesting the occurrence of alveolar recruitment. The amount of alveolar recruitment is also related to the degree of improvement in oxygenation.

Further studies are needed to define the optimal levels of PEEP and tidal volume during general anaesthesia in obese patients that will open up and the lung and keep it open, improving oxygenation and respiratory mechanics.

Respiratory function in the postoperative period

Respiratory function is profoundly altered in the postoperative period [2]. Both upper abdominal and thoracic surgery result in a postoperative pulmonary restrictive syndrome. This restriction of pulmonary function can persist for several days, leading to a high incidence of postoperative pulmonary complications, such as sputum retention, atelectasis and bronchopulmonary infection, even in the absence of a previous demonstrable intrinsic lung disease. These complications produce further worsening of pulmonary function and cause secondary hypoxaemia [46]. Several factors may be involved in modifying ventilatory function during the postoperative period, such as reflex inhibition of the phrenic nerve, anaesthesia and postoperative pain.

In one group of morbidly obese patients respiratory function was compared with that in normal subjects in the immediate postoperative period after abdominal interventions [19]. In this series of patients we first found a markedly lower FRC in obese patients than in normal subjects, since FRC was about one third of the normal value in the obese patients. On considering the compliance of respiratory system partitioned into its lung and chest wall components, we found that the reduction in respiratory system compliance was caused by a decrease in both lung and chest wall compliance. Reduced chest wall compliance may be due to an increased adiposity around the ribs, diaphragm and abdomen, limited movements of the ribs caused by thoracic kyphosis and lumbar hyperlordosis resulting from excessive abdominal fat content. Another possible cause is the decreased total thoracic and pulmonary volume, which may pull the chest wall below its resting level and therefore to a flatter portion of its pressure–volume curve. However, the most likely cause of the reduction in chest wall compliance during the postoperative period is probably the increased intra-abdominal pressure, which prevents the diaphragm from moving freely, at least some cases, and affects the shape of the upper and lower thorax [37]. Other abnormalities in the respiratory function during the postoperative period are a reduction in the effectiveness of gas exchange, which is strictly dependent on the decreased lung volumes, and an increase in work of breathing, resulting mainly from a reduction in lung and chest wall compliance and high pulmonary resistances [19].

On the basis of all these data, we support the hypothesis that marked derangement of FRC, elastic (reduction in lung and chest wall compliance) and resistive (increase in lung resistance) components of the respiratory system might account for the significant respiratory dysfunction and arterial hypoxaemia occurring in the postoperative period.

How to manage obese patients in the postoperative period

All these alterations can explain the higher incidence of postoperative pulmonary complications in obese than in nonobese patients [2]. Various techniques and treatments have been proposed to reduce the incidence of postoperative pulmona-

ry complications, such as chest physiotherapy, incentive spirometry, and intermittent positive pressure breathing [46, 47]. Some authors have proposed the use of continuous positive airway pressure (CPAP)[48] or bi-level positive airway pressure (BIPAP) administered by noninvasive techniques in the first 24 h of the postoperative period [49].

The aim is to give ventilatory support to allow more rapid restoration of lung volumes to the preoperative values, improving oxygenation and reducing the work of breathing. Moreover, for several days after surgery patients should remain in semi-recumbent position (30°–45°) [50] to reduce abdominal pressure on the diaphragm. These data suggest that a more physiological approach to respiratory treatment in the postoperative period could be useful in improving respiratory outcome.

The role of preventive admission of morbidly obese patients undergoing abdominal surgery to intensive care units (ICUs) during the postoperative period is not yet defined [51, 52]. Some advantages of ICU admission are gentler weaning from the ventilator for easy performance of chest physiotherapy and noninvasive ventilatory treatment, optimised fluid treatment and more careful pain control. On the other hand, there are increased costs and more difficulties in organising the time schedule for surgical operations.

To define the role of preventive ICUs admission in the postoperative morbidly obese patients we compared the incidence of postoperative pulmonary complications and mortality in 38 morbidly obese patients (18 male, ages 37.5±9.9 years, BMI 48.5±6.6) admitted to our ICU after abdominal surgery between 1993 and 1998 with historical controls who had not been admitted to the ICU in the postoperative period [50, 52–56]. Mean age, BMI and type of abdominal surgery were comparable in the two groups.

After the end of surgical procedures (20 for gastric binding and 18 for jejunoileal bypass), all the study patients were admitted to the ICU for their postoperative treatment while still intubated and mechanically ventilated. The fluid treatment was titrated to achieve diuresis higher than 0.5 ml h^{-1} per kg ideal body weight, and antibiotic treatment was given for 2–3 days after surgery. Patients were mechanically ventilated in synchronised intermittent mechanical ventilation (SIMV) and pressure support to achieve a tidal volume of 13 ml/kg of ideal body weight and $PaCO_2$ within the normal range, with a PEEP level set to give the 'best oxygenation' (a PaO_2 increase by at least 10 mmHg). Patients were successively weaned from the ventilator, FiO_2 first being reduced to obtain a PaO_2 of 90–100 mmHg at 40% FiO_2, followed by progressive reduction of PEEP and of the ventilatory support. We performed extubation when the following criteria were satisfied: (1) forced vital capacity (FVC) higher than 1 l; (2) spontaneous unassisted tidal volume higher than 400 ml; (3) spontaneous respiratory rate lower than 25 breaths/min; (4) PaO_2 higher than 80 mmHg at 30% FiO_2 during spontaneous breathing, and haemodynamic stability; and (5) no clinical or laboratory signs of infection.

In this population of morbidly obese patients we evaluated the incidence of postoperative pulmonary complications, defined as the new occurrence of three or more of the following signs or symptoms [46]: cough, positive sputum culture,

dyspnoea, chest pain or discomfort, fever (temperature higher than 38°C), tachycardia (more than 100 b/min), and positive chest X-ray (atelectasis, abnormal hemidiaphragm elevation, new pleural effusion, new infiltrate).

Table 2. Postoperative pulmonary complications and mortality in obese patients admitted and not admitted to the ICU[a] (*BMI* body mass index, *PPC* postoperative pulmonary complications)

[Reference]	Patients (*n*)	BMI (kg/m^2)	Age (years)	PPC (%)	Mortality (%)
No ICU admission					
[50]	70	–	–	–	5.7
[52]	46	142[a]	34	0	–
[53]	17	147[a]	36	47	0
[54]	110	135[a]	35	21.8	0
[55]	102	>25.0	54	26.5	0
[56]	181	28.5	58	29.3	0
Total	526	–	48	24.6	0.8
ICU admission					
Our experience	38	48.5	37	7.9*	0

[a]Data refer only to average data
*p.05 vs No ICU admission
**Weight (kg)

As seen in Table 2, the incidence of postoperative pulmonary complications was significantly lower in obese patients admitted to the ICU than in the population of historical controls not admitted to the ICU in the immediate postoperative period. Prospective randomised studies are needed for better definition of the role of ICU in the treatment of morbidly obese patients in the postoperative period.

Conclusions

The important alterations in the respiratory function of morbidly obese patients in the perioperative period may play a significant part in determining pulmonary complications in the intra- and postoperative periods. In morbidly obese patients, adequate ventilatory settings in the intraoperative period and ICU admission in the postoperative period may help to reduce the incidence of pulmonary complications.

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References

1. Jack DB (1996) Fighting obesity the Franco-British way. Lancet 347:1756
2. Luce JM (1980) Respiratory complication of obesity. Chest 78:626-631
3. Shenkman Z, Shir Y, Brodsky JB (1993) Perioperative management of the obese patients. Br J Anaesth 70:349-359
4. Ray CS, Sue DY, Bray G et al (1983) Effects of obesity on respiratory function. Am Rev Respir Dis 128:501-506
5. Rochester DF (1995) Obesity and abdominal distention. In: Roussos C (ed) The thorax, 2nd edn, part C: Disease. Marcel Dekker, New York, pp 1951-1973
6. Zerah F, Harf A, Perlemuter L et al (1993) Effects of obesity on respiratory resistance. Chest 103:1470-1476
7. Eriksen J, Andersen J, Rasmussen JP et al (1978) Effects of ventilation with large tidal volumes or positive end-expiratory pressure on cardiorespiratory function in anesthetized obese patients. Acta Anaesthesiol Scand 22:241-248
8. Naimark A, Cherniack RM (1960) Compliance of the respiratory system and its components in health and obesity. J Appl Physiol 15:377-382
9. Smetana GM (1999) Preoperative pulmonary evaluation. N Engl J Med 340:937-940
10. Ferretti A, Giampiccolo P, Cavalli A et al (2001) Expiratory flow limitation and orthopnea in massively obese subjects. Chest 119:1401-1408
11. Diaz O, Villafranca C, Ghezzo M et al (2000) Role of inspiratory capacity on exercise tolerance in COPD patients with and without tidal expiratory flow limitation at rest. Eur Respir J 16:269-275
12. Pelosi P, Croci M, Ravagnan I et al (1998) The effects of body mass on lung volumes, respiratory mechanics, and gas-exchange during general anesthesia. Anesth Analg 87:645-660
13. Damia G, Mascheroni D, Croci M et al (1988) Perioperative changes in functional residual capacity in morbidly obese patients. Br J Anaesth 60:574-578
14. Hedenstierna G, Strandberg A, Brismar B et al (1985) Functional residual capacity, thoracoabdominal dimensions, and central blood volume during general anesthesia with muscle paralysis and mechanical ventilation. Anesthesiology 62:247-254
15. Warner DO, Warner MA, Ritman EL (1995) Human chest wall function while awake and during halothane anesthesia. I. Quiet breathing. Anesthesiology 82:6-19
16. Brismar B, Hedenstierna G, Lundquist H et al (1985) Pulmonary densities during anesthesia: a proposal of atelectasis. Anesthesiology 62:422-428
17. Froese AB, Bryan CH (1974) Effects of anesthesia and paralysis on diaphragmatic mechanics in man. Anesthesiology 41:242-255
18. Pelosi P, Croci M, Ravagnan I et al (1997) Respiratory system mechanics in anesthetized, paralyzed, morbidly obese patients. J Appl Physiol 82:811-818
19. Pelosi P, Croci M, Ravagnan I et al (1996) Total respiratory system, lung and chest wall mechanics in anesthetized-paralyzed morbidly obese patients. Chest 109:144-151
20. Hedenstierna G, Svensson J (1976) Breathing mechanics, dead space and gas exchange

in the extremely obese, breathing spontaneously and during anesthesia with intermittent positive pressure ventilation. Acta Anaesthaesiol Scand 20:248-254
21. Pelosi P, Croci M, Calappi E et al (1995) The prone positioning during general anesthesia minimally affects respiratory mechanics while improving functional residual capacity and increasing oxygen tension. Anesth Analg 80:955-960
22. Pelosi P, Croci M, Calappi E et al (1996) Prone positioning improves pulmonary function in obese patients during general anesthesia. Anesth Analg 83:578-583
23. Pelosi P, Tubiolo D, Mascheroni D et al (1998) Effects of prone position on respiratory mechanics and gas exchange during acute lung injury. Am J Respir Crit Care Med 157:387-393
24. Samsoon GL, Young JR (1987) Difficult tracheal intubation: a retrospective study. Anaesthesia 42:487-490
25. Horner RL, Mohiaddin RH, Lowell DG et al (1989) Sites and sizes of fat deposits around the pharynx in obese patients with obstructive sleep apnea and weight matched controls. Eur J Respir 2:613-622
26. Vaughan RW, Bauer S, Wise L (1975) Volume and pH of gastric juice in obese patients. Anesthesiology 43:686-689
27. Murphy P (1967) A fiber-optic endoscope used for nasal intubation. Anaesthesia 22:489-491
28. Ovassapian A, Yelich SJ, Dykes MH et al (1983) Blood pressure and heart rate changes during awake fiberoptic nasotracheal intubation. Anesth Analg 62:951-954
29. Marrel J, Magnusson L (2004) Videolaryngoscopy improves intubation in morbidly obese patients. ESA 2004 Proceedings A 279
30. Markowitz SD, White PF, Issioni T et al (2002) Initial evaluation of a new optic laryngoscope blade. J Clin Anesth 14:604-607
31. Frappier J, Guenoun T, Journois D et al (2003) Airway management using the intubating laryngeal mask airway for the morbidly obese patient. Anesth Analg 96:1510-1515
32. Langeron O, Masso E, Huraux C et al (2000) Prediction of difficult mask intubation. Anesthesiology 92:1229-1236
33. Keller C, Brimacombe J, Kleinsasser A et al (2002) The larybgel mask airway Proseal ™ as a temporary ventilatory device in grossly and morbidly obese patients before laryngoscope guided tracheal intubation. Anesth Analg 12:732-740
34. Coussa M, Proietti S, Schnyder P et al (2004) Prevention of atelectasis formation during the induction of general anesthesia in morbidly obese patients. Anesth Analg 98:1491-1497
35. Rothen HV, Sporre B, Engber G et al (1993) Reexpansion of atelectasis during general anesthesia: a computed tomography study. Br J Anaesth 71:788-795
36. Pelosi P, Ravagnan I, Giurati G et al (1999) Positive end-expiratory pressure improves respiratory function in obese patients but not in normal subjects during anesthesia and paralysis. Anesthesiology 91:1221-1231
37. Rothen HV, Sporre B, Engber G et al (1995) Influence of gas composition on recurrence of atelectasis after a reexpansion maneuver during general anesthesia. Anesthesiology 82:832-842
38. Bardoczky GI, Yernault JC, Houben JJ et al (1995) Large tidal volume ventilation does not improve oxygenation in morbidly obese patients during anesthesia. Anesth Analg 81:385-388
39. Rothen HV, Sporre B, Engber G et al (1995) Reexpansion of atelectasis during general anesthesia may have a prolonged effect. Acta Anaesthesiol Scand 39:118-125
40. Pelosi P, Cadringher P, Bottino N et al (1999) Sigh in acute respiratory distress syndrome. Am J Respir Crit Care Med 159:872-880

41. Wyche MQ, Teichner RL, Kallos T et al (1973) Effects of continuous positive pressure breathing on functional residual capacity and arterial oxygenation during intra-abdominal operations: studies in man during nitrous oxide and *d*-tubocurarine anesthesia. Anesthesiology 38:68-74
42. Salem MR, Dalal FY, Zygmunt MP et al (1978) Does PEEP improve intraoperative oxygenation in grossly obese patients? Anesthesiology 48:280-281
43. Eriksen J, Andersen J, Rasmussen JP et al (1978) Effects of ventilation with large tidal volumes or positive end-expiratory pressure on cardiorespiratory function in anesthetized obese patients. Acta Anaesthesiol Scand 22:241-248
44. Santesson J (1976) Oxygen transport and venous admixture in the extremely obese: influence of anaesthesia and artificial ventilation with and without positive end-expiratory pressure. Acta Anaesthesiol Scand 20:387-394
45. Soderberg M, Thomson D, White T (1977) Respiration, circulation and anaesthetic management in obesity. Investigation before and after jejunoileal bypass. Acta Anaesthesiol Scand 21:55-61
46. Celli BP, Rodriguez K, Snider GL (1984) A controlled trial of intermittent positive pressure breathing, incentive spirometry and deep breathing exercise in preventing pulmonary complications after abdominal surgery. Am Rev Respir Dis 130:12-15
47. Fagevik Olsen M, Halin I, Nordgven S et al (1997) Randomized controlled trial of prophylactic chest physiotherapy in major abdominal surgery. Br J Surg 84:1535-1538
48. Fagevik Olsen M, Wennberg E, Johnsson E et al (2002) Randomized clinical study of the prevention of pulmonary complications after thoraco-abdominal resection by two different breathing techniques. Br J Surg 89:1228-1234
49. Joris JL, Sottiaux TM, Chiche JD et al (1997) Effect of Bi-Level positive airway pressure (BiPAP) nasal ventilation on the postoperative pulmonary restrictive syndrome in obese patients undergoing gastroplasty. Chest 111:665-670
50. Vaughan RW, Wise L (1975) Postoperative arterial blood gas measurement in obese patients: effect of position on gas exchange. Ann Surg 182:705-709
51. Marik P, Varon J (1988) The obese patients in the ICU. Chest 113:492-498
52. Postlethwait RW, Johnson WD (1972) Complications following surgery for duodenal ulcer in obese patients. Arch Surg 105:438-440
53. Vaughan RW (1974) Anesthetic considerations in jejunoileal small bowel bypass for morbid obesity. Anesth Analg 53:421-429
54. Fox GS, Whalley DG, Bevan DR (1981) Anaesthesia for the morbidly obese. Experience with 110 patients. Br J Anaesth 53:811-816
55. Hall JC, Tarala RA, Hall JL, Mander J (1991) A multivariate analysis of the risk of pulmonary complications after laparotomy. Chest 99:923-927
56. Brooks-Brunn JA (1997) Predictors of postoperative pulmonary complications following abdominal surgery. Chest 111:564-571

Chapter 35

Is the acute respiratory distress syndrome a systemic disease?

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The acute respiratory distress syndrome

The acute respiratory distress syndrome (ARDS) is a severe form of acute lung injury (ALI) and frequently develops following sepsis, pneumonia, aspiration of gastric contents, major trauma, and other clinical disorders, such as acute pancreatitis, drug overdose, and transfusion of blood products [1].

Despite important advances in intensive care medicine, the mortality rate of ARDS remains high [2]. Although the most obvious clinical abnormalities are referable to the lung, the most common cause of death is not due to hypoxia but to multiple organ dysfunction syndrome (MODS). Over the past decade, it has become evident, that the ventilatory strategy itself has an important impact on the outcome of patients with ARDS [3].

In this article, we focus on the relationship between mechanical ventilation and remote organ dysfunction and highlight the suggested pathways.

Mechanical ventilation and cardiac function

Impaired oxygenation in conjunction with diffuse alveolar infiltrates in chest X-ray are the most obvious clinical findings in ARDS. Mechanical ventilation is the main therapeutic intervention measure to improve oxygenation and to decrease the work of breathing. However, ventilatory strategies commonly used in ARDS patients may alter haemodynamics, resulting in a reduction of cardiac output and perhaps in an impairment of regional blood flow and oxygen delivery to distal organs [4-7]. A hypermetabolic state comparable to severe sepsis is a typical clinical feature in ARDS [8]. Thus, high systemic and regional blood flows are required to meet the increased metabolic demands.

Right ventricular dysfunction has been identified as an important prognostic factor in patients with ARDS [9]. Clinical features common in patients with ARDS, such as hypoxemia, destruction of lung tissue, airway collapse, and mechanical ventilation, can increase right ventricular output impedance [10]. Vieillard-Baron et al. recently found echocardiographic evidence of acute cor pulmonale in 19 of 75 ARDS patients ventilated with a tidal volume of 8 $ml \cdot kg^{-1}$ and identified arterial

blood PCO_2 levels as the sole factor independently associated with acute cor pulmonale in a multivariate analysis [11].

The influence of positive end-expiratory pressure (PEEP) on right ventricular performance is defined by the overall balance between its effects on pre- and afterload. Schmitt et al. evaluated the effect of different PEEP levels on right ventricular outflow impedance in patients with ARDS [12]. While zero PEEP and high PEEP levels (13 ± 4 cm H_2O) were associated with an increased right ventricular outflow impedance during tidal ventilation, this association disappeared at a moderate PEEP level (6 ± 3 cm H_2O) and cardiac output was preserved with the moderate but not with the higher PEEP level.

Ventilator-induced biophysical and biochemical injury

Applying excessive mechanical stretch forces on primary cultured lung epithelial cells [13], or ventilating non-perfused lungs ex vivo [13, 14], and intact animals in vivo [15] can result in loss of morphological integrity of lung cells and tissue. Altered alveolar epithelial integrity is an important factor leading to increased lung permeability and alveolar oedema, a hallmark of ALI/ARDS.

Mechanotransduction describes the conversion of mechanical stimuli into biochemical and biomolecular cellular alterations [16]. Mechanical stretch translated into overdistension as well as recruitment/derecruitment of the alveoli during mechanical ventilation are both involved in the cellular response [14, 17]. It has been suggested that activation of stretch-sensitive ion channels [18, 19], disruption of plasma membrane integrity [20, 21], and conformational changes in membrane-associated molecules and cytoskeleton components [22, 23] may play important roles in the injury response.

Lung epithelial cells [24-27], alveolar macrophages [28] and neutrophils [29] have been suggested as cell types producing inflammatory mediators in response to mechanical ventilation. The interaction between lung structural cells and immune cells results in a synergic effect with respect to cytokine production [30].

Activation of lung cells by mechanical ventilation

Application of mechanical stretch to alveolar macrophages induced release of inflammatory mediators, such as tumour necrosis factor-α (TNF-α), interleukin (IL)-6, IL-8, and matrix metalloproteinase-9 [28]. Lentsch et al. showed that alveolar macrophages have an important role in the activation of the transcriptional regulatory factor nuclear factor-kB [31]. Whitehead et al. recently reported far fewer macrophages recovered in BAL fluid after ventilation with high tidal volumes (15 and 40 $ml \cdot kg^{-1}$) than with low tidal volume ventilation (7 $ml \cdot kg^{-1}$) in an ex-vivo lung model. About 30-40% of macrophages were localized in the alveolar space of lungs ventilated with low tidal volume whereas in lungs ventilated with high tidal volume almost all macrophages were found in the interstitial space [32]. This may well

explain the systemic inflammatory response following ventilator-induced lung injury (VILI). However, ventilation with high tidal volumes resulted in higher concentrations of TNF-α and IL-1β in lung lavage fluid as compared to ventilation with low tidal volume, suggesting that lung parenchyma cells are an important source to produce cytokines in the absence of immune cells.

There is a large marginated neutrophil pool in the lung vasculature. Once the neutrophils have transmigrated into the lungs, they appear to act as effectors cells in the context of VILI. Postmortem studies in ARDS patients demonstrated pulmonary accumulation of neutrophils, and neutrophil counts in the lung lavage fluid were higher in non-survivors than in survivors [33]. In patients with sepsis-related ARDS, there was good correlation between increased neutrophil counts in the lung and risk of death [34]. Pulmonary function has been shown to deteriorate in patients with lung injury as neutropenia resolves [35], and lung vascular permeability was attenuated after induction of neutropenia [36].

We have demonstrated that exposure of resting neutrophils to lung lavage fluids obtained from ARDS patients who were ventilated with a high tidal volume (11.7 ± 1 ml·kg^{-1}, PEEP 6.5 ± 1.7 cm H_2O) for 36 h resulted in an increased expression of oxidant burst, surface CD18 and CD63, and increased shedding of l-selectin as compared to exposure to lung lavage fluid from patients ventilated with a low tidal volume (7.5 ± 0.8 ml·kg^{-1}, PEEP 14.8 ± 2.7 cm H_2O) [29]. These findings suggest that mechanical ventilation has the potential to activate neutrophils, which in turn contribute to the excessive systemic inflammatory responses.

Biotrauma – ventilator-induced systemic inflammation in ARDS

Biotrauma describes the association between ventilation-induced mechanical stresses and the release of various mediators by the lungs [37]. Mechanical ventilation of injured lungs can result in release of inflammatory mediators [38]. Given the vast surface area of the lung in contact with the blood, a stimulus resulting in release of even small quantities of inflammatory mediators per cell could result in a significant influx of these mediators into the circulation. Several clinical studies have shown increased mortality in patients who had elevated serum cytokine levels [39-41]. Protective ventilatory strategies using a low tidal volume decreased serum cytokine levels, MODS, and mortality in patients with ARDS [3, 38, 42].

In an animal ARDS model (surfactant-depleted rabbits), high tidal volume mechanical ventilation, as opposed to high-frequency ventilation, increased the concentration of inflammatory mediators (platelet-activating factor, thromboxanes, prostaglandins) in lung lavage fluid [43] and alveolar expression of TNF-α [44]. A ventilation strategy with zero PEEP and/or excessive end-inspiratory lung volume increased the concentration of lung lavage cytokines in isolated rat lungs [14]. After induction of acute lung injury with HCl in rats, Chiumello et al. found higher concentrations of TNF-α and macrophage inflammatory protein-2 (MIP-2) in lung lavage fluid and serum of animals ventilated with high tidal volumes (V_T 16 ml·kg^{-1},

PEEP zero) than in those ventilated with low tidal volumes (V_T 9 ml·kg^{-1}, PEEP either zero or 5 cm H_2O) [45].

The relevance of inflammatory mediators in the context of VILI has been demonstrated by several studies using anti-TNF-a antibody and protease inhibitors in animals [46, 47].

ARDS/VILI and remote organ dysfunction and failure

In the large, multicentre ARDS Network trial, the number of days without MODS was significantly higher in patients ventilated with lower tidal volumes (6.2 ± 0.8 ml·kg^{-1} predicted body weight; mean plateau pressure 25 ± 6 cm H_2O on day 1-3) than in those ventilated with high tidal volumes (11.8 ± 0.8 ml·kg^{-1} predicted body weight; mean plateau pressure 33 ± 8 cm H_2O [3]. Ranieri et al. reported that MODS scores were significantly higher 3 days after admission in ARDS patients ventilated with a higher tidal volume (11.1 ± 1.9 ml·kg, PEEP 6.5 ± 1.7 cmH_2O) than in patients ventilated with low tidal volume (7.6 ± 1.1 ml·kg, PEEP 14.8 ± 2.7 cmH_2O) [42]. They showed a correlation between the changes in overall MODS score and the changes in serum levels of cytokines, including IL-6, TNF-α, IL-1β, and IL-8 [42].

The mechanisms by which high tidal volume mechanical ventilation induces MODS remain unclear [48]. Theoretically, biotrauma may lead to MODS via spillover of lung-borne inflammatory mediators, bacteria, and soluble pro-apoptotic factors into the systemic circulation. Compartmentalization of the increased immune response to the lungs with concomitant suppression of the peripheral immune response has been suggested to be another contributing factor in the development of MODS [49].

The development of early cellular apoptosis may also be a factor in the context of ventilator-associated MODS in ARDS patients [50,51]. The Fas pathway is important in the regulation of apoptosis. Binding of Fas ligand (a circulating pro-apoptotic factor) to Fas (a cell-surface receptor present on most cells of the body) initiates an intracellular apoptotic signalling pathway [50]. In patients with ARDS, concentrations of soluble Fas, Fas ligand and nuclear matrix proteins are high in lung lavage fluids and remain high in patients who developed MODS and died [50-52]. Albertine et al. recently showed that Fas expression is increased in the alveolar epithelium of patients who died with ARDS and that Fas ligand is measurable in pulmonary oedema fluids of patients with ALI [53].

In a HCl-induced lung injury model in rabbits, high tidal volume ventilation, as opposed to low tidal volume ventilation, was associated with an increased rate of epithelial cell apoptosis in the kidney and in the small intestine [54]. Exposure of kidney LLC-RK1 cells to the plasma obtained from the rabbits ventilated with the high tidal volumes resulted in higher numbers of apoptotic cells, suggesting that circulating soluble factors are involved in this process. Blocking soluble Fas ligand attenuated the rate of LLC-RK1 cell apoptosis [54]. In ARDS patients, there was a correlation between changes in soluble Fas ligand concentrations and changes in plasma creatinine levels [38].

The presence of acute renal failure has been identified as an important prognostic factor in ARDS [55]. Brun et al. recently reported that renal failure was the most prevalent non-pulmonary organ failure in patients with ARDS [56]. A number of mechanisms have been proposed to explain the effects of mechanical ventilation on renal function, including a reduction in cardiac output, redistribution of intrarenal blood flow, stimulation of sympathetic and hormonal pathways, and release of systemic inflammatory mediators as a consequence of VILI in ARDS [57, 58].

The hepatosplanchnic region plays an important role in the development of MODS. Guery et al. examined the effect of pre-treatment with intravenous anti-TNF-a antibody on gut permeability in rats ventilated either with high (30 $ml \cdot kg^{-1}$) or low (10 $ml \cdot kg^{-1}$) tidal volumes [46]. Gut permeability was significantly increased in the former group and was largely abrogated by pre-treatment with TNF-a neutralizing antibodies.

Clinical implications and conclusions

ARDS becomes a systemic disease in association with mechanical ventilation. There is an increasing amount of evidence in the literature showing that mechanical ventilation has a significant impact on the remote organ systems in ARDS. Research in VILI-associated MODS has focussed on the mechanisms of an up-regulated and imbalanced systemic inflammatory response and increased rates of apoptosis in the lungs and the remote organs as well as on impaired global and regional haemodynamics. Cellular and molecular biology research has suggested key elements in this context that may serve as therapeutic targets for future treatment of patients with ARDS.

Reference

1. Ware LB, Matthay MA (2000) The acute respiratory distress syndrome. N. Engl. J Med. 342(18):1334-1349
2. Vincent JL, Sakr Y, Ranieri VM (2003) Epidemiology and outcome of acute respiratory failure in intensive care unit patients. Crit Care Med. 31:S296-S299
3. The Acute Respiratory Distress Syndrome Network (2000) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 342(18):1301-1308
4. Brienza N, Revelly JP, Ayuse T et al (1995) Effects of PEEP on liver arterial and venous blood flows. Am J Respir Crit Care Med 152(2):504-510
5. Fessler HE, Brower RG, Wise RA et al (1991) Effects of positive end-expiratory pressure on the gradient for venous return. Am Rev Respir Dis 143(1):19-24
6. Ranieri VM, Mascia L, Fiore T et al (1995) Cardiorespiratory effects of positive end-expiratory pressure during progressive tidal volume reduction (permissive hypercapnia) in patients with acute respiratory distress syndrome. Anesthesiology 83(4):710-720
7. Robotham JL, Lixfeld W, Holland L et al (1980) The effects of positive end-expiratory pressure on right and left ventricular performance. Am Rev Respir Dis 121(4):677-683

8. Kiiski R, Takala J (1994) Hypermetabolism and efficiency of CO_2 removal in acute respiratory failure. Chest 105(4):1198-1203
9. Monchi M, Bellenfant F, Cariou A et al (1998) Early predictive factors of survival in the acute respiratory distress syndrome. A multivariate analysis. Am J Respir Crit Care Med 158(4):1076-1081
10. Vieillard-Baron A, Loubieres Y, Schmitt JM et al (1999) Cyclic changes in right ventricular output impedance during mechanical ventilation. J Appl Physiol 87(5):1644-1650
11. Vieillard-Baron A, Schmitt JM, Augarde R et al (2001) Acute cor pulmonale in acute respiratory distress syndrome submitted to protective ventilation: incidence, clinical implications, and prognosis. Crit Care Med 29(8):1551-1555
12. Schmitt JM, Vieillard-Baron A, Augarde R et al (2001) Positive end-expiratory pressure titration in acute respiratory distress syndrome patients: impact on right ventricular outflow impedance evaluated by pulmonary artery Doppler flow velocity measurements. Crit Care Med 29(6):1154-1158
13. Liu M, Tanswell AK, Post M (1999) Mechanical force-induced signal transduction in lung cells. Am J Physiol 277(4 Pt 1):L667-L683
14. Tremblay L, Valenza F, Ribeiro SP et al (1997) Injurious ventilatory strategies increase cytokines and c-fos m-RNA expression in an isolated rat lung model. J Clin Invest 99(5):944-952
15. Gurkan OU, O'Donnell C, Brower R et al (2003) Differential effects of mechanical ventilatory strategy on lung injury and systemic organ inflammation in mice. Am J Physiol Lung Cell Mol Physiol 285(3):L710-L718
16. Wang N, Butler JP, Ingber DE (1993) Mechanotransduction across the cell surface and through the cytoskeleton. Science 260(5111):1124-1127
17. Dreyfuss D, Saumon G (1993) Role of tidal volume, FRC, and end-inspiratory volume in the development of pulmonary edema following mechanical ventilation. Am Rev Respir Dis 148(5):1194-1203
18. Parker JC, Ivey CL, Tucker JA (1998) Gadolinium prevents high airway pressure-induced permeability increases in isolated rat lungs. J Appl Physiol 84(4):1113-1118
19. Waters CM, Ridge KM, Sunio G et al (1999) Mechanical stretching of alveolar epithelial cells increases Na(+)-K(+)-ATPase activity. J Appl Physiol 87(2):715-721
20. Grembowicz KP, Sprague D, McNeil PL (1999) Temporary disruption of the plasma membrane is required for c-fos expression in response to mechanical stress. Mol Biol Cell 10(4):1247-1257
21. Hinman LE, Beilman GJ, Groehler KE et al (1997) Wound-induced calcium waves in alveolar type II cells. Am J Physiol 273(6 Pt 1):L1242-L1248
22. Bhullar IS, Li YS, Miao H et al (1998) Fluid shear stress activation of IkappaB kinase is integrin-dependent. J Biol Chem 273(46):30544-30549
23. Hubmayr RD, Shore SA, Fredberg JJ et al (1996) Pharmacological activation changes stiffness of cultured human airway smooth muscle cells. Am J Physiol 271(5 Pt 1):C1660-C1668
24. Vlahakis NE, Schroeder MA, Limper AH et al (1999) Stretch induces cytokine release by alveolar epithelial cells in vitro. Am J Physiol 277(1 Pt 1):L167-L173
25. Windsor AC, Walsh CJ, Mullen PG et al (1993) Tumor necrosis factor-alpha blockade prevents neutrophil CD18 receptor upregulation and attenuates acute lung injury in porcine sepsis without inhibition of neutrophil oxygen radical generation. J Clin Invest 91(4):1459-1468
26. McRitchie DI, Isowa N, Edelson JD et al (2000) Production of tumour necrosis factor alpha by primary cultured rat alveolar epithelial cells. Cytokine 12(6):644-654

27. Tremblay LN, Miatto D, Hamid Q et al (2002) Injurious ventilation induces widespread pulmonary epithelial expression of tumor necrosis factor-alpha and interleukin-6 messenger RNA. Crit Care Med 30(8):1693-1700
28. Pugin J, Dunn I, Jolliet P et al (1998) Activation of human macrophages by mechanical ventilation in vitro. Am J Physiol 275(6 Pt 1):L1040-L1050
29. Zhang H, Downey GP, Suter PM et al (2002) Conventional mechanical ventilation is associated with bronchoalveolar lavage-induced activation of polymorphonuclear leukocytes: a possible mechanism to explain the systemic consequences of ventilator-induced lung injury in patients with ARDS. Anesthesiology 97(6):1426-1433
30. Chollet-Martin S, Jourdain B, Gibert C et al (1996) Interactions between neutrophils and cytokines in blood and alveolar spaces during ARDS. Am J Respir Crit Care Med 154(3 Pt 1):594-601
31. Lentsch AB, Czermak BJ, Bless NM et al (1999) Essential role of alveolar macrophages in intrapulmonary activation of NF-kappa B. Am J Respir Cell Mol Biol 20(4):692-698
32. Whitehead TC, Zhang H, Mullen B et al (2004) Effect of mechanical ventilation on cytokine response to intratracheal lipopolysaccharide. Anesthesiology 101(1):52-58
33. Steinberg KP, Milberg JA, Martin TR et al (1994) Evolution of bronchoalveolar cell populations in the adult respiratory distress syndrome. Am J Respir Crit Care Med 150(1):113-122
34. Miller EJ, Cohen AB, Matthay MA (1996) Increased interleukin-8 concentrations in the pulmonary edema fluid of patients with acute respiratory distress syndrome from sepsis. Crit Care Med 24(9):1448-1454
35. Azoulay E, Darmon M, Delclaux C et al (2002) Deterioration of previous acute lung injury during neutropenia recovery. Crit Care Med 30(4):781-786
36. Abraham E (2003) Neutrophils and acute lung injury. Crit Care Med 31(4 Suppl):S195-S199
37. Tremblay LN, Slutsky AS (1998) Ventilator-induced injury: from barotrauma to biotrauma. Proc Assoc Am Physicians 110(6):482-488
38. Ranieri VM, Suter PM, Tortorella C et al (1999) Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. JAMA 282(1):54-61
39. Goodman RB, Strieter RM, Martin DP et al (1996) Inflammatory cytokines in patients with persistence of the acute respiratory distress syndrome. Am J Respir Crit Care Med 154(3 Pt 1):602-611
40. Meduri GU, Headley S, Kohler G et al (1995) Persistent elevation of inflammatory cytokines predicts a poor outcome in ARDS. Plasma IL-1 beta and IL-6 levels are consistent and efficient predictors of outcome over time. Chest 107(4):1062-1073
41. Meduri GU, Kohler G, Headley S et al (1995) Inflammatory cytokines in the BAL of patients with ARDS. Persistent elevation over time predicts poor outcome. Chest 108(5):1303-1314
42. Ranieri VM, Giunta F, Suter PM et al (2000) Mechanical ventilation as a mediator of multisystem organ failure in acute respiratory distress syndrome. JAMA 284(1):43-44
43. Imai Y, Kawano T, Miyasaka K et al (1994) Inflammatory chemical mediators during conventional ventilation and during high frequency oscillatory ventilation. Am J Respir Crit Care Med 150(6 Pt 1):1550-1554
44. Takata M, Abe J, Tanaka H et al (1997) Intraalveolar expression of tumor necrosis factor-alpha gene during conventional and high-frequency ventilation. Am J Respir Crit Care Med 156(1):272-279
45. Chiumello D, Pristine G, Slutsky AS (1999) Mechanical ventilation affects local and

systemic cytokines in an animal model of acute respiratory distress syndrome. Am J Respir Crit Care Med 160(1):109-116
46. Guery BP, Welsh DA, Viget NB et al (2003) Ventilation-induced lung injury is associated with an increase in gut permeability. Shock 19(6):559-563
47. Imai Y, Kawano T, Iwamoto S et al (1999) Intratracheal anti-tumor necrosis factor-alpha antibody attenuates ventilator-induced lung injury in rabbits. J Appl Physiol 87(2):510-515
48. Plotz FB, Slutsky AS, Van Vught AJ et al (2004) Ventilator-induced lung injury and multiple system organ failure: a critical review of facts and hypotheses. Intensive Care Med
49. Munford RS, Pugin J (2001) The crucial role of systemic responses in the innate (non-adaptive) host defense. J Endotoxin Res 7(4):327-332
50. Hetts SW (1998) To die or not to die: an overview of apoptosis and its role in disease. JAMA 279(4):300-307
51. Matute-Bello G, Liles WC, Steinberg KP et al (1999) Soluble Fas ligand induces epithelial cell apoptosis in humans with acute lung injury (ARDS). J Immunol 163(4):2217-2225
52. Papathanassoglou ED, Moynihan JA, Vermillion DL et al (2000) Soluble fas levels correlate with multiple organ dysfunction severity, survival and nitrate levels, but not with cellular apoptotic markers in critically ill patients. Shock 14(2):107-112
53. Albertine KH, Soulier MF, Wang Z et al (2002) Fas and fas ligand are up-regulated in pulmonary edema fluid and lung tissue of patients with acute lung injury and the acute respiratory distress syndrome. Am J Pathol 161(5):1783-1796
54. Imai Y, Parodo J, Kajikawa O et al (2003) Injurious mechanical ventilation and end-organ epithelial cell apoptosis and organ dysfunction in an experimental model of acute respiratory distress syndrome. JAMA 289(16):2104-2112
55. Esteban A, Alia I, Gordo F et al (2000) Prospective randomized trial comparing pressure-controlled ventilation and volume-controlled ventilation in ARDS. For the Spanish Lung Failure Collaborative Group. Chest 117(6):1690-1696
56. Brun-Buisson C, Minelli C, Bertolini G et al (2004) Epidemiology and outcome of acute lung injury in European intensive care units. Results from the ALIVE study. Intensive Care Med 30(1):51-61
57. Annat G, Viale JP, Bui XB et al (1983) Effect of PEEP ventilation on renal function, plasma renin, aldosterone, neurophysins and urinary ADH, and prostaglandins. Anesthesiology 58(2):136-141
58. Qvist J, Pontoppidan H, Wilson RS et al (1975) Hemodynamic responses to mechanical ventilation with PEEP: the effect of hypervolemia. Anesthesiology 42(1):45-55

CARDIOVASCULAR CRITICAL CARE

Chapter 36

Invasive versus non-invasive haemodynamic monitoring in major vascular surgery

B. Allaria, M. Resta

In discussing this topic, a premise must be made: the international literature has extensively demonstrated that patients with vascular disease who undergo surgery on the aorta or arteries are almost invariably coronary patients as well. Therefore, we must always bear in mind that, even with patients who do not have a positive history of coronary disease, and even if there is no clinical or diagnostic evidence demonstrating its presence, our behaviour must be oriented towards treating all vascular patients as patients who are potentially at risk for myocardial ischaemia. It should also be added that there are two other vascular regions particularly at risk in such patients: the intestinal region and the renal region. Consequently, it is essential that appropriate cardiovascular checks be performed on patients in order to prevent ischaemic events and/or provide a prompt diagnosis if they occur so that problems can be corrected as quickly as possible.

While it is relatively simple to make prompt note of the onset of myocardial ischaemia via ST monitoring on a sufficient number of electrocardiographic leads, and to detect reduced renal perfusion merely by observing urinary flow and measuring the urinary sodium/potassium (Na_u/K_u) ratio, it is anything but simple to detect a drop in intestinal perfusion. This represents a serious limitation in our conventional monitoring systems, because affected patients often have mesenteric arterial lesions, and drops in intraoperative and postoperative perfusion in this region can cause prolonged intestinal paresis, which extends the patient's hospitalisation and promotes bacterial translocation and ensuing sepsis. For this reason, the goal of cardiovascular monitoring is to prevent ischaemic events in every vascular region, optimising circulatory filling, the efficiency of the cardiac pump, and the extent of peripheral vascular resistances, and thus of the arterial pressure that is the result of the interaction of these elements.

In this chapter, the discussion is divided into two sections: (1) methods that are useful for preventing a drop in perfusion in various vascular regions (first and foremost, the coronary one); (2) methods that are useful for the early diagnosis of reduced perfusion in order to permit prompt treatment.

Preventing ischaemic events

While exploring all the classic cardiovascular diagnostics commonly used in patients who must undergo major vascular surgery is beyond the scope of this article, it should nonetheless be noted that, quite often, these diagnostics are "oversized". Even if sophisticated equipment were to detect coronary disease in asymptomatic patients, knowledge of this pathology would not influence treatment because, as was noted, the vascular patient must be treated as a coronary patient, even if there is no evidence as such. Moreover, in asymptomatic patients there is currently no tendency to perform invasive examinations, such as coronarography procedures and/or revascularisation prior to performing vascular surgery. Diagnostic and therapeutic invasiveness is limited to patients with unstable angina and, if vascular surgery is not urgent, to those patients with a history of frequent anginal episodes. Instead, two fundamental tests, the echocardiogram and an "educated" check of arterial pressure, will be described.

The echocardiogram is important because it provides information that can orient monitoring towards either invasive methods (Swan-Ganz catheter, REF) or non-invasive ones (impedance cardiography, CO_2 partial rebreathing, transoesophageal Doppler echocardiography with HemoSonic, indocyanine green densitometry). There are essentially five conditions that can be diagnosed via echocardiogram that would indicate the use of invasive monitoring: aortic stenosis, mitral stenosis, hypertrophic subaortic stenosis, pulmonary hypertension, and severe left ventricular failure). To this list, a sixth can be added, i.e. severe anaemia (Hb <8 g/dl), which can certainly benefit from monitoring using a Swan-Ganz catheter, as will be discussed shortly.

In all other cases, non-invasive monitoring strategies can be chosen. Some of those offer the advantage that they can be started prior to surgery and continued postoperatively (impedance cardiography and indocyanine green densitometry), while others must be limited to the operative stage because they can currently be conducted only if the patient is intubated (CO_2 partial rebreathing) or heavily sedated (HemoSonic).

An 'educated' check of arterial pressure is a test that does not aim to measure 'absolute' pressure values but to understand the reasons for a particular pressure value. For example, there are two aspects of pressure measurements that are often undervalued, diastolic pressure and the variation in pressure when switching from a recumbent position to an upright one.

For decades, suspicion has been cast on diastolic pressure only when it was over 90 mmHg, as if only high pressure values represented a risk factor. Following this same line of thought, certain diastolic pressures under 70 mmHg, often encountered in the elderly, were viewed with a sense of curiosity, as if they were almost too favourable and, in any event, not worthy of note. Instead, diastolic hypotension, which is a characteristic of vascular patients who are undergoing major vascular surgery, is in itself a risk factor for myocardial ischaemia. If the causes of diastolic hypotension are considered, the reasons for this will immediately become clear.

Normally, as it propagates peripherally, the sphygmic wave encounters a reflec-

tion when it meets the branches of the arterial tree. The outcome is a retrograde wave that reaches the aortic arch in the diastolic phase and thus sustains aortic pressure in this phase. When anomalous rigidity of the aorta and the large vessels occurs, as in atherosclerotic processes, the reflected wave is faster and it reaches the aortic arch earlier – and thus the systolic phase – thereby sustaining the pressure value of this phase.

The result is systolic hypertension and diastolic hypotension. Given that the consumption of myocardial O2 depends above all on contraction and thus on the systolic phase, and since coronary flow is closely dependent on diastolic aortic pressure (that of the left ventricle, in any case), it is evident that in patients with systolic hypertension and diastolic hypotension, the risk of myocardial ischaemia is particularly high [1, 2].

Checking arterial pressure with the patient in both a recumbent and an upright position serves a specific purpose: it evaluates baroreflex speed. With these reflexes, changing from a recumbent to an upright position pressure does not drop, and may even rise slightly. However, in the elderly (who often undergo vascular surgery), baroreflexes are altered and these patients can easily experience orthostatic hypotension. Preoperative gauging of inefficient baroreflexes is very important, because it allows identification of patients who might experience problems postoperatively, when mobilisation begins. It must also be noted that orthostatic hypotension and the faintness that ensues occur frequently, above all in early mobilisation, and it is likely that they are accentuated by the residual effects of anaesthesia and analgesia [3]. In keeping with these observations, Kirkeby-Garstad [4] reported important O2 desaturation in mixed venous blood (SVO2) in patients undergoing aortic-valve replacement who were mobilised on the first day postoperatively. During mobilisation, O2 (VO2) consumption increased without a corresponding increase in DO2, and thus with a decisive increase in O2ER. In all likelihood, this was due to inadequate baroreflexes which do not permit an increase in CO and DO2, essential for dealing with the increase in VO2 caused by mobilisation.

This does not mean that early mobilisation in this type of surgery should be reconsidered, but it must only take place together with frequent pressure checks, above all in patients who have shown orthostatic hypotension preoperatively.

The above considerations make it clear that "educated checks of arterial pressure" yield valuable – and low-cost – information that, like the echocardiogram, can help to pinpoint patients with a risk of ischaemia who require more in-depth cardiovascular monitoring than what is usually provided during surgery. This type of monitoring must preferably commence in the preoperative phase so that unfavourable situations can be identified and addressed.

The first and probably most important unfavourable situation is hypovolaemia, regardless of whether it is absolute (anaemic patients, patients in chronic treatment with diuretics) or relative (patients being treated with drugs that increase compliance of the venous system, such as nitro derivatives). In both cases, cardiac output may not be adequate and should be corrected before surgery. Inadequate cardiac output may also be due to the fact that, because of the effect of general anaesthesia on venous compliance, the disproportion between the circulatory bed

and the circulating mass is accentuated. This paves the way for further drops in output that can be worsened by the well-known depressive effect on venous return caused by artificial ventilation.

A relatively simple method for ensuring safe operating conditions is to perform surgery with DO2 over 600 ml/min/m² (CI×CaO2×10) [5, 6]. However, this is only possible when cardiac output (CO) is known. The problem can easily be overcome – even without a Swan-Ganz catheter – if at least one of three methods currently on the market is readily available: (1) indocyanine green densitometry (which also makes it possible to measure volaemia) [7] (Fig. 1); (2) thoracic electrical bioimpedance (TEB) [8, 9] (Fig. 2); and (3) rebreathing of inert gases, which uses a photoacoustic gas analyser to measure CO in a very short time-frame at a relatively low cost, using a portable instrument the size of a briefcase [10] (Fig. 3).

Fig. 1. Indocyanine Green Densitometry (DDG)

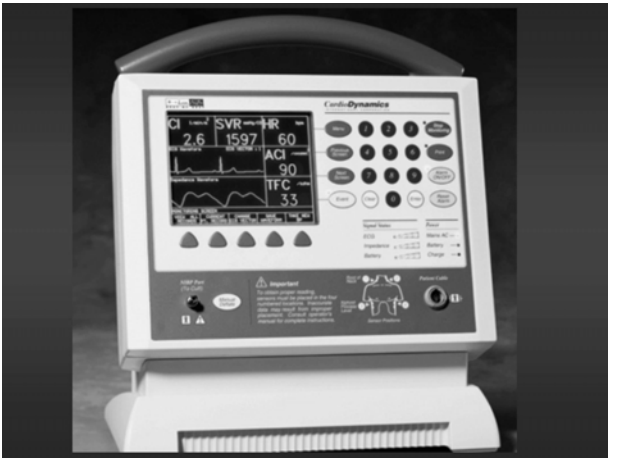

Fig. 2. Thoracic Electrical Bioimpedance (TEB)

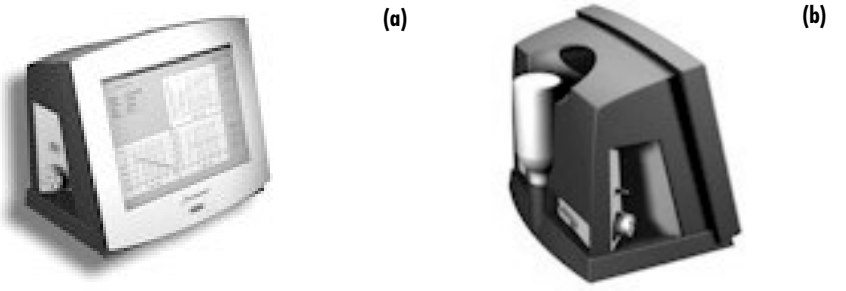

Fig. 3a. Rebreathing of inert gases, front view
Fig. 3b. Rebreathing of inert gases, rear view

CO is the result of the interaction between circulatory filling, myocardial contractility and post-loading, and thus a good output with optimum DO_2 represents a good guarantee of satisfactory cardiocirculatory structure, above all when there is also a satisfactory echocardiogram.

However, it is also possible to obtain more specific preoperative information on cardiac filling and on the contractility of the left ventricle. In particular, TEB provides information on both cardiac filling and myocardial contractility. Two parameters are monitored beat-to-beat using this instrument: ejection period (PEP) and Weissler's quotient, in which PEP is the numerator and ejection time (ET) is the denominator. PEP is particularly sensitive to filling of the left ventricle, and it can be used as a variable in a circulatory filling test. As long as fluid boluses permit reductions in PEP and increases in stroke volume (SV), the administration of fluids can be considered desirable, whereas in cases in which PEP and SV do not respond favourably, the administration of fluids must be stopped.

TEB also permits indirect evaluation of extravascular lung water (EVLW), which is a useful guide to the administration of fluids [11].

If, as noted, a DO_2I value of 500 ml/min/m² is the target to be reached, it can also be achieved by administering fluids until PEP drops, SV rises and EVLW does not increase. Once a certain level of fluid therapy is reached, if these responses are not optimum and the target has not been reached yet, inotropes must be administered. In this case, the guideline will be the Weissler quotient (PEP/ET), which must drop as DO_2I rises.

TEB also allows two other parameters to be measured that are useful for evaluating filling of the left ventricle and its contractility: the index of contractility, which is volume-dependent and can thus be used similar to PEP in filling tests, and the acceleration index (ACCI), which is independent of volume and is tied to contractility; thus, like PEP/ET it is useful for evaluating response to inotropes or, in general anaesthesia, for gaining an immediate understanding of the cardiopressor effect of the anaesthetics.

Early diagnosis of haemodynamic imbalances

The only non-invasive, perioperative monitoring method that can be used during surgery is TEB. Indocyanine green is not a continuous monitoring method because it permits measurements only with the administration of a dye bolus (this bolus is also rather expensive). Rebreathing inert gas calls for patient collaboration and thus cannot be applied with patients on artificial ventilation, at least not for the time being. However, TEB also has a limitation in vascular surgery when carotid surgery is involved. Since TEB entails placing skin electrodes at the neck and chest, it cannot be used when surgery involves these sites.

Nevertheless, there are also diagnostic methods that cannot be used preoperatively but that can instead be applied during surgery. The simplest of these is capnography. $PETCO_2$ is the outcome of three factors: alveolar ventilation, the production of CO_2 (and thus energy metabolism) and pulmonary capillary flow (i.e. the amount of CO that participates in respiratory exchanges). Alveolar ventilation is often slightly excessive in artificial ventilation, while energy metabolism is lowered by general anaesthesia and by the exclusion of certain territories from the circulation, as is the case when the aorta is clamped. These two aspects tend to lower $PETCO_2$; however, this reduction is very gradual and is well known to anaesthesiologists. The drop in $PETCO_2$ caused by a drop in CO is quite different, as it is sudden and notable, occurring in just a few breaths; its significance is therefore important. When $PETCO_2$ drops suddenly while ventilation is constant, it is entirely likely that this is due to a drop in output. The rise in $PETCO_2$ in response to the rapid administration of fluids makes it possible to diagnose the drop in CO triggered by absolute hypovolaemia (blood loss) or relative hypovolaemia (venous vasodilatation caused by anaesthetics, with difficulties in venous return due also to the coexistence of artificial ventilation). Failed response to filling must lead to suspect myocardial depression caused by anaesthetics (particularly halogenated ones) and to recommend a reduced dosage. Boccara et al. suggested an interesting use of capnography to predict hypotension at unclamping in aortic surgery and thus prevent it [12]. The authors demonstrated that a drop of more than 15% in $PETCO_2$ when the aorta is clamped is predictive of hypotension at unclamping, with a drop in systolic arterial pressure of more than 20%. The reduction in $PETCO_2$ when the aorta is clamped has a sensitivity of 100% in predicting hypotension at unclamping. The authors suggest using infusions to correct the drop in $PETCO_2$ and administering inotropes if fluid therapy is insufficient [13].

Nevertheless, various monitoring methods with a low level of invasiveness can be implemented during surgery, such as transoesophageal echocardiography (HemoSonic) (Fig. 4); transpulmonary thermodilution (PICCO) (Fig. 5) [14], which requires a central venous catheter and one in a peripheral artery; the lithium dilution system (LIDCO) (Fig. 6) [15], which requires only a catheter through the radial artery; and the CO_2 partial rebreathing system ($NICO_2$) (Fig. 7), which is completely non-invasive because it works solely through a sensor for $PETCO_2$ that is placed at the Y branch of the respirator together with a spirometer.

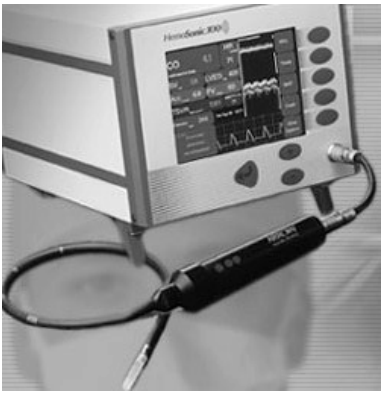

Fig. 4. HEMOSONIC - Transoesophageal echocardiograpy

Fig. 5. PICCO - Thermodilution method

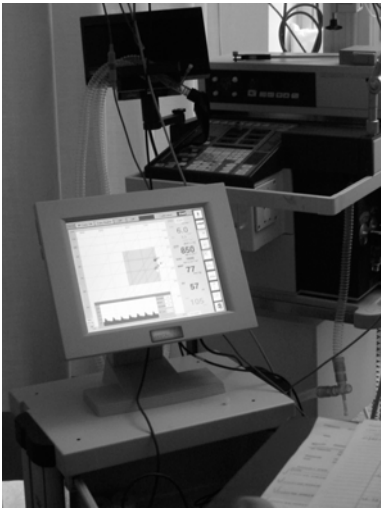

Fig. 6. LIDCO – Lithium dilution system

Fig. 7. NICO - CO_2 partial rebreathing system

Each of these monitoring systems has it own specific features that provide useful information. All of these methods measure cardiac output and thus permit measurement of DO_2I, whose great importance was noted earlier.

Moreover, the HemoSonic also makes it possible to have an independent parameter with respect to volume and post-loading, and thus provides a good index of left ventricular contractility, i.e. ACC (maximum acceleration of blood flow), which permits sophisticated supervision of the cardiodepressor effect of anaesthetics. The PICCO system provides information on volumes, specifically, global end diastolic volume (GEDV) and intrathoracic blood volume (ITBV). These parameters are now universally recognised for their usefulness in guiding the administration of fluids. Like the TEB system, PICCO also permits indirect evaluation of EVLW. An added benefit of the PICCO system is that it measures systolic pressure variation (SPV), a parameter that has also been accepted universally in evaluating circulatory filling in artificial ventilation.

It is widely known that the poorer the circulatory filling, the greater the influence of the artificial respirator on systolic peaks of arterial pressure, thereby raising SPV, which will also be reduced by the infusion of fluids. Consequently, SPV is another valuable parameter in guiding the infusion of fluids. The PICCO system performs an initial measurement of CO by transpulmonary thermodilution. Thus, it initially requires the administration of a cold fluid bolus, and then uses measured SV as a correction factor for beat-to-beat monitoring of SV, based on an analysis of the arterial pulse profile.

A similar philosophy guided the invention of the LIDCO system: a bolus of lithium is required for initial measurement of CO and SV, and then the instrument measures beat-to-beat SV by analysing pulse profile. The LIDCO System also monitors SPV.

$NICO_2$ is an instrument that combines volumetric capnography with CO_2 partial rebreathing to permit measurement of the amount of CO that participates

in respiratory exchanges, thus measuring pulmonary capillary blood flow (PCBF). In addition to the PCBF measurement, this instrument also measures shunt fraction (the CO that does not participate in respiratory exchanges) using the Nunn diagram, which describes the relation between FIO_2 and SpO_2, both of which are available data. Using this method, CO is obtained by summing PCBF+QS/QT. $NICO_2$ also makes it possible to measure alveolar dead space (VD/VT) which, as is known, increases in hypovolaemia due to an increase in ventilated and poorly perfused zones. Continuous monitoring of VD/VT adds indirect information on the patient's volaemic status, and it is useful in guiding the reinfusion of fluids and optimising artificial ventilation [16].

$NICO_2$ has recently been tested in aortic surgery and, although it tends to underestimate CO (not significantly) immediately following aortic clamping and immediately after unclamping, the authors who tested it consider it valid for monitoring patients undergoing this type of surgery [17].

Classic monitoring with the Swan-Ganz catheter will not be discussed in detail, except to emphasise that there are relatively few indications for its use: aortic valve stenosis, hypertrophic subaortic stenosis, mitral stenosis, severe left ventricular failure, pulmonary hypertension and severe anaemia. Pulmonary hypertension, which should be evaluated appropriately with an instrument that semi-continuously monitors not only CO, but also right ventricle ejection fraction (RVEF) and right ventricular end-diastolic volume (RVEDV): the new "CEDV vigilance" (Fig. 8). The difficulty in deciding on the quantity of fluids to infuse in patients with concomitant pulmonary hypertension is greatly facilitated by constant monitoring of PAP, RVEDV and RVEF [18].

The usefulness of the Swan-Ganz catheter in managing major vascular surgery in anaemic patients should also be mentioned briefly. For DO_2I to remain at optimum levels (600 ml/min/m²) even in conditions of low Hb, cardiac index (CI) must increase. The difficulty lies in establishing the extent to which CI must increase in order to ensure sufficient DOI to satisfy the body's consumption of O_2.

Fig. 8. CEDV Vigilance – cardiac output semi-continuously, right ventricle; ejection fraction (RVEF), right ventriclar end-diastolic volume (RVEDV)

Yalavatte et al., who are part of J.L. Vincent's group, published a study several years ago in *Chest* [19], proposing the CI/O2ER quotient as an index of the adjustment of CO to the condition of anaemia. According to the authors, this quotient should always be maintained at a value of 10. Given the fact that the value of CVO2 is used to calculate O2ER, the Swan-Ganz catheter is clearly indispensable for following this indication.

The difficulties involved in obtaining information on intestinal perfusion were noted above. As a rule, if optimum circulatory filling and good cardiac output are kept constant, then intestinal ischaemia is infrequent. Nonetheless, this type of surgery engenders a higher rate of ischaemic colitis or intestinal infarctions. Sigmoid capnometry is a monitoring technique that has not reaped success but that nevertheless boasts convinced backers specifically for this type of surgery [20].

A gap between regional PCO2 and arterial PCO2 4 kPa suggests insufficient intestinal perfusion and portends ischaemic colitis, above all if this value does not improve after aortic unclamping and in the hours immediately following surgery. In this case, colonoscopy is indicated. Leluppe and Vallet [21], experts in this monitoring technique, consider it valuable for the prevention and/or early diagnosis of alterations in intestinal perfusion.

So far, the present discussion of monitoring techniques for major vascular surgery has not included TOE (transoesophageal echocardiography). This is certainly not because it is not useful in this type of surgery, but because, unfortunately, it is not yet within the scope of all anaesthesiologists. Introduced about 20 years ago, TOE has been highly successful in cardiac surgery, whereas its use in non-cardiac surgery remains limited, indubitably because of the combination of two factors: the high cost of the equipment and the specialisation required in order to use it. As a result, it is not surprising that, in its guidelines, the Society of Cardiovascular Anesthesiologists recommends the use of TOE only for type I and type II patients [22]. In non-cardiac surgery, type I patients are those who are haemodynamically stable; type II patients are those with a high risk of myocardial ischaemia and haemodynamic imbalance. Nevertheless, while the utility of TOE in type I patients is undisputed, its use in type II patients continues to be controversial.

A study published a few months ago in *Anaesthesia* (2004) seems to confirm the added value of TOE in influencing decisions on fluid therapy and the use of inotropes, vasopressors or vasodilators also in type II patients. Moreover, the superiority of TOE with respect to the Swan-Ganz catheter in revealing myocardial ischaemia and in evaluating filling of the heart chambers, ventricular kinetics and, in general, alterations in cardiac physiology has been acknowledged for years [23, 24]. Therefore, it can be concluded that in monitoring patients undergoing major vascular surgery, TOE can play an important role if the method is simplified and costs are lowered.

References

1. Safar ME, Levy BI, et al (2003) Current perspectives on arterial stiffness and pulse pressure in hypertension and cardiovascular disease. Circulation 107:2864-2869
2. McVeigh GE (2003) Pulse waveform analysis and arterial wall properties Hypertension 41:1010-1011
3. Cowie DA, Shoemaker JK, et al (2004) Orthostatic hypotension occurs frequently in the first hour after anesthesia. Anesth Analg 98:40-44
4. Kirkeby-Garstad I, Olaf FM et al (2004) Marked venous desaturation during early mobilization after aortic valve surgery. Anesth Analg 98:311-317
5. Poeze JWM, Ramsay G (2000) Goal oriented haemodynamic therapy: a plea for a closer look at using perioperative oxygen transport optimisation. Int Care Med 26:635-637
6. Wilson J, Woods I, Fawcett S et al (1999) Reducing a risk of major elective surgery: randomised controlled trial of preoperative optimization of oxygen delivery. BMJ 318:1088-1103
7. Haruna M, Kumon K, Yahagi N et al (1998) Blood volume measurement at the bedside using ICG pulse spectrophotometry. Anesthesiology 89:1322-1328
8. Shoemaker WC, Thangathurai D, Wo CC et al (1999) Intraoperative evaluation of tissue perfusion in high-risk patients by invasive and noninvasive hemodynamic monitoring. Crit Care Med 27:2147-2152
9. Favaro M, Resta M, Allaria B (2003) Thoracic impedence. APICE. Crit Care Med Springer, Milan, pp. 171-184
10. Clemensen P, Christensen P, Norsk P et al (1994) A modified photo- and magnetoacoustic multigas analyzer applied in gas exchange measurements. J Appl Physiol 76:2832-2839
11. Jonsson F, Madsen P, Jorgensen LG et al (1995) Thoracic electrical impedence and fluid balance during aortic surgery. Acta Anaesth Scand 39:513-517
12. Boccara G, Jaber S, Eliet J et al (2001) Monitoring of end-tidal carbon dioxide partial pressure changes during infrarenal aortic cross clamping: a non invasive method to predict unclamping by hypotension. Acta Anaesth Scand 45:188-193
13. Allaria B, Defilippi L, et al (1996) Capnography and circulation. APICE. Crit Care Med, Springer Milan, pp. 169-178
14. Della Rocca G, Costa MG, Coccia C et al (2003) Transpulmonary thermodilution: analysis of beat by beat peak pressure and stroke volume variations: GEDV, ITBV, VLW. APICE. Crit Care Med, Springer, Milan, pp. 185-199
15. Allaria B, Favaro M, Resta M (2003) Non-invasive cardiovascular monitoring: focus on LIDCO. APICE. Crit Care Med, Springer, Milan, 151-169
16. Allaria B (2001) Monitoring pulmonary capillary blood flow and alveolar dead space using the combined methods of volumetric capnography and partial CO_2 rebreathing. APICE. Crit Care Med Springer Milan, pp. 275-290
17. Kotake Y, Moriyama K (2003) Performance of non-invasive partial CO_2 rebreathing cardiac output and thermodilution cardiac output in patients undergoing aortic reconstruction surgery. Anesthesiology 99:283-288
18. Leeper A (2003) Monitoring right ventricular volumes. AACN Clinical Issues 14:208-219
19. Yalavatte GS, De Backer D, Vincent JL (2000) Assessment of cardiac index in anemic patients. Chest 118:782-787
20. Björk CM, Broman G, Lindberg F et al (2000) pHi-monitoring of the sigmoid colon after aorto-iliac surgery. A five-years prospective study. Eur J Vasc Endovasc Surg 20:273-280
21. Lebuffe G, Decoere C, Raingeval X et al (2001) Pilot study with air automated capno-

metry in abdominal aortic aneurysm surgery. Eur J Anesthesiol 18:585-592
22. Kolev N, Brase R, Swanevelder J et al (1998) The influence of TOE on intraoperative decision making. A European multicenter study. European perioperative TOE research group Anaesthesie 53:767-773
23. Swenson JD, Harkin C, Pace NL et al (1996) TOE: an objective tool in defining maximum ventricular response to intravenous fluid therapy
24. Wolrab C, Weber T, Tschernich H et al (1997) Assessment of left ventricular preload: TOE versus filling pressure. Acta Anaesth Scand Suppl 111:283-286

Chapter 37

Analysis of arterial pulse – clinical implications

P. Giomarelli, S. Scolletta, S.M. Romano

Changes in volume, which occur in all arterial vessels, are principally due to radial expansion of the arterial wall in response to blood pressure changes. The latter on various physical factors, such as the power of heart contraction, arterial impedance and compliance, and peripheral vessel resistances. These variables are interdependent and must be clinically evaluated at the same time [1].

Pulsatile phenomena and arterial stiffness, according to recent studies confirming the importance of arterial pressure in cardiac disease, seem to be in the foreground as regards diastolic and mean pressure in human adults [2-5]. Pulse pressure and systolic pressure may be different in central and peripheral arteries even if diastolic and mean pressures appear to be equal [3, 4]. This inequality can lead to errors in assessment of myocardial oxygen requirements and of left ventricular load, as well as to different responses to vasodilator agents [6-8].

Arterial stiffness is not only a well-known risk factor of cardiovascular disease, but also a predictor of cardiovascular events; in addition it has important haemodynamic consequences [9]. The wall of large arteries is normally very compliant and able to accommodate the wide pressure variations occurring during the cardiac cycle [10]. Vascular stiffness controls, in great part, the speed of aortic wave propagation (pulse wave velocity = PWV) [11]. The aortic wave is reflected from the periphery in diastole maintaining a normal coronary flow rate. When in old age arterial stiffness and PWV increase, the reflected wave appears in the aorta during systole, raising central aortic pressure. Thus, central aortic pressure will be greater than the peripheral one commonly measured with sphygmomanometer [12]. The full arterial waveform also provides a great deal of information on arterial stiffness.

The central aortic pressure wave is made up of two important parts: the first one is generated by left ventricular ejection, and the second one, which occurs later than the first, is characterised by the wave reflected from the periphery. When aortic and arterial stiffness increase, the wave reflected from the periphery arrives earlier in the central aorta, because of an increased transmission of both the waves; this event results in an augmented pressure in late systole. Consequently, augmentation of central aortic pressure is a sign of early wave reflection, and it is evident in the graphic of aortic waveform as the boost of pressure from the shoulder of the first wave to the peak. We can identify this event in absolute terms, e.g. augmented pressure (AP), or as a percentage of the pulse pressure (AIx). AIx, when determined invasively, serves as a predictor of coronary artery disease [13, 14].

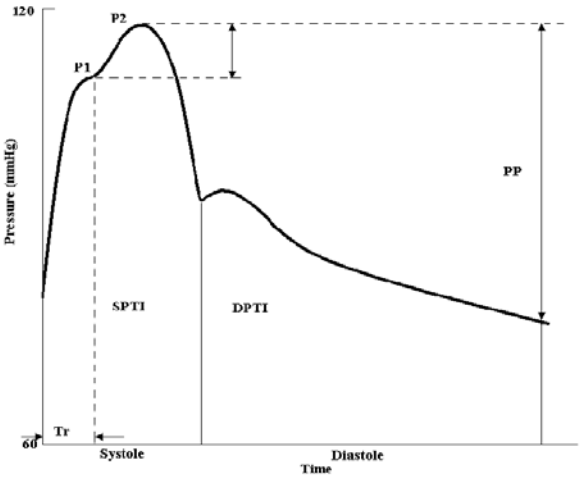

Fig. 1. Representative ascending aortic pressure time curve, as determined by pulse wave analysis. The AIx is defined as the difference between the second and first systolic peak (P2-P1), expressed as a percentage of the pulse pressure. AIx is usually negative in young healthy subjects, about zero at the age of 35 and becomes increasingly positive thereafter. The *SPTI* and *DPTI* represent the area under the curve during systole and diastole, respectively. Tr is the time interval from start of systole until the beginning of the augmented wave, that is, the travel time of the augmented wave [2]

Isolated systolic hypertension, can be considered an important predictor of cardiovascular morbidity. Solomon et al. [16] found that isolated systolic hypertension corresponds to an increased perioperative risk of 40% for adverse outcomes after coronary artery bypass grafting; the adjusted value of the risk is 30%.

In patients with end-stage renal disease who are undergoing haemodialysis, the disappearance of pulse pressure amplification is a classical consequence of the age-induced increase in arterial stiffness, and the altered wave reflection is a significant predictor of mortality [17].

In a univariate analysis of 465 symptomatic patients undergoing coronary angiography, higher AIx was associated with an increased risk for coronary disease. In a multivariate analysis, after controlling for age, height, presence of hypertension, HDL cholesterol and medications, the association with coronary artery disease risk remained significant. The results were exclusively driven by an increased risk of premature vessel stiffening in the younger patient group, with an unadjusted OR between AIx quartiles and IV of 8.25 and a multiple adjusted OR between quartile of 16.81[12].

Arterial stiffness was assessed non-invasively in related studies using the Sphygmocore (PWV Medical, Sydney, Australia). In brief, peripheral pressure waveforms were recorded from the radial artery at the wrist, using applanation tonometry with a high-fidelity micromanometer. Central aortic pressure can be evaluated accurately applying a mathematical transforming factor to the radial artery waveform [12, 18].

Soderstrom et al. [19] found that, in elderly patients undergoing coronary artery bypass grafting, a clear correlation was found not only between the AI in radial artery (RaAI) and aortic pulse pressure but also between the RaAI and changes in the systolic pressure gradient from the aorta to radial artery. Changes in RaAI, during mechanical ventilation are mainly a result of cyclic changes in stroke volume and are seldom associated with an increased systolic pressure gradient from aorta to radial artery.

Arterial pulse contour analysis has been used to calculate stroke volume and its change during mechanical ventilation; calculating the stroke volume variation (SVV) or arterial pulse pressure variation (PPV) allows preload responsiveness to be determined [20].

In the management of haemodynamically unstable patients, inappropriate or delayed treatment can increase the risk of mortality and morbidity. Arterial pulse contour analysis is very promising in these patients for several reasons: first, cardiac output changes can be calculated and serve as a guide to assessing global cardiovascular responsiveness to vasoactive therapies, e.g. fluid resuscitation or inotrope infusions; second, since the ratio of PPV to SVV reflects central capacitor tone and because the ratio of mean arterial blood pressure changes to SVV reflects arterial tone, these ratios could be used to continuously monitor arterial tone, a major determinant of cardiovascular performance.

Finally, by noting the product of maximal pressure-to-stroke volume ranges over a breath, the operative cardiac power range, a primary output measure of ventricular pump function, could be determined [21].

However, this approach has been criticized for the following reasons: (1) positive pressure ventilation alters the arterial pressure power spectrum in the time domain, inducing phase-dependent changes in arterial impedance [21]. (2) Furthermore, Denault et al. [22] demonstrated that, in cardiac surgery patients, this power variation might exceed the actual change in left ventricular stroke volume. Because the use of SVV assumes both accurate measurement of mean stroke volume and its degree of variation over a breath, both of which are important for the assessments of haemodynamic instability, until validation studies document its accuracy under specifical clinical conditions, such as exemplified in the study of Wiesenak et al. [23] the use of arterial pulse contour-derived SVV for clinical decision-making cannot be recommended.

Many frequency-dependent models to determine the aortic waveform derived from the brachial pressure and from the finger to brachial pressure were proposed in the past. Instead, Romano et al. [24] have described the use of an ARX filter in order to obtain the aortic waveform from the finger waveform over time with a 1-kHz sampling frequency.

This point-by-point reconstruction of aortic waveform from the peripheral one is the basis for evaluating impedance, which is necessary to calculate stroke volume (SV). If this evaluation is done with fixed impedance, for example with a calibration model or using precalculated parameters from other patients, the reconstruction from the aortic wave will be less accurate. Romano et al. [24] used simultaneous aorta and finger pressures of 123 beats in 41 cardiopathic patients. From each beat,

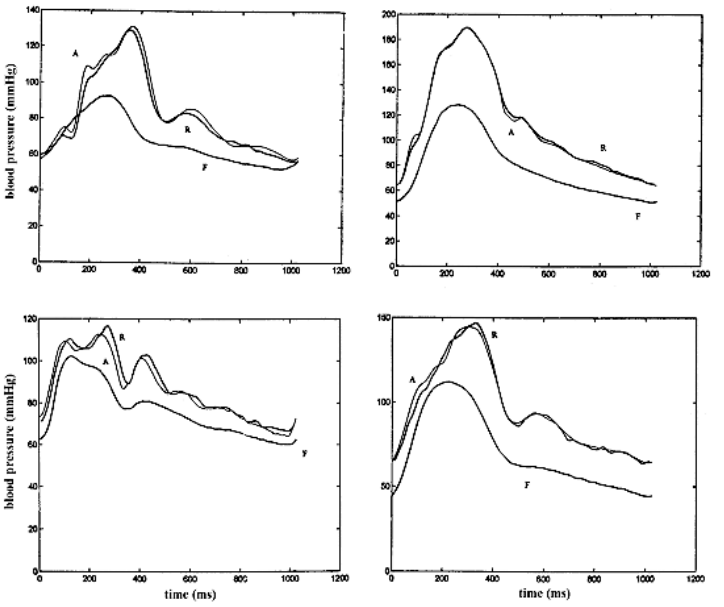

Fig. 2. Waveform reconstructed (*R*) from the finger pressure (*F*), and waveform measured invasively in the ascending aorta (*A*). The subjects age from left to right and top to bottom are 40, 59, 60 and 77 years old

samples were interpolated on a 1024-point grid. For each point a linear multiple regression was calculated in order to reconstruct the single aorta point derived from the finger pulse. Comparing the different levels between the aortic and the finger pressures it was found that the reconstruction with respect to time was very accurate.

The pulse contour method (PCM), unlike thermodilution, which measure CO over a limited time span, operates on a beat-to-beat basis and, for this reason, could be suitable for the continuous monitoring of CO. PCM is based on the main assumption that the pressure rise during systole is related to the systolic filling of the aorta and proximal large arteries. Various models of the arterial system have been devised to approximate the relationship between arterial pressure and flow. The most common PCM approach relies on the aortic-pressure/cross-sectional-area relationship modelled from unrelated in vitro measurements on segments of human thoracic aorta. PCM can monitor CO changes over prolonged periods of time either from the pressure signal recorded in a systemic artery or from that detected non-invasively at the finger. To obtain absolute values of CO, it is, however, necessary to determine, at least once for each patient, a calibrating factor of the model parameters by comparison of the PCM result with an absolute CO estimate. This greatly limits the usefulness of PCM, since the calibrating technique

is either invasive (e.g. thermodilution) or cumbersome (e.g. inert-gas rebreathing), and it must be repeatedly applied when changes in the experimental procedure that may alter the physical properties of the arteries are induced [24-27].

The pressure recording analytical method (PRAM) is a new for real-time beat-to-beat quantification of peripheral flow, based on the analysis of arterial waveform morphology [24]. The concept behind PRAM is the practical application of a theoretical model totally developed a priori, and requiring no retrospective adjustments whatsoever. The concept behind PRAM is based on the physical theory of perturbations, by which each physical system under the effects of a perturbing term tends to react in order to reacquire its own condition of stability, i.e. the situation of minimal energy required.

In PRAM, the entire systolic area below the pressure curve is measured at each cardiac cycle. Simultaneously, Z is directly obtained based on the morphology of both the pulsatory and the continuous contributions to the SV, with no need for predicted data or calibrating factors [24]. Giomarelli et al. [1], in a small series of homogeneous patients undergoing coronary artery bypass grafting, have demonstrated good agreement between PRAM and thermodilution. PRAM has shown to be accurate for real-time monitoring of cardiac output, during cardiac surgery and in the intensive care unit, despite variations of arterial pressure profile caused by temperature changes, inotropic or vasodilator drugs or the use of an arterial line for blood sampling. In conclusion, this method seems a practical alternative to the traditional ones when the indwelling of a pulmonary artery catheter is deemed

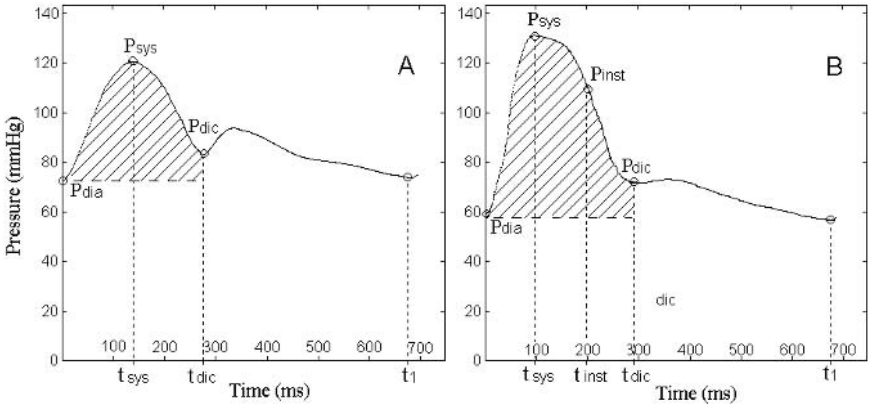

Fig. 3. Typical experimentally determined pressure waves recorded from the catheter in ascending aorta (**A**) and using a photoplethysmographic probe at the finger (**B**). The pressure waveforms were obtained from the same heartbeat in a 70-year-old man with dilated cardiomiopathy. The finger pressure curve is more distorted and shows a point of instability between peak systolic pressure and the pressure at the dicrotic notch. *t1* Total duration of cardiac cycle, *t inst* instability time. The *dashed areas* in **A** and **B** represent the integral of the pulsatile systolic portion of the pressure wave used for the computation of the stroke volume by the pulse contour method. The entire area under the systolic contour is included in the computation by the pressure recording analytical method (PRAM) [24]

harmful or not essential for clinical management. In addition, because of a point-to-point reconstruction of the aortic waveform, it allows SV to be calculated with no other prefixed parameters and avoids the inaccuracies derived from patient variability and from instant variations of impedance [28].

References

1. Giomarelli P, Biagioli B, Scolletta S (2004) Cardiac output monitoring by pressure recording analytical method in cardiac surgery. Eur J Cardiothorac Surg 26:115-120
2. Klocke R, Cockcroft JR, Taylor GJ et al (2003) Arterial stiffness and central blood pressure, as determined by pulse wave analysis, in rheumatoid arthritis. Ann Rheum Dis 62:414-418
3. Franklin SS, Khan SA,Wong N et al (2001) Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham Heart study. Circulation.103:1245-1249
4. Nichols WW, O'Rourke MF (1997) McDonald's blood flow in arteries. 4th edn. Arnold, London
5. Pauca AL, Wallenhaupt SL, Kon ND, et al (1992) Does radial artery pressure accurately reflect aortic pressure? Chest 102:1193-1198
6. Moffit EA, Sethna DH, Gray RJ et al (1984) Rate pressure product correlates poorly with myocardial oxygen consumption during anaesthesia in coronary patients. Can Anaesth Soc J 31:5-12
7. Chen CH, Ting CT, Lin SJ et al (1995) Different effects of fosinopril and atenolol on wave reflections in hypertensive patients. Hypertension 25:1034-1041
8. Mitchell GF, Pfeffer MA, Finn PV et al (1996) Equipotent antihipertensive agents variously effect pulsatile hemodinamics and aggression of cardiac hypertrophy in spontaneously hypertensive rats. Circulation 94:2923-2929
9. Arnett DK, Evans GW, Riley WA (1994) Arterial stiffness:- a new cardiovascular risk factor? Am J Epidemiol 140:669-682
10. Franklin SS, Khan SA,Wong N D et al (1999) Is pulse pressure useful in predicting risk for coronary artery disease? The Framingham Heart study. Circulation 100:354-360
11. O'Rourke MF, (1999) Wave travel and reflection in the arterial system. J Hypertens 17(suppl 5):S45-S47
12. Weber T, Auer J, O'Rourke MF et al (2003) Arterial stiffness, wave reflection, and the risk of coronary artery disease. Circulation 109:184-189
13. Nichols WW, Singh BM (2002) Augmentation index as a measure of peripheral vascular disease state. Curr Opin Cardiol 17:543-551
14. O'Rourke MF, Mancia G (1999) Arterial stiffness. J Hypertension 17:1-4
15. Hayashi T, Nakayama Y, Tsumura K et al (2002) Reflection in the arterial system and the risk of coronary heart disease. Am J Hypertens 15:405-409
16. Solomon A, Boisvert D, Lapp W et al (2002) Isolated systolic hypertension is associated with adverse outcomes from coronary artery bypass grafting surgery. Anesth Analg 94:1079-1084
17. Safar ME, Blacher J, Pannier B et al (2002) Central pulse pressure and mortality in end-stage renal disease. Hypertension 39:735-738
18. Chen CH, Nevo H, Fetics B et al (1997) Estimation of central aortic pressure waveform by mathematical transformation of radial tonometry pressure. Circulation 95:1827-1836

19. Sodestrom S, Sellgren J, Aneman A et al (2002) Interpretation of radial pulse contour during fentanyl/nitrous oxide anesthesia and mechanical ventilation. Acta Anest Scand 46:866-874
20. Michard F, Chemia D, Richard C et al (1999) Clinical use of respiratory change in arterial pulse pressure to monitor haemodynamic effects of PEEP. Am J Respir Crit Care Med 159:935-939
21. Pinsky MR (2003) Probing the limits of arterial pulse contour analysis to predict preload responsivness. Anest. Analg 96:1245-1247
22. Denault AY, Gasior TA, Goresan J et al (1999) Determinants of aortic pressure variation during positive-pressure ventilation in men. Chest 116:176-186
23. Wiesenak C, Prasser C, Rodig G et al (1996) Stroke volume variation as a continuous parameter of cardiac preload using pulse contour analysis in mechanically ventilated patients. Anest Analg 96:1254-7
24. Romano SM, Pistolesi M (2002) Assessment of cardiac output from systemic arterial pressure in humans. Crit Care Med 30:8
25. Alderman EL, Branzi A, Sanders W et al (1972) Evaluation of the pulse-contour method of determining stroke volume in man. Circulation 46:546-558
26. Wesseling KH, Jansen JRC, Settels JJ et al (1993) Computation of aortic flow from pressure in humans using a nonlinear, three-element model. J Appl Physiol 74:2566-2573
27. Jansen JRC, Wesseling KH, Settels JJ et al (1990) Continuous cardiac output monitoring by pulse contour during cardiac surgery. Eur Heart J 11(Suppl I): 26-32
28. Romano SM, Lazzeri C, Chiosti M et al (in press) Beat to beat analysis of pressure wave morphology for pre-symptomatic detection of orthostatic intolerance head-up tilt. JACC

Chapter 38

Beat-by-beat monitoring of cardiac output with pressure recording analytical method

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Intermittent thermodilution is the most widely employed clinical method for the assessment of cardiac output (CO) and derived parameters. According to the hypothesis that continuous monitoring of CO during cardiac surgery could allow the detection of sudden haemodynamic changes that may influence patients management and outcome [1–4], different approaches, such as continuous thermodilution [5, 6], the pulse contour method [7], bioimpedance [8] and several Doppler ultrasonographic techniques [9, 10] have been used lately. Although CO cannot be measured continuously by intermittent bolus thermodilution (CO TD), this is still the standard reference method for validation and/or calibration of all other methodologies.

The thermodilution method [11] requires that several conditions are met, such as complete mixing of the thermal indicator with blood, no loss of indicator within the dilution volume and constant blood flow during the dilution time [12]. If these are not consistently met, as can occur in many clinical conditions, this will lead to inaccuracy in CO measurements. In particular, variability of blood flow can result from haemodynamic instability related to changes in heart rate, cardiac arrhythmias, valvular or congenital heart disease and mechanical ventilation [13–16].

The pulse contour method (PCM), unlike thermodilution, which measures CO over a limited time span, operates on a beat-to-beat basis, which means it could be suitable for continuous monitoring of CO. PCM is based on the main assumption that the pressure rise during systole is related to the systolic filling of the aorta and proximal large arteries [17–21]. Various models of the arterial system have been devised to approximate the relationship between arterial pressure and flow [22–25]. The most frequently used PCM approach [26] relies on the aortic pressure–cross-sectional area relationship that is modelled from unrelated in vitro measurements on segments of human thoracic aorta [27]. PCM can monitor CO changes over prolonged periods of time, either from the pressure signal recorded in a systemic artery [26, 28–31] or from that detected noninvasively at the finger [32–34]. To obtain absolute values of CO, it is, however, necessary to determine a calibrating factor of the model parameters at least once for each patient, by comparison of the PCM result with an absolute CO estimate. This greatly limits the usefulness of PCM, since the calibrating technique is either invasive (e.g. thermodilution) or cumbersome (e.g. inert gas rebreathing) and it must be applied repeatedly when changes in the experimental procedure that might alter the physical properties of the

arteries are induced [33, 35]. Recently, a less invasive method has been developed: beat-to-beat values of CO can be obtained by a pressure recording analytical method (PRAM) [36]. This new method is based on mathematical analysis of the arterial pressure profile changes. It allows beat-by-beat stroke volume (SV) assessment from the pressure signal recorded in the radial artery [37].

Basic physical principles of PRAM

Changes in volume, which occur in all arterial vessels, are mostly due to wall radial expansion in response to blood pressure changes. Such expansion depends on various physical factors, such as the force of cardiac contraction, the arterial impedance and compliance, and the peripheral vascular resistance. These variables are closely interdependent and need to be evaluated at the same time. To this end, a variable called Z, aimed at representation of the relationship between changes in pressure and changes in volume with time, is taken into account for the evaluation of SV in the various approaches to determine CO by PCMs. The conversion of pulse pressure to SV is obtained by calculating the area under the pulsatile portion of the pressure wave, and Z (mmHg $\times$ s/cm^3) is calculated as a dimensional factor retrospectively approximated from the results of in vitro experiments or by calibration with an independent measure of SV (i.e. thermodilution bolus).

At variance with other PCMs, PRAM is the practical application of a model developed completely a priori and with no requirement for retrospective adjustments [36]. This new method was developed a few years ago by Romano, a physicist doctor from University of Florence. With Romano's method, the whole area under the pressure curve is measured in each cardiac cycle rather than the pulsatile systolic part. At the same time, Z is obtained directly by morphological analysis of both the pulsatile and continuous components of the pressure waveform, without the use of predicted data or calibration factors.

Briefly, according to PRAM [36], Z is equal to $(P/t) \times K$, and SV (cm^3) is calculated as follows:

$$SV = \frac{A}{P/t \times K}$$

where:

A (mmHg $\times$ s) is the whole of the area under the systolic portion of the pressure curve; P/t (mmHg/s) is the analytical description of the pressure wave profile expressed as the variations in pressure (P) over time (t) during the entire cardiac cycle (systolic and diastolic portion); and K is a dimensional factor inversely related to the instantaneous acceleration of the vessel cross-sectional area (s^2/cm) $\times$ (1/cm^2). The value of K is obtained from the ratio between expected and measured mean blood pressure. The numerator of the relationship is constant (theoretical mean value), and the denominator is measured. As a consequence, K can change from one cardiac cycle to another and the constant value at the numerator is taken as a reference to gauge the deviation of the mean arterial pressure from normality. Because mean arterial pressure is lower at the peripheral level with respect to

central arteries, Romano uses two different values of expected mean pressure for computation of *K* at the central (aorta) and peripheral levels (e.g. radial) for PRAM, namely the values originally indicated by Burton [38] and Guyton [39] (i.e. 100 mm Hg at the central and 90 mmHg at the peripheral level). Since PRAM allows the use of two proper algorithms for central or peripheral artery to obtain SV for each cardiac cycle, we were able to monitor cardiac output by applying the proper formula (i.e. expected mean value = 90 mmHg) for radial artery [37]. The *A*, *P*/*t* and *K* variables are closely interdependent in each cardiac cycle [36].

Objective

This paper describes the usefulness of PRAM in cardiac surgery and the comparison of CO values obtained by PRAM with those obtained simultaneously by the intermittent bolus thermodilution method (CO TD) in the course of cardiac surgery with extracorporeal circulation (ECC).

Materials and methods

Patients

A total of 30 patients (19 male, 11 female; mean age 67±4 years) undergoing elective coronary artery bypass grafting (CABG) with ECC were enrolled in a study designed to assess the accuracy and reliability of PRAM in the clinical setting. A Cleveland Clinic Score in excess of 4 was an exclusion criterion. We also excluded patients with valvular heart disease or contraindications to the use of a pulmonary artery catheter (PAC) and those with known peripheral vascular disease. Written informed consent was obtained from all patients after approval of the study by the Institutional Review Board. Standardised pre- and postoperative management and cardiopulmonary bypass conduction were performed [40].

PRAM data acquisition

Two standard arterial catheters (20 G or 18 G) were inserted into the radial and femoral arteries. A 150-cm Baxter pressure tube connection and a Baxter Truwave PX-600F transducer (Baxter-Edwards, Irvine, Calif.) were connected to the two parametric modules of the monitoring system (Hewlett Packard, Andover, Mass.) for continuous simultaneous recording of the systemic arterial pressure waves from the radial and femoral arteries and the subsequent computation of CO PRAM-rad (at radial artery) and CO PRAM-fem (at femoral artery). The pressure signals were acquired at 1000 Hz by means of an analogue-digital multifunction card (DAQ Card-700, National Instruments Corp., Austin, Tex.). All the signals were recorded on a personal computer (Acer, TravelMate 507-DX, Taipei Hsien, Taiwan, ROC). The computed values of CO PRAM-rad were displayed in real time

by the dedicated software. The corresponding waves were recorded and stored for subsequent computations and comparison with the results of thermodilution. An event marker on the pressure recordings was used to identify the start of each thermal bolus injection. PRAM provided arterial pressure values and beat-by-beat CO data continuously throughout the study (Fig. 1).

Thermodilution data acquisition

After induction of anaesthesia, a thermodilution pulmonary artery catheter (7F Baxter-Edwards, Irvine, Calif.) was inserted into the right internal jugular vein and advanced through the right atrium and right ventricle into the pulmonary artery

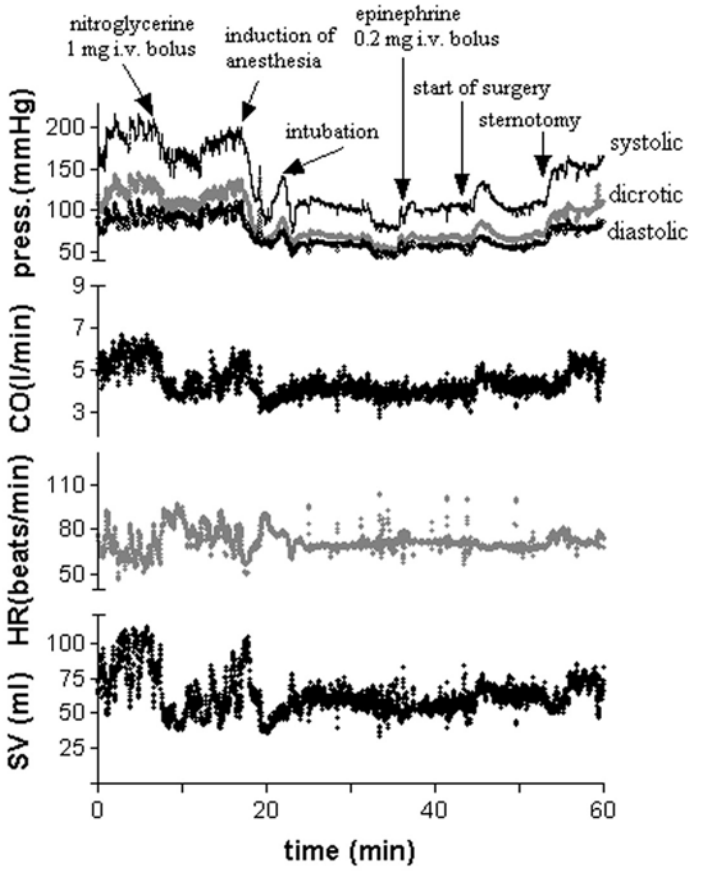

Fig. 1. Recording of haemodynamic parameters during the first hour of surgery by pressure recording analytical method (PRAM). Recording starts at the induction of anaesthesia and ends around 5 min after sternotomy. Systolic, diastolic and dicrotic pressures, cardiac output (*CO*), heart rate (*HR*) and stroke volume (*SV*) changes due to drugs administration and surgical or anaesthesiological procedures are recorded beat by beat by PRAM

so that wedge pressure was achieved with balloon inflation of 1–1.5 ml air. CO was measured by the pulmonary artery temperature variation analysis after the rapid injection of 10 ml of cold 5% glucose cold solution. To minimise the noise and variability within data, in all instances the bolus injections were given by the same individual at end-expiration. To improve haemodynamic stability, major surgery was suspended during CO determinations and bolus administration was never attempted when dysrhythmia was recorded. In the absence of haemodynamic stability the series of CO measurements was discarded and repeated until satisfactory measurements were obtained.

Study intervals

All determinations of CO were carried out on four separate occasions: 15 min after induction of anaesthesia (T1), 30 min after ECC (T2), and 1 and 3 h after arrival in the intensive care unit (ICU) (T3 and T4, respectively).

Statistical analysis

A paired-sample t-test was used to ascertain differences between values obtained by ThD-CO and by PRAM-CO at each time point. Differences were considered statistically significant at p=0.05. For further comparison of data acquired by the two techniques, concordance correlations were calculated. Finally, the agreement between different measurements of CO was assessed using the Bland-Altman procedure; this one takes into account the fact that neither modality being compared is the de facto gold standard [41].

Table 1. Cardiac output values, correlations and agreement between thermodilution and pressure recording analytical method (*PRAM*) (*ThD-CO* cardiac output by thermodilution, *PRAM-CO* cardiac output by PRAM, *SD* standard deviation, *MAP* mean arterial pressure, *HR* heart rate)

	T1[a]	T2[a]	T3[a]	T4[a]
ThD-CO (l/min) (mean±SD)	3.8±0.6	4.0±0.8	4.3±0.7	4.0±0.5
PRAM-CO (l/min) (mean±SD)	3.9±0.5	4.1±0.6	4.4±0.8	4.1±0.7
ThD-CO vs PRAM-CO				
R^2 (Pearson)	0.83	0.71	0.76	0.87
Bias, SD;	0.02, 0.61	−0.40, 0.59	0.03, 0.85	0.01, 0.33
Limits of agreement	−1.19+1.23	−1.58+0.78	−1.68 +1.75	−0.57 +0.75
MAP (mmHg) (mean±SD)	86.4±13.1	83.3±8.7	87.4±11.1	87.3±6.5
HR (b/min) (mean±SD)	68.1±12.4	91.7±11.1	91.5±12.0	90.4±8.7

[a]T1 15 min after induction of anaesthesia, T2 30 min after cardiopulmonary bypass, T3 1 h after ICU admission, T4 3 h after ICU admission

Results

A total of 120 measurements were obtained. All patients remained haemodynamically stable throughout the study period. CO values (range 2.2–7.5 l/min) were successfully collected by both ThD and PRAM at all predetermined points in the study for each patient. CO values and correlations between ThD and PRAM at all time points are presented in Table 1. Distribution of the differences in CO values was normal, and no significant differences were noted between evaluations made with the two methods at any point of the study according to the paired-sample t-test. Overall, a good linear correlation (R^2=0.79) was found between CO-ThD and PRAM-CO (Fig. 2a). Bland-Altman analyses demonstrated good agreement between measurements obtained by PRAM and ThD at each time point (data shown in Table 1) and for all the data collected (Fig. 2b). The highest degree of correlation (R^2=0.87) between ThD-CO and PRAM-CO was obtained at T4 (3 h after arrival in

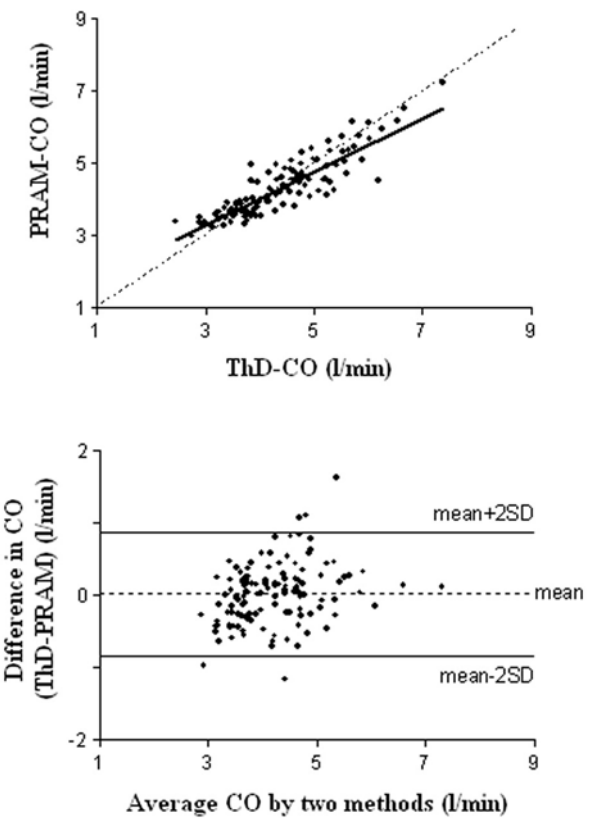

Fig. 2a. Correlation of CO values collected at all time-points by ThD-CO and PRAM-CO; (R^2=0.79; *p*.001).

Fig. 2b. Corresponding Bland-Altman analysis (mean = 0.027; standard deviation (*SD*) = 0.43; mean±2SD, limits of agreement = –0.83 and +0.89)

ICU). Conversely, a lower degree of correlation (R^2=0.71) was observed at T2 (Table 1). In this phase (30 min after ECC), a tendency to loss of agreement was noted at extreme values of ThD-CO: PRAM seemed to overestimate CO when it was very low and to underestimate CO when it was high. An excellent correlation was found between PRAM-rad and PRAM-fem CO values (R^2=0.96). It is noteworthy that PRAM provided a real-time estimate of the combined cardiac and pump flow during weaning from ECC following aortic declamping and resumption of cardiac function. Calculation of the difference between total output indicated by PRAM and the instantaneous pump readings made it easy to estimate the cardiac contribution to flow at any given time. Two patterns of adaptation to weaning were observed: in 24 patients (80%) CO remained substantially stable (i.e. lessened by no more than 10% compared with the steady ECC phase; Fig. 3a); in 6 patients (20%) CO fell markedly, by more than 10% in all these patients, and by as much as 38% (Fig. 3b). All patients were extubated within 9 h of arriving in the ICU (6.6±1.4 h). The duration of stay in the ICU was 22.7±0.4 h. There were no major postoperative complications in any patient up to discharge from hospital, and none of the patients experienced adverse events related to the use of the PAC.

Comment

Surgeons and anaesthesiologists have become increasingly concerned to identify a less invasive means of monitoring cardiac performance in patients. It has recently been shown that beat-to-beat absolute values of CO, which compare favourably

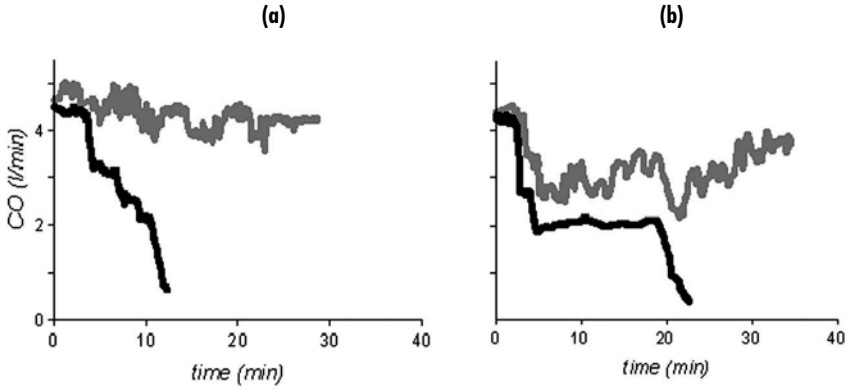

Fig. 3a. Patterns of cardiac adaptation to weaning from extracorporeal circulation (*ECC*) recorded by PRAM. **A**. Rapid and stable recovery of cardiac output (*grey line*) following reduction of pump-infused volumes (*black line*).

Fig. 3b. Marked fall in CO (*grey line*) following reduction of pump-infused volumes (*black line*), requiring longer weaning time

with those obtained by direct oxygen Fick and thermodilution methods, can be obtained by pressure recording analytical method (PRAM) [36, 37].

The concept behind the measurement and monitoring of CO based on the analysis of the arterial blood pressure waveform is not new. Similar approaches have been studied by several authors in the course of the last three decades, and have led to the development of important clinical applications (e.g. PiCCO system, LiDCO system, Modelflow method) [7, 26, 42]. However, the PiCCO system does not start without a thermodilution CO; moreover, even if both the LiDCO system and the Modelflow methods start pulse contour CO computations directly after connection to a radial artery pressure signal with a trending of CO, these two methods have a higher accuracy only when age and sex and external calibration data are taken into account. This means that the evaluation of CO is bound up more with either predicted values for age and sex that do not directly pertain to the subject under scrutiny or with a previously measured calibrating factor, rather than depending on the actual pressure wave morphology at the time of SV determination. In contrast, PRAM can measure absolute values of SV independently of calibration by determining parameters that are able to characterise the elastic properties of the arteries, such as time to peak of the systolic curve, presence of sudden slope changes, and length of the diastolic phase from the objective analysis of the pressure wave profile [36].

CO estimates obtained by PRAM during cardiac surgery show good agreement with those simultaneously obtained by conventional bolus thermodilution. Over the intervals studied, no significant differences between these two techniques emerged. This similarity persisted despite changes in volume infusions and losses; vascular resistance and arterial compliance; the use of vasoactive drugs; and the use of arterial line for blood sampling. PRAM seemed to overestimate lower values and underestimate higher values of ThD-CO in the T2 phase (30 min after ECC). Besides the possibility of inaccuracy of PRAM, we also considered the hypothesis that this result may be due to a loss of reliability of ThD, which would be possible after the end of ECC [43, 44]. In fact, patients subjected to ECC may show a transient increase in the magnitude of respiratory variations in pulmonary artery blood temperature after ECC, and this increased 'thermal noise' has been cited as a potential source of significant error in ThD measurements within the first 30–45 min after ECC [2, 13, 45, 46]. Unfortunately, this interpretation cannot be demonstrated in the absence of a third method or a gold standard that is superior to ThD, and we cannot offer a definitive explanation of the discrepancy between PRAM and ThD after the end of ECC. Besides, several factors may intervene to exert a negative effect on the performance of thermodilution [47–52]. We believe that the most important problem is the possibility that neither thermodilution methods nor other temperature-dependent devices reflect the true CO in the early phase after hypothermic ECC, which may result in wrong decisions being made on therapy.

The capability offered by PRAM of providing real-time beat-to-beat information proved particularly relevant at the time of weaning from ECC, which is usually one of the most critical phases for patients undergoing cardiac surgery. During this phase, as spontaneous cardiac contractility is gradually restored the contribution

of the roller pump to flow is progressively reduced and finally interrupted. Occasionally, the transition from artificial to spontaneous flow following aortic declamping is characterised by marked haemodynamic instability and low CO, which may require longer weaning times and inotropic or mechanical support.

With PRAM, we were able to identify two patterns of cardiac response during the weaning phase from ECC: whereas most patients showed stable values of CO following reduction of pump flow, one-fifth showed a sharp decline, by percentages in excess of 10 and up to almost 40, requiring longer weaning times. Continuous monitoring of output by PRAM at the end of ECC might thus prove valuable in identifying patients at risk of developing a low-flow state and may represent a useful guide for the titration of drugs during weaning.

Generally, PCMs may have some advantages over PAC-derived thermodilution measurements. (1) Measurement of CO by PRAM does not depend on specific assumptions about haemodynamic and/or thermal conditions, but on the objective analytical measurement of numerical parameters, reflecting the relationship between arterial pressure and flow derived from the pressure curve profile. (2) PRAM does not require external calibration by thermodilution or any other additional invasive procedures (a central line can be avoided completely), which both waves time and avoids potential complications [36]. (3) Finally, because PCMs provide a beat-to-beat readout, abrupt changes in CO resulting from blood loss, tamponade or changes in arterial resistance may be detected more quickly [53] (Fig. 1 is an example of a beat-to-beat recording started before the induction of anaesthesia and showing haemodynamic changes).

The limitations of this study are the enrolment only of patients at low risk and the very homogeneous population of patients. The patients in whom such monitoring is needed are a heterogeneous population of high-risk patients, which dictates the availability of significant variability in the surgical and anaesthesiological management, and careful haemodynamic control because of the likelihood of sudden haemodynamic changes.

In summary, further studies will be required to assess this method in heterogeneous and higher risk patients and in the setting of haemodynamic instability or arrhythmias. However, the results of this study show that absolute values of CO that compare favourably with those obtained by established methods, can be obtained on a beat-to-beat basis and for the desired length of time from the pressure signal recorded in the radial or the femoral artery. These results should be confirmed in a broader series of patients with various haemodynamic conditions and with clinically and experimentally induced haemodynamic transients in pressure and flow before we can consider the possibility of replacing the currently used methods for measuring CO with the method described in this paper. PRAM seems to be a practical alternative to the traditional ThD method in patients in whom an indwelling PAC is deemed harmful or not essential for clinical management.

References

1. Kirklin JR, McGiffin DC (1987) Early complications following cardiac surgery. Cardiovasc Clin 17:321-343
2. Dalen JE, Bone RC (1996) Is it time to pull the pulmonary artery catheter? JAMA 276:916-918
3. Polonen P, Ruokonen E, Hippelainer M et al (2000) A prospective, randomized study of goal-oriented hemodynamic therapy in cardiac surgical patients. Anesth Analg 90:1052-1059
4. Jansen JRC, Schreuder JJ, Mulier JP et al (2001) A comparison of cardiac output derived from the arterial pressure wave against thermodilution in cardiac surgery patients. Br J Anaesth 87:212-222
5. O'Malley P, Smith B, Hamlin R et al (2000) A comparison of bolus versus continuous cardiac output in an experimental model of heart failure. Crit Care Med 28:1985-1990
6. Singh A, Juneja R, Mehta Y et al (2002) Comparison of continuous, stat, and intermittent cardiac output measurements in patients undergoing minimally invasive direct coronary artery bypass surgery. J Cardiothorac Vasc Anesth 16:186-190
7. Gödje O, Hoke K, Goetz AE et al (2002) Reliability of a new algorithm for continuous cardiac output determination by pulse-contour analysis during hemodynamic instability. Crit Care Med 30:52-58
8. Donovan KD, Dobb GJ, Woods WP et al (1986) Comparison of transthoracic electrical impedance and thermodilution methods for measuring cardiac output. Crit Care Med 14:1038
9. Singer M (1993) Esophageal Doppler monitoring of aortic blood flow: beat-by-beat cardiac output monitoring. Int Anesthesiol Clin 31:99-125
10. Katz WE, Gasior TA, Quinlan JJ et al (1993) Transgastric continuous-wave Doppler to determine cardiac output. Am J Cardiol 71:853-857
11. Ganz W, Swan HJC (1972) Measurement of blood flow by thermodilution. Am J Cardiol 29:241-246
12. Hamilton WF, Moore JW, Kinsman JM et al (1932) Studies on the circulation. IV. Further analysis of the injection method, and of changes in hemodynamics under physiological and pathological conditions. Am J Physiol 99:534-551
13. Bassingthwaighte JB, Knopp TJ, Anderson DU (1970) Flow estimation indicator dilution (bolus injection). Reduction of errors due to time-averaged sampling during unsteady flow. Circ Res 27:277-291
14. Levett JM, Replogle RL (1979) Thermodilution cardiac output: a critical analysis and review of the literature. J Surg Res 27:392-404
15. Snyder JV, Powner DJ (1982) Effects of mechanical ventilation on the measurement of cardiac output by thermodilution. Crit Care Med 10:677-682
16. Jansen JRC, Schreuder JJ, Settels JJ et al (1996) Single injection thermodilution. A flow-corrected method. Anesthesiology 85:481-490
17. Frank O (1899) Die Grundform des arteriellen Pulses. Z Biol 37:483-526
18. Broemser P, Ranke OF (1930) Über die Messung des Schlagvolumens des Herzens auf unblutigem Weg. Z Biol 90:467-507
19. McDonald DA, Nichols WW (1973) Cardiac output derived from the time derivative and phase velocities of the aortic pressure wave. Med Biol Eng 11:678-690
20. Toorop GP, Westerhof N, Elzinga G (1987) Beat-to-beat estimation of peripheral resistance and arterial compliance during pressure transients. Am J Physiol Heart Circ Physiol 252:H1275-H1283

21. Burkhoff D, Alexander JJ, Schipke J (1988) Assessment of Windkessel as a model of aortic input impedance. Am J Physiol Heart Circ Physiol 255:H742-H753
22. Alderman EL, Branzi A, Sanders W et al (1972) Evaluation of the pulse-contour method of determining stroke volume in man. Circulation 46:546-558
23. Starmer CF, McHale PA, Cobb FR et al (1973) Evaluation of several methods for computing stroke volume from central aortic pressure. Circ Res 33:139-148
24. Tajimi T, Sunagawa K, Yamada A et al (1983) Evaluation of pulse contour methods in calculating stroke volume from pulmonary artery pressure curve (comparison with aortic pressure curve). Eur Heart J 4:502-511
25. Wesseling KH, De Wit B, Weber JAP et al (1983) A simple device for the continuous measurement of cardiac output. Its model basis and experimental verification. Adv Cardiol Phys 5 (Suppl II):16-52
26. Wesseling KH, Jansen JRC, Settels JJ et al (1993) Computation of aortic flow from pressure in humans using a nonlinear, three-element model. J Appl Physiol 74:2566-2573
27. Langewouters GJ, Wesseling KH, Goedhard WJA (1984) The static elastic properties of 45 human thoracic and 20 abdominal aortas in vitro and the parameters of a new model. J Biomech 17:425-435
28. Jansen JRC, Wesseling KH, Settels JJ et al (1990) Continuous cardiac output monitoring by pulse contour during cardiac surgery. Eur Heart J 11 (Suppl I):26-32
29. Sprangers RL, Wesseling KH, Imholz AL et al (1991) Initial blood pressure fall on stand up and exercise explained by changes in total peripheral resistance. J Appl Physiol 70:523-530
30. Jellema WT, Imholz BPM, van Goudoever J et al (1996) Finger arterial versus intrabrachial pressure and continuous cardiac output during head-up tilt testing in healthy subjects. Clin Sci 91:193-200
31. Stock WJ, Baisch F, Hillebrecht A et al (1993) Noninvasive cardiac output measurement by arterial pulse analysis compared to inert gas rebreathing. J Appl Physiol 74:2687-2693
32. Harms MPM, Wesseling KH, Pott F et al (1999) Continuous stroke volume monitoring by modelling flow from non-invasive measurement of arterial pressure in humans under orthostatic stress. Clin Sci 97:291-301
33. Houtman S, Oeseburg B, Hopman MTE (1999) Non-invasive cardiac output assessment during moderate exercise: pulse contour compared with CO_2 rebreathing. Clin Physiol 19:230-237
34. Jellema WT, Wesseling KH, Groeneveld ABJ et al (1999) Continuous cardiac output in septic shock by simulating a model of the aortic input impedance. A comparison with bolus injection thermodilution. Anesthesiology 90:1317-1328
35. Stock WJ, Stringer RCO, Karemaker JM (1999) Noninvasive cardiac output measurement in orthostasis: pulse contour analysis compared with acetylene rebreathing. J Appl Physiol 87:2266-2273
36. Romano SM, Pistolesi M (2002) Assessment of cardiac output from systemic arterial pressure in humans. Crit Care Med 30:1834-1841
37. Giomarelli P, Biagioli B, Scolletta S (2004) Cardiac output monitoring by pressure recording analytical method in cardiac surgery. Eur J Cardiothorac Surg 26:115-120
38. Burton AC, Hamilton WF (eds) (1961) Physical principles of circulatory phenomena: The physical equilibria of the heart and blood vessels. (Handbook of physiology) American Physiological Society, Washington
39. Guyton AC (1991) Textbook of physiology. Saunders, Philadelphia
40. Giomarelli P, Scolletta S, Borrelli E et al (2003) Myocardial and lung injury after cardiopulmonary bypass: role of interleukin (IL)-10. Ann Thorac Surg.76:117-123

41. Bland JM, Altman DG (1986) Statistical methods for assessing agreement between two methods of clinical measurement. Lancet I:307-310
42. Jonas MM, Tanser SJ (2002) Lithium dilution measurement of cardiac output and arterial pulse waveform analysis: an indicator dilution calibrated beat-by-beat system for continuous estimation of cardiac output. Curr Opin Crit Care 8:257-261
43. Bazaral MG, Petre J, Novoa R (1992) Errors in thermodilution cardiac output measurements caused by rapid pulmonary artery temperature decreases after cardiopulmonary by-pass. Anesthesiology 77:31-37
44. Latson TW, Whitthen CW, O'Flaherty D (1993) Ventilation, thermal noise, and errors in cardiac output measurements after cardiopulmonary bypass. Anesthesiology 79:1233-1243
45. Bottiger BW, Rauch H, Bohrer H et al (1995) Continuous versus intermittent cardiac output measurement in cardiac surgical patients undergoing hypothermic cardiopulmonary bypass. J Cardiothorac Vasc Anesth 9:405-411
46. Bottiger BW, Soder M, Rauch H et al (1996) Semi-continuous versus injectate cardiac output measurement in intensive care patients after cardiac surgery. Intensive Care Med 22:312-318
47. Rauch H, Muller M, Fleischer F et al (2002) Pulse contour analysis versus thermodilution in cardiac surgery patients. Acta Anaesthsiol Scand 46:424-429
48. van Grondelle A, Ditchey RV, Groves BM et al (1983) Thermodilution method overestimate low cardiac output in humans. Am J Physiol 245:H690-H692
49. Nishikawa T, Dohi S (1993) Errors in the measurements of cardiac output by thermodilution. Can J Anaesth 40:142-153
50. Sherman MS, Kosinski R, Paz HL et al (1997) Measuring cardiac output in critically ill patients: disagreement between thermodilution-, calculated-, expirated gas-, and oxygen consumption-based methods. Cardiology 88:19-25
51. Dhingra VK, Fenwick JC, Walley KR et al (2002) Lack of agreement between thermodilution and Fick cardiac output in critically ill patients. Chest 122:990-997
52. Gonzales J, Delafosse C, Fartouk M et al (2003) Comparison of bedside measurement of cardiac output with the thermodilution method and the Fick method in mechanically ventilated patients. Critical Care 7:171-178
53. Hamilton TT, Huber LM, Jessen ME (2002) Pulse CO: a less-invasive method to monitoring cardiac output from arterial pressure after cardiac surgery. Ann Thorac Surg 74:S1408-S1412

Chapter 39

Haemodynamic standardisation procedures in high-risk surgery

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During the perioperative period there are many situations that can affect the haemodynamic variables such as anaesthesia induction, hypovolaemia, bleeding, mechanical ventilation, and pain. Early detection of haemodynamic disturbances and treatment based on haemodynamic measurements improve the quality of care and might reduce complications in high-risk surgical patients [1].

A combination of blood pressure monitoring, ECG, pulse oximetry and capnography can recognise most cardiovascular complications associated with the perioperative period. However, in some groups of patients, advanced monitoring to access cardiovascular function and cardiac contractility might help to improve safety and outcome, and further studies are needed to identify criteria for the use of advanced monitoring in these patients [2].

The thermodilution technique using a pulmonary artery catheter is still a standard method of obtaining cardiac output and filling pressures. The assumption that the correlation of filling pressures and flow (cardiac output) is correct allows contractility to be based on the Starling curve. These physiological data represent the basis for pharmacological treatment in several clinical conditions. Cardiac output can also be obtained by means of oesophageal Doppler investigations. Introduced in the 1970s, this technique allows minimally invasive measurement of immediate blood flow velocity in the descending aorta, from which stroke volume and cardiac output can be calculated with acceptable consistency [3]. Measuring flow (cardiac output) is useful in surgical patients, because flow is a sensitive indicator of global cardiovascular performance. A reduction in cardiac output may be expected with a reduction in venous return resulting from hypovolaemia or vasoplegia or from true cardiac dysfunction. Most important in surgical patients, however, is that flow measurement allows the verification of cardiovascular responsiveness to fluid overload, since adequate preload to its maximal value has been proved to be of paramount importance for a favourable outcome in surgical patients [1].

Nevertheless, isolated filling pressure measurements may not be sufficient, and even when flow measurements are also available, pressure may depend on ventricular chamber compliance and is subject to the influence of mechanical ventilation. End-diastolic volume obtained by echocardiography instead of pressure, for instance, has been found more reliable than end-diastolic pressure in giving the real optimal cardiovascular preload.

The validity of functional cardiovascular monitoring, including measurement of volumetric variables for cardiac preload and cardiovascular filling status, has been confirmed during recent years [4].

Particularly for the management of high-risk patients scheduled for cardiac surgery, the determination of haemodynamic goals for the major haemodynamic variables such as preload, heart rate, systemic vascular resistance, pulmonary vascular resistance and contractility, is mostly emphasised. Patients who can be considered at high risk are those scheduled for surgery who have poor ventricular function, severe pulmonary hypertension, severe aortic stenosis, acute infective endocarditis with incarcerated sepsis, and/or acute mechanical complications of myocardial infarction, such as acute mitral insufficiency or acute intraventricular communication. Patients with acute aortic disease, such as any kind of aortic dissection that requires cardiopulmonary bypass, can also be included in this group. Unlike the situation in noncardiac surgery patients, these parameters depend on the type of cardiac disease and its pulmonary repercussions. When ventricular filling is impaired because of hypertrophy, the goals for preload are high filling pressures, adequate volume administration and avoidance of factors that decrease venous return. In the presence of severe heart dysfunction or pulmonary hypertension, vasoactive drugs should be judiciously tailored according to haemodynamic parameters. Heart rate must be maintained at low normal levels in patients with dynamic ventricular outflow obstructions (hypertrophic obstructive cardiomyopathy) to allow adequate filling and ejection. Systemic vascular resistance should be reduced in patients with mitral regurgitation, to promote forward ejection of blood, and it should be maintained, or even augmented, in patients with aortic stenosis, to provide adequate coronary artery blood flow. Patients who have coronary artery disease may have a normal ejection fraction, but in most cases they are receiving medication to reduce myocardial oxygen consumption. These agents are calcium or beta blockers, which act primarily by reducing contractility and heart rate. With this effect, the heart becomes very sensitive to abrupt changes in volaemia and even contractility, which may be altered by vasodilating agents or still boluses of anaesthetic agents used in anaesthetic induction. The matching of adequate preload to cardiac output during anaesthesia is a difficult task, especially in patients with systolic and diastolic dysfunction. Transoesophageal echocardiography could be regarded as the gold standard for evaluation of the ventricular end-diastolic chambers providing the parameters needed to optimise volaemia. A new generation of pulmonary catheters may offer an alternative to echocardiography by measuring end-diastolic volume of RV and ejection fraction [5].

This case report illustrates the importance of monitoring for early detection of haemodynamic disturbances and adequate treatment.

Case Report

A 54-year-old female patient was admitted to the hospital for an elective off-pump coronary artery bypass graft (OPCABG) surgery after a 2-week history of angina

pectoris. Her past medical history was significant for hypertension and hypercholesterolaemia. Her medications included aspirin, atenolol and synvastatin. Cardiac catheterisation showed a 50% stenosis at the proximal portion of the left anterior descending artery, severe stenosis of the circumflex artery, and 50% stenosis of the right coronary artery with hypertrophic ventricle with normal contractility. Preoperative laboratory testing showed normal results. A coronary artery bypass graft was scheduled for this patient.

On the day of surgery, oral midazolam 7.5 mg was given 30 min before the patient was taken into the operating room. For the OPCAB procedure, the anaesthetic regimen included induction of general anaesthesia with sufentanyl, propofol and atracurium. General anaesthesia was maintained with varying concentrations of isoflurane (0.7–0.9%), sufentanyl and atracurium. Monitoring was performed with a nasopharyngeal thermometer, 5-lead electrocardiography (with computerised ST-segment analysis), pulse oximetry, anaesthetic gas and end-tidal CO_2 analysers, invasive recording of arterial blood pressure by right radial artery cannulation, and continuous recording of cardiac output (CCO). The CCO measurement was obtained by insertion of a volumetric thermodilution catheter (CCOMBO/EDV) through the right internal jugular vein after induction, which was connected to a Vigilance monitor (Baxter Edwards Critical Care, Irvine, Calif., USA). The haemodynamic parameters are displayed in Table 1.

After the induction of anaesthesia, low values were observed for cardiac index and venous oxygen saturation. The filling pressures, PWCP and CVP, and RV end-diastolic volume (normal values: RV EDV 100-160 ml; RV EDVI 60–100 ml/m^2) were normal. Despite these normal values, volaemic expansion with 700 ml of hidroxyethyl starch 6% (450/0.7) was started and was completed in 1 h, resulting in improvement of cardiac output and venous oxygen saturation. As observed in Table 1, a minimal variation in PCWP and CVP occurred as well as that in RV end-diastolic volume. Nevertheless, a sharp increase in cardiac output was observed just after fluid infusion. Contrary to our expectations, the augmentation in cardiac output was not accompanied by a simultaneous and proportional increment in filling pressures and end-diastolic volume. These findings are in concordance with reports in the medical literature, showing that in most clinical situations there is no linear correlation between the end-diastolic pressure, represented by PCWP and CVP, and volume.

PWCP obtained from PAC is routinely used to guide fluid therapy. It should be appreciated, however, that at times this measurement correlates poorly with intravascular blood volume, particularly in patients with cardiovascular disease. Compliance of the ventricle itself can significantly alter the normal passive pressure–volume relationship. Decreased compliance (increased 'stiffness') of the myocardium increases left ventricular end-diastolic pressure at any end-diastolic volume. This being the case, pressure may not be a good indicator of ventricular volume status. Although the literature has shown that with this new generation of PAC there is a better correlation between that RV end-diastolic volume as preload and cardiac output, compared with traditional end-diastolic pressure indices, in our present case this was not observed. In this case, only RV ejection fraction and oxygen

Table 1. Haemodynamic data (*CO* cardiac output, *CI* cardiac index, *CPB* cardiopulmonary bypass, *CVP* central venous pressure, *HR* heart rate, *MAP* mean arterial pressure, *MPAP* mean pulmonary artery pressure, *PAOP* pulmonary artery occlusion pressure, *PVR* pulmonary vascular resistance, *SVRI* systemic vascular resistance, *LVSWI* left ventricular stroke work index, *RVSWI* right ventricular stroke work index, *EF* ejection fraction, *EDV* right ventricular end-diastolic volume, *EDVI* right ventricular end-diastolic volume index, SvO_2 oxygen venous saturation, O_2ER oxygen extraction ratio)

	After anaesthesia induction	Immediately after fluid infusion[a]	1 h after fluid infusion[a]
HR(min^{-1})	69	95	76
MAP (mmHg)	66	95	76
CVP (mmHg)	8	6	10
MPAP (mmHg)	16	17	19
PAOP (mmHg)	9	8	12
CO (l/min)	3.4	7.3	5.2
CI ($l\ min^{-1}\ m^{-2}$)	2.0	4.2	3.0
SVR ($dyn\ s^{-1}\ cm^{-5}$)	1365	1332	1707
PVR ($dyn\ s^{-1}\ cm^{-5}$)	165	171	187
LVSWI ($g\ m^{-1}\ m^2$)	22	41	33
RVSWI ($g\ m^{-1}\ m^2$)	3	7	5
EF 40–60%	28	41	37
EDVI 60–100 ml/m^2	115	120	107
EDV 100–160 ml	202	209	185
SvO_2	61	80	74.2
O_2ER (%)	21.3	29.7	16.9
VO_2I	76	200	78
DO_2I	357	674	459
Ht	37	35	33
Nitroprussate ($\mu g\ kg^{-1}\ min^{-1}$)		0.5	0.5
Nitroglycerin ($\mu g\ kg^{-1}\ min^{-1}$)		0.3	

[a]After infusion of 700ml of hydroxyethyl starch 6% (450/0.7)

venous saturation presented positive variation together with cardiac output after volaemic expansion [6].

Another interesting case that illustrates the importance of monitoring for detection of haemodynamic disturbances and adequate treatment was described by Rex et al. [7]. A 78-year-old female patient presented with a history of syncope and congestive heart failure. Cardiac catheterisation revealed severe aortic valve stenosis (aortic valve area 0.48 cm^2, mean pressure gradient 58 mmHg), mitral valve insufficiency (grade II), critical stenosis of the left main coronary artery, impaired left ventricular function, and hypokinesia of the anterior and apical left inferior wall. Furthermore, severe pulmonary hypertension was diagnosed (pulmonary artery pressure, 80/30 mmHg; mean pulmonary artery pressure, 65 mmHg; pulmonary artery occlusion pressure, 45 mmHg). Combined bivalve surgery and coronary artery bypass grafting were programmed for this patient. After the induction of anaesthesia, nitroglycerin was administered intravenously to decrease PVR; how-

ever, the nitroglycerin was not effective. After sternotomy, PVR increased, probably because of increased RV preload caused by the reduction in intrathoracic pressure. Therefore, 12.5 μg of aerosolised iloprost was administered over 15 min. The administration of iloprost significantly decreased pulmonary artery pressure and PVR and was accompanied by an increase in cardiac output. CPB was performed using moderate hypothermia (30°C), and cardioplegic arrest was instituted with 2 l crystalloid cardioplegia. The patient underwent aortic valve replacement, mitral valve repair and aortocoronary bypass grafting to the left anterior descending and circumflex arteries. The duration of ischaemia was 140 min. After 80 min of reperfusion, 12.5 μg of inhaled iloprost was again administered over 15 min. Weaning from CPB was completed after a reperfusion time of 97 min. Moderate doses of vasoactive agents were administered to achieve adequate haemodynamic parameters. Transoesophageal echocardiography showed an improvement in RV-function parameters after CPB: the RV-fractional area change increased from 18% (pre-CPB) to 38% (post-CPB). The patient was transferred to the intensive care unit, and endotracheal extubation was performed 13 h postoperatively.

Impaired RV function is associated with poor outcome in surgical and nonsurgical settings. Adequate treatment of RV failure requires various strategies. The main goal is to decrease RV afterload by using vasodilating agents. The use of intravenously administered vasodilators is limited, as they are not selective for the pulmonary circulation and often cause arterial hypotension. Therefore, the administration of selective pulmonary vasodilators such as inhaled nitric oxide (INO) and prostacyclin (PGI_2) may be beneficial.

Inhaled NO is a valuable agent in the treatment of patients with pulmonary hypertension and acute RV failure after cardiac surgery. The selective pulmonary vasodilatation reduces RV afterload, thereby improving RV ejection fraction and cardiac output, without decreasing SAP and jeopardising blood flow to major organs. Inhaled PGI_2 has similar effects on the pulmonary circulation, inducing relaxation of vascular smooth muscle. Potential advantages over INO are the lack of toxicity of PGI_2 or its metabolites and the inexpensive and readily available apparatus for the delivery of inhaled PGI_2 [8].

Iloprost is the stable carbacyclin derivative of PGI2. Studies examining the actions of inhaled iloprost have shown that it has comparable pulmonary haemodynamic effects to INO and PGI_2. Its advantages over PGI_2 include its solubility in saline, obviating the need for an alkaline buffer, lower viscosity, which aids nebulisation, and a significantly longer duration of action, permitting effective intermittent rather than continuous nebulisation. The plasma half-life of iloprost is 20–30 min, and the haemodynamic effects of a single inhaled dose last approximately 1 h [8].

The objective in the treatment of circulatory insufficiency is to restore oxygen delivery to tissues while correcting the underlying cause (e.g. surgical intervention to correct aortic dissection or eradicate infection presented in an infected valve or prosthesis). Delays in making the diagnosis and initiating treatment, and also suboptimal maintenance of circulation below optimal goals, contribute to the development of peripheral vascular failure and irreversible defects in oxygen use, which can culminate in vital organ dysfunction.

Preload optimisation is highlighted by some studies as an efficient way to increase cardiac output, and it is essential for restoring tissue perfusion. The circulating volume must be replaced within minutes, since rapid restoration of cardiac output and tissue perfusion pressure reduces the chances of serious organ damage, and especially acute renal failure [9].

As well as being fundamental to the management of hypovolaemic shock, replacement of the circulating volume is important in managing patients with impaired tissue perfusion from cardiogenic, distributive and obstructive causes. Adequate perioperative volume replacement also reduces morbidity and mortality in high-risk surgical patients.

If signs of peripheral oxygen utilisation are abnormal despite volume replacement, perfusion of vital organs is jeopardised, and inotropic or other vasoactive agents may then be given to improve cardiac output and blood pressure. In high-risk cardiac patients circulatory assistance by means of an intraaortic balloon pump (IAPB) or even by other methods should be considered. The effects of a particular drug in an individual patient are unpredictable, and the response must be closely monitored. In many cases, this requires pulmonary artery catheterisation. Some patients are given inotropes or vasopressors to restore cardiac output and blood pressure, while in others inodilators are used to redistribute blood flow, e.g. dopexamine to improve splanchnic perfusion and phosphodiesterase inhibitors to control RV dysfunction.

Although resuscitation has conventionally been aimed at achieving normal haemodynamic values, better survival of high-risk surgical patients is associated with raised values for cardiac output, oxygen delivery and oxygen consumption.

The literature has shown that raising these variables to supranormal values is associated with improved outcome in victims of major trauma and high-risk surgical patients. The benefit may be due mainly to optimal expansion of the circulating volume with consequent improvements in oxygen delivery and regional flow. The strategy has no benefit when it is started after admission to intensive care [10, 11].

In patients and/or those undergoing surgery associated with rapid haemodynamic changes, adequate haemodynamic monitoring should be available at all times. Although outcome changes are difficult to prove, it is reasonable to assume that appropriate haemodynamic monitoring is likely to reduce the incidence of major cardiovascular complications providing that the data obtained are interpreted correctly and therapeutic decisions are implemented promptly.

Standard monitoring for cardiac surgical patients includes blood pressure (BP), electrocardiogram (ECG), central venous pressure (CVP), urine output, temperature, capnometry, pulse oximetry and intermittent arterial blood gas analysis. Monitoring can also include use of pulmonary artery catheters (PAC), left atrial pressure catheters, thermodilution cardiac output (CO) measurements, echocardiography, and indices of tissue oxygen transport and consumption. All measurements and any derivatives from them should be interpreted by an anaesthesiologist who has expertise in cardiac thoracic anaesthesia and who is aware of the patient's overall condition and the limitations of these monitors.

Elelctrocardiography. The detection of myocardial ischaemia depends at least in part on the way the ECG is monitored. Myocardial ischaemia can be detected with quite low sensitivity when the common three-lead ECG is used, but sensitivity increases when the five-lead ECG is used and leads II and V5 are continuously monitored. However, there is only a moderate correlation between ECG abnormalities and new regional wall motion abnormalities detected echocardiographically as an early predictor of myocardial ischaemia, indicating that the ECG is a relatively nonspecific way of monitoring for myocardial ischaemia [12, 13].

Pressure. Pressure-based measurements are the most commonly used for assessment of the cardiovascular system. The magnitude of BP is directly related to the CO and the systemic vascular resistance, and mean arterial pressure is probably the most useful parameter to measure when assessing organ perfusion, except for the heart. Numerous methods of noninvasive BP measurement are clinically available, but direct intra-arterial monitoring is more suitable for cardiac surgery. In addition to providing a beat-to-beat indication of the arterial pressure, the arterial waveform tracing correlates with additional haemodynamic information [14].

Arterial catheters also provide a reliable method for obtaining arterial blood samples frequently, allowing proper management of blood gas, blood chemistry, and coagulation abnormalities.

The absolute value of pressure within a large intrathoracic vein is often not helpful, except in extreme hypovolaemia, fluid overload or heart failure. Correct interpretation requires assessment of the change in central venous pressure in response to a fluid challenge in conjunction with alterations in other monitored variables and clinical signs.

The introduction of pulmonary artery catheters has been a major advance in the monitoring of patients in the perioperative period. Information can be gathered with PAC, and quantitative measurements of cardiovascular and pulmonary function can be derived from them. The use of PAC has significantly contributed to the understanding and care of patients with cardiac disease [15].

Transoesophageal echocardiography [16, 17]. The common applications of transoesophageal echocardiography (TEE) in the operating room include assessment of valve function or vegetations, detection of intracardiac defects, evaluation of thoracic aorta, and assessment of systolic and diastolic function. There are classic views of transverse or longitudinal anatomy, which are the ones that are mainly used and taught, but our focus is on parameters that are important for haemodynamic evaluation.

Cardiovascular function, such as the global or regional indices of muscle contraction, is assessed by analysing dynamic echocardiographic images, especially in the evaluation of patients with ischaemic heart disease. Echocardiographic indices of left ventricular function can be used to estimate cardiac output, stroke volume, ejection fraction and parameters of ventricular relaxation and filling. In echocardiography, preload can be determined by measuring LV end-diastolic dimensions or calculating LV end-diastolic pressures. Another approach is to

examine the flow across the mitral valve with the pulsed-wave Doppler system. Integration of partial areas under the flow velocity curve can be used for the assessment of the ventricular filling and diastolic function. Afterload can be determined by the combination of ventricular dimensions with ventricular wall thickness and systolic arterial pressure. Contractility can be evaluated during the ejection phase of contraction, through maximal acceleration of blood flow in the aorta, and calculating end-systolic pressure-volume relationship.

Inadequate cardiac output or inappropriate low systemic vascular resistance, or both, cause hypotension. TEE is remarkably well suited to addressing this differential diagnosis. During severe hypotension, qualitative TEE estimates of ventricular filling and function serve as the practical guides for administration of fluids, inotropes and vasopressors. For example, in severe left-ventricular failure, ventricular filling (as assessed by end-diastolic area) is increased and ejection is decreased, whereas in inappropriately low systemic vascular resistance ventricular filling is usually normal or slightly decreased and ejection is markedly increased. Hypovolaemia is easily recognised as a marked decrease in ventricular filling and a marked increase in ejection.

TEE was used in a study of 60 consecutive patients with severe, persistent hypotension after cardiac surgery despite intensive therapy guided by invasive monitors [18]. TEE confirmed the assumed aetiology in only 30 of these patients. Moreover, TEE has prognostic value, because when it reveals nonventricular causes of hypotension (e.g. valvar or pericardial), patients are twice as likely to survive as are patients with hypotension from other causes [19].

A comprehensive TEE examination can take more than 15 min, but when time is critical a simpler examination can be carried out. A basic TEE examination consists of a minimum number of cross sections required to detect most of the life-threatening causes of severe hypotension, including those that are difficult or impossible to diagnose with other readily available perioperative techniques. This basic rescue examination may detect markedly abnormal ventricular filling or function, extensive myocardial ischaemia or infarction, large cardiac masses or thrombi, large pericardial effusions and major lesions of great vessels [17]. TEE is of fundamental importance to confirm valvar competence after repair or functioning after replacement.

In the next section, a brief description of techniques in routine use in cardiac surgery and of less commonly used haemodynamic monitors will be presented [20].

Oesophageal Doppler

With the Doppler technique, the velocity of blood flow across the aortic valve or in the descending aorta can be measured. With the oesophageal approach, the Doppler probe measures flow in the descending aorta. The cardiac output (CO) value derived from EDM is therefore only an estimate of CO based on descending aortic blood flow. Therefore, a correction factor must be added to account for this discrepancy. In 1998, Cariou et al. [21] found that aortic blood flow is proportional

to CO over a wide range of CO values ($r = 0.80$) and that aortic diameter can be more reliably measured by M-mode ultrasound than by transoesophageal echocardiography. Measurements of CO by oesophageal Doppler monitoring (EDM) have been correlated with both thermodilution and Fick methods [22–26]. It is noteworthy that all of these studies used a nomogram based on the patient's age, gender and weight to estimate the cross-sectional area of the descending aorta.

EDM allows the measurement of corrected flow time (FTc) as a measure of cardiac preload and peak flow velocity and acceleration as measures of contractility. The FTc is the systolic flow time corrected for heart rate expressed in milliseconds. In a small series of critically ill surgical patients, the FTc correlated more closely with CO than with pulmonary artery occlusion pressure [23]. Clinically, EDM has proved beneficial for perioperative monitoring as a means of decreasing morbidity in elective femur fracture fixation [27] and has been reported to yield information that is useful in the treatment of sepsis in humans [28].

EDM is well suited to use in the ICU and can be applied to a wide spectrum of patients with few contraindications (e.g., severe agitation, severe bleeding diathesis, aortic dissection). However, it is limited by the variability that can occur with probe positioning, and additional training is required to ensure proficiency [29].

Thoracic Electrical Bioimpedance

The thoracic bioimpedance (TEB) is the electrical resistance of the thorax to a high-frequency, very-low-magnitude current. In this technique, six electrodes are placed on the patient: two in the upper thorax/neck area and four on the lower thorax. As the amount of thoracic fluid increases, the TEB decreases. This measure varies with cyclic thoracic aorta distension, and changes in cardiac output may be reflected as a change in overall bioimpedance or total fluid conductivity.

There are many clinical situations in which results from TEB do not correspond to measures obtained with thermodilution or echocardiography; this is more commonly the case with cardiac dysrhythmia, aortic valvular disease, sepsis, use of electric cauterisation, and muscle spasm. A less accurate estimate of CO is provided in patients with significant thoracic fluid overload such as pulmonary oedema, pleural effusions, or massive peripheral oedema [30]. The prevalence of these conditions in the ICU will limit TEB use in that setting.

Transpulmonary Cardiac Output

CO can also be measured noninvasively by using the transpulmonary thermodilution technique. Cold injectate is administered intravenously (usually in the central circulation), and the change in temperature is detected in the arterial system. Several clinical validation studies have suggested a good correlation between transpulmonary thermodilution and PA thermodilution [31–33].

Pulse Contour Analysis

The analysis of the contour of the arterial pressure waveform is based on the notion that it is proportional to SV and that is also influenced by the impedance of the aorta. Most studies of the pulse contour method show excellent correlation with PA thermodilution [31, 32]. Clinical validation studies for pulse contour were done with the arterial catheter in the femoral position, and its accuracy seems to lessen when the arterial waveform analysis is obtained from a peripheral location.

Pulse contour devices also allow measurement of global end-diastolic volume (GEDV) to approximate intrathoracic blood volume (ITBV) and extravascular lung water (EVLW) as a substitute for cardiac preload. It has been suggested that using EVLW to guide fluid management in medical intensive care patients reduces the duration of mechanical ventilation and length of stay in the ICU [34]. The ITBV has been supposed to be a better indicator of cardiac preload than pulmonary artery occlusion pressure and central venous pressure [34]. Based on accumulated clinical experience, ITBV may be an alternative measure to predict cardiac preload in critically ill patients.

Conclusions

There is growing evidence that preoperative optimisation of organ function can substantially improve perioperative outcome. An advanced monitoring may help the anaesthesiologist to identify and correctly treat different haemodynamic disturbances that accompany high-risk patients subjected to cardiac surgery [35, 36].

References

1. Gan TJ, Soppitt A, Maroof M et al (2002) Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery. Anesthesiology 97:820-826
2. Buhre W, Rossaint R (2003) Perioperative management and monitoring in anaesthesia. Lancet 362:1839-1846
3. Cholley BP, Singer M (2003) Esophageal Doppler: noninvasive cardiac output monitor. Echocardiography 20:763-769
4. Sakka SG, Bredle DL, Reinhart K et al (1999) Comparison between intrathoracic blood volume and cardiac filling pressures in the early phase of hemodynamic instability of patients with sepsis or septic shock. J Crit Care 14:78-83
5. Wagner JG, Leatherman JW (1998) Right ventricular end-diastolic volume as a predictor of the hemodynamic response to a fluid challenge. Chest 113:1048-1054
6. Caruso LJ, Layon AJ, Gabrielli A (2002) What is the best way to measure cardiac output? Who cares, anyway? Chest 122:771-774.
7. Rex S, Busch T, Vettelschoss M et al (2003) Intraoperative management of severe pulmonary hypertension during cardiac surgery with inhaled iloprost. Anesthesiology 99:745-747
8. Lowson SM (2002) Inhaled alternatives to nitric oxide. Anesthesiology 96:1504-1513

9. Rivers E, Nguyen B, Havstad S et al (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345:1368-1377
10. Hinds CJ, Watson D (1999) ABC of intensive care: circulatory support. BMJ 318:1749-1752
11. Lobo SM, Salgado PF, Castillo VG et al (2000) Effects of maximizing oxygen delivery on morbidity and mortality in high-risk surgical patients. Crit Care Med 28:3396-3404
12. Comunale ME, Body SC, Ley C et al (1998) The concordance of intraoperative left ventricular wall-motion abnormalities and electrocardiographic S-T segment changes: association with outcome after coronary revascularization. Multicenter Study of Perioperative Ischemia (McSPI) Research Group. Anesthesiology 88:945-954
13. Jain U, Laflamme CJ, Aggarwal A et al (1997) Electrocardiographic and hemodynamic changes and their association with myocardial infarction during coronary artery bypass surgery. A multicenter study. Multicenter Study of Perioperative Ischemia (McSPI) Research Group. Anesthesiology 86:576-591
14. Reich DL, Moskowitz DM, Kaplan JA (1999) Hemodynamic monitoring. In: Reich DL, Konstadt SN, Kaplan JA (eds) Cardiac anesthesia, 4th edn. Saunders, Philadelphia, pp 321-358
15. Pulmonary Artery Catheter Consensus Conference (1997) Consensus statement. Crit Care Med 25:910-925
16. Kahn R, Konstadt S, Louie E et al (1999) Intraoperative echocardiography. In: Reich DL, Konstadt SN, Kaplan JA (eds) Cardiac anesthesia, 4th edn. Saunders, Philadelphia, pp 401-483
17. American Society of Anesthesiologists and Society of Cardiovascular Anesthesiologists Task Force on Transesophageal Echocardiography (1996) Practice guidelines for perioperative transesophageal echocardiography. Anesthesiology 84:986-1006
18. Reichert CL, Visser CA, Koolen JJ et al (1992) Transesophageal echocardiography in hypotensive patients after cardiac operations. Comparison with hemodynamic parameters. J Thorac Cardiovasc Surg 104:321-326
19. Heidenreich PA, Stainback RF, Redberg RF et al (1995) Transesophageal echocardiography predicts mortality in critically ill patients with unexplained hypotension. J Am Coll Cardiol 26:152-158
20. Chaney JC, Derdak S (2002) Minimally invasive hemodynamic monitoring for the intensivist: current and emerging technology. Crit Care Med 30:2338-3245
21. Cariou A, Monchi M, Joly LM et al (1998) Noninvasive cardiac output monitoring by aortic blood flow determination: evaluation of the Sometec Dynemo-3000 system. Crit Care Med 26:2066-2072
22. DiCorte CJ, Latham P, Greilich PE et al (2000) Esophageal Doppler monitor determinations of cardiac output and preload during cardiac operations. Ann Thorac Surg 69:1782-1786
23. Madan AK, UyBarreta VV, Aliabadi-Wahle S et al (1999) Esophageal Doppler ultrasound monitor versus pulmonary artery catheter in the hemodynamic management of critically ill surgical patients. J Trauma 46:607-611; discussion 611-612
24. Valtier B, Cholley BP, Belot JP et al (1998) Noninvasive monitoring of cardiac output in critically ill patients using transesophageal Doppler. Am J Respir Crit Care Med 158:77-83
25. Leather HA, Wouters PF (2001) Oesophageal Doppler monitoring overestimates cardiac output during lumbar epidural anaesthesia. Br J Anaesth 86:794-797
26. Bernardin G, Tiger F, Fouche R et al (1998) Continuous noninvasive measurement of aortic blood flow in critically ill patients with a new esophageal echo-Doppler system. J Crit Care 13:177-183

27. Sinclair S, James S, Singer M (1997) Intraoperative intravascular volume optimisation and length of hospital stay after repair of proximal femoral fracture: randomised controlled trial. BMJ 315:909-912
28. Eachempati SR, Young C, Alexander J et al (1999) The clinical use of an esophageal Doppler monitor for hemodynamic monitoring in sepsis. J Clin Monit Comput 15:223-225
29. Lefrant JY, Bruelle P, Aya AG et al (1998) Training is required to improve the reliability of esophageal Doppler to measure cardiac output in critically ill patients. Intensive Care Med 24:347-352
30. Shoemaker WC, Belzberg H, Wo CC et al (1998) Multicenter study of noninvasive monitoring systems as alternatives to invasive monitoring of acutely ill emergency patients. Chest 114:1643-1652
31. Tibby SM, Hatherill M, Marsh MJ (1997) Clinical validation of cardiac output measurements using femoral artery thermodilution with direct Fick in ventilated children and infants. Intensive Care Med 23:987-991
32. Godje O, Peyerl M, Seebauer T et al (1998) Central venous pressure, pulmonary capillary wedge pressure and intrathoracic blood volumes as preload indicators in cardiac surgery patients. Eur J Cardiothorac Surg 13:533-539; discussion 539-540
33. Gust R, Gottschalk A, Bauer H et al (1998) Cardiac output measurement by transpulmonary versus conventional thermodilution technique in intensive care patients after coronary artery bypass grafting. J Cardiothorac Vasc Anesth 12:519-522
34. Lichtwarck-Aschoff M, Zeravik J, Pfeiffer UJ (1992) Intrathoracic blood volume accurately reflects circulatory volume status in critically ill patients with mechanical ventilation. Intensive Care Med 18:142-147
35. Wilson RJ, Woods I (2001) Cardiovascular optimization for high-risk surgery. Curr Opin Crit Care 7:195-199
36. Weldon BC, Monk TG (2000) The patient at risk for acute renal failure. Recognition, prevention, and preoperative optimization. Anesthesiol Clin North America 18:705-717

Chapter 40

From Frank-Starling relationships to ventriculo-arterial coupling

R. Naeije

Cardiovascular responses to volume loading are often described with reference to Frank-Starling's law of the heart. However, the exact formulation of this law, and how it effectively applies to various haemodynamic conditions is not always clear. It may therefore be useful to revisit the original observations by Otto Frank and Ernest Starling, and discuss the different ventricular function curves that have been derived from their pioneer experiments.

Otto Frank and the isolated frog heart preparation

In 1895, the German physiologist Otto Frank described the response of isolated frog heart to progressively increased filling pressures [1]. As illustrated in Fig. 1, which

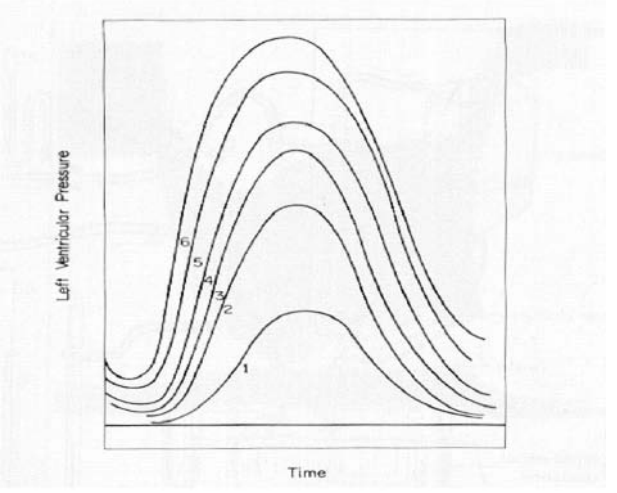

Fig. 1. Left ventricular pressure as a function of time at progressively increased filling pressure (from 1 to 6) in the isolated frog ventricle. Increased filling pressure is associated with an increased systolic ventricular pressure [1]

represents the frog's left ventricular pressure as a function of time recorded during one of his experiments, the increase in initial tension, or the ventricular pressure at the onset of contraction, was associated with an increase in the peak pressure developed during systole. Frank recognised that such changes in the initial tension were probably accompanied by changes in the resting fibre length. He proposed that this behaviour of cardiac muscle was similar to that of skeletal muscle when it is stretched progressively to greater initial lengths prior to contraction.

In 1898, Frank went further to characterise the contractions of the frog ventricle in a pressure-volume diagram [2]. As shown in Fig. 2, the diagram was made of an upper curve ("isomet maxima") corresponding to the peak pressures produced by the ventricle during isovolumic contractions at increasing resting volumes, thus defining systolic elastance, and a lower curve ("isomet minima") corresponding to pressures passively increased at progressively increased resting volume, thus defining diastolic elastance. In the condition of an ejecting beat (stippled line), systolic isotonic pressures ("isoton maxima") fell below the systolic elastance curve, while diastolic pressures were on the diastolic elastance curve, as one would expect. However, end-systolic pressure remained below the systolic elastance curve, which is surprising because end-systole is the only point of the ejecting beat pressure-volume curve with entirely isometric ventricular contraction. Frank attributed this to history dependence, meaning that the same end-systolic elastance is obtained only at pre-defined end-diastolic volume and time course of pressure-volume events. Later studies demonstrated that such a history dependence is in fact trivial in mammalian hearts. Therefore, end-systolic pressure at a given end-systolic volume

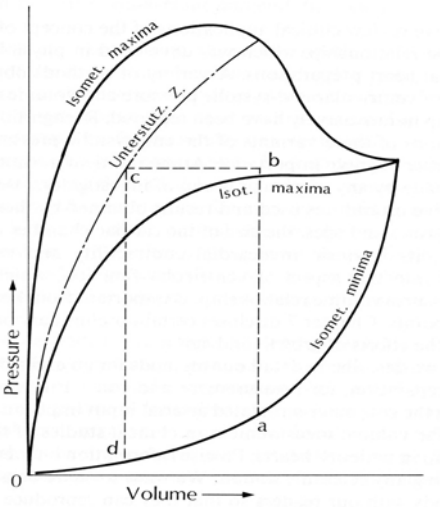

Fig. 2. Pressure-volume diagram of a frog ventricle, in non-ejecting and ejecting conditions. The systolic elastance curve (isomet maxima) shows a maximum followed by a downsloping portion. The diastolic elastance curve (isomet minima) shows a curvilinear increase in slope. The end-systolic point of the ejecting ventricle pressure-volume loop (stippled line) falls on a curve (unterstutz) that is below the systolic elastance curve, in keeping with a history-dependence phenomenon [2]

can be used as an index of contractility as well as the quasi-linear portion of the systolic elastance curve.

Ernest Starling and the canine heart-lung preparation

In 1914, Ernest Starling and his coworkers described the intrinsic response of the heart to changes in venous return and arterial pressure in a canine heart-lung preparation [3]. In that preparation, the right atrium was connected to a blood-filled reservoir allowing controlled changes in venous return, the right ventricle pumped the blood through the pulmonary circulation with lung artificially ventilated to allow for normal oxygenation, the pulmonary venous return returned to the left atrium and from there to the left ventricle, which pumped the blood into a systemic blood pressure circuit returning the blood into the reservoir. Peripheral resistance was adjusted by means of a pressure-limiting device made of a collapsible tube within a pressure chamber, since then called a "Starling resistor". Cardiac output was measured by temporarily diverting the flow returning to the venous return reservoir. Atrial pressures and arterial pressure were measured using manometers. Ventricular volumes were measured using a cardiometer made of a glass chamber connected to a volume recorder.

The effects of an isolated sudden change in venous return on the heart-lung preparation are illustrated in Fig. 3. On these original tracings of ventricular volume, aortic pressure and right atrial pressure as a function of time, it is apparent

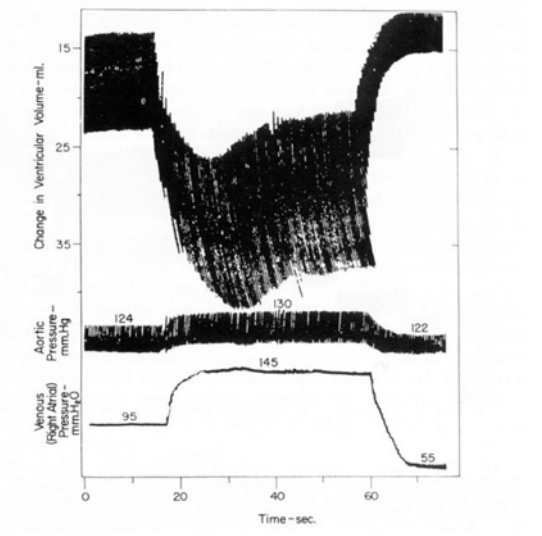

Fig. 3. Effects of a sudden increase in venous return on ventricular volume, aortic pressure, and right atrial pressure, in the canine heart-lung preparation. Both end-systolic and end-diastolic volumes increase with an increase in stroke volume. Ventricular volumes are decreased after venous return is back to baseline [3]

that the sudden increase in venous return increased atrial pressure, while blood pressure was maintained almost unchanged by manipulation of the Starling resistor. Both diastolic and systolic volumes increased rapidly, with an increase in stroke volume that accommodated for the increase in venous return, and ejection fraction was increased. Thus, stroke volume increased with the increase in end-diastolic volume. Since end-diastolic volume represents the maximum myocardial fibre length before contraction, and can therefore be taken as an adequate estimate of preload, a formulation of Starling's law of the heart could be that stroke volume increases with preload.

The effects of a rapid increase in blood pressure are illustrated in Fig. 4, which also reproduces Starling's original recordings. The increase in aortic pressure induced by a manipulation of the Starling resistor was accompanied by a rapid increase in right atrial pressure and in both systolic and diastolic ventricular volumes. Stroke volume was maintained in the presence of increased blood pressure through an increase in ventricular volumes and a decrease in ejection fraction. In this experiment, the formulation of a Starling's law of the heart as proportional changes in stroke volume and preload would not be valid anymore. However, the product of stroke volume by blood pressure actually increased in proportion to preload. Therefore, a more-adequate formulation of Starling's law of the heart that

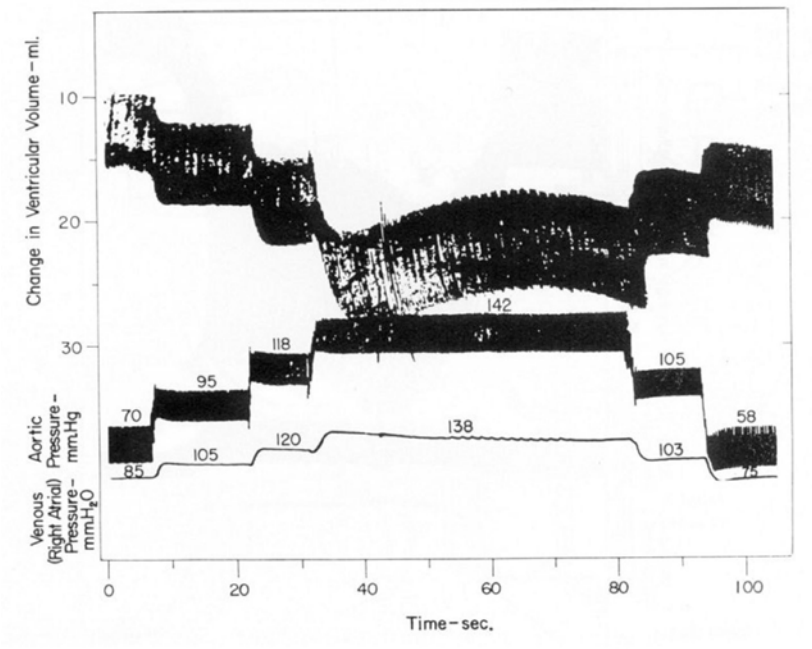

Fig. 4. Effects of a sudden increase in aortic pressure return on ventricular volume, aortic pressure, and right atrial pressure, in the canine heart-lung preparation. Both end-systolic and end-diastolic volumes increase with a maintained stroke volume [3]

holds in the presence of changes in preload as well as in blood pressure is that stroke work increases in proportion to preload.

This was recognised by Starling when he wrote: "Now here are two conditions in which the work of the heart is increased and in which this organ adapts itself by increasing the chemical changes in its muscle at each contraction to the increased demands made upon it. It is evident that there is one factor, which is common to both cases, and that is the increased volume of the heart when it begins to contract. So we may make the following general statement. Within physiological limits, the larger the volume of the heart, the greater are the energy of its contraction and the amount of chemical change at each contraction" [4]. This is the most-advanced formulation made by Starling himself of what would be called his law. It is interesting that he included the notion of "chemical changes", which was premonitory of major advances in the molecular understanding of myocardial mechanics that occurred during the ensuing decades.

Ventricular function curves

The functional state of a skeletal muscle is best described by active and passive tension-length relationships. This extrapolates to the intact ventricle as a pressure-volume diagram. As already mentioned, Frank used this diagram to describe the functional state of frog ventricles. Isovolumic pressure-volume relationships illustrated the paper by Patterson et al. [3], but Starling never built such curves from raw data generated by the canine heart-lung preparation. Ventricular pressure-volume curves were validated by Suga et al. in the late sixties [5, 6]. It is now well established that instantaneous measurements of ventricular pressures and volumes allow for the definition of preload as end-diastolic volume and load-independent contractility as end-systolic or maximal elastance (Emax) [7]. The assumption that end-systolic pressure-volume coordinates are reasonably well described by a linear approximation has been verified to be correct over physiological ranges of pressures and volumes. The approach has been demonstrated to be valid for the right ventricle as well as for the left ventricle, although with pressure-volume loops of different shapes. While the left ventricular pressure-volume loop is rectangular, with a well-defined upper left corner allowing for an accurate definition of end-systolic elastance that coincides with Emax, the right ventricular pressure-volume loop has a triangular shape with a rounded upper left shoulder, and Emax occurs before end-systole because of the normally low pulmonary arterial impedance [8].

Afterload can be defined by maximum wall stress, which is dependent on the product of ventricular pressure and volume, corrected for wall thickness [7]. Afterload corresponds to the upper right corner of the pressure volume loop. Since maximum wall stress is dependent on both volume and pressure, it is evident that an increase in end-diastolic volume at unchanged mean blood pressure is associated with an increase in afterload. As any increase in afterload is quickly accompanied by an adaptative increase in ventricular volumes, it appears that, in intact

ventricles, like demonstrated in isolated myocardial strips, preload and afterload are necessarily interdependent.

Afterload can also be defined by arterial hydraulic load, calculated from a spectral analysis of arterial pressure and flow waves, or more simply by arterial elastance, that is mean arterial pressure divided by stroke volume [7].

Generating ventricular pressure-volume curves at the bedside is limited by the technical difficulties of the measurements of instantaneous pressures and volumes. Accordingly, surrogate cardiac, or ventricular function curves still called Starling curves, can be built by plotting stroke volume or stroke work as a function of atrial pressure, as introduced by Sarnoff et al. [9] (Fig. 5) or ventricular output as a

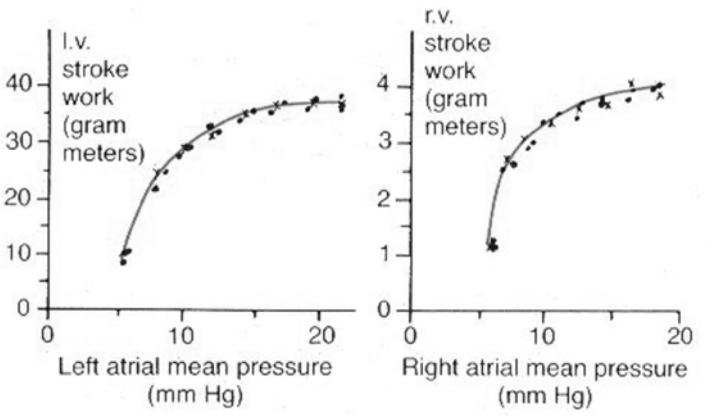

Fig. 5. Ventricular function curves expressed as ventricular stroke work versus atrial pressure [9]

function of atrial pressure as introduced by Guyton et al. [10] (Fig. 6). Both functional curves are easily generated from bedside haemodynamic measurements, and have been shown to be relatively sensitive to changes in preload, afterload and contractility. The ventricular output curve is the less-accurate reflection of ventricular function changes, but the expression of cardiac output as a function of right atrial pressure has the advantage of allowing a graphical analysis of the coupling between cardiac function and systemic venous return [10].

Heterometric versus homeometric autoregulation of ventricular function

A close inspection of Starling's original recordings of the effects of changes in loading conditions on ventricular volumes shows a tendency for ventricles to return to initial control volumes while increased loading is maintained, and a marked decrease in ventricular volumes after return to the initial baseline loading

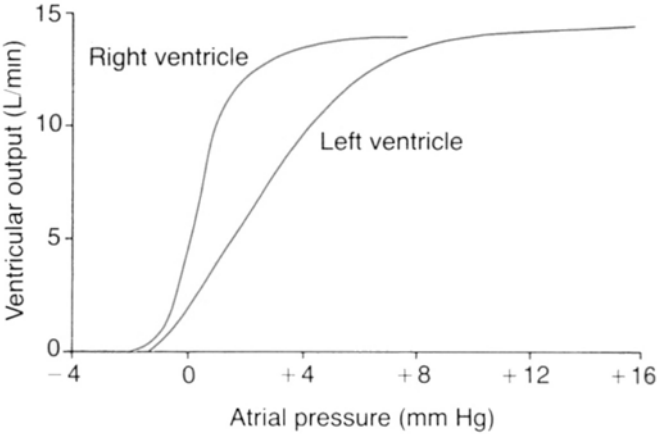

Fig. 6. Ventricular function curves expressed as ventricular output versus atrial pressure [10]

conditions (Fig. 3). In fact, later experiments showed that dimension-related autoregulation, or heterometric autoregulation, would reach a maximum after 20 to 30 s, with a progressive return to initial volumes within the next 5 minutes while maintaining increased stroke work, indicating the existence of another dimension-independent mechanism. This mechanism has been named "homeometric" autoregulation by Sarnoff et al. [11], and is also alluded to as the "Anrep effect" [12]. Homeometric autoregulation of the heart corresponds to an increase in contractility in the presence of afterload. The molecular mechanisms of stretch-induced increase in contractility allowing for the heart to adapt to loading conditions with limited dimension change remain incompletely understood. Heterometric autoregulation is important essentially for beat-by-beat ventricular adaptation to changes in venous return and/or arterial impedance. However, homeometric autoregulation takes over most of the adaptative process after only a few minutes, and is predominant in the longer term.

Ventriculo-arterial coupling

Ventricular function is coupled to venous return, and this coupling can be graphically analysed using ventricular function and venous return curves [10]. Ventricular function is also coupled to arterial hydraulic load. Sunagawa et al. showed that this coupling can be graphically analysed on a pressure-volume diagram, as shown in Fig. 7 [7, 13]. The diagram allows for the determination of Emax and of arterial elastance (Ea), and the calculation of an Emax/Ea ratio. Complex mathematical modelling shows that the optimal matching of systolic ventricular and arterial elastances occurs at an Emax/Ea ratio around 1.5. Isolated increase in Ea, or decrease in Emax, reduce the Emax/Ea ratio, suggesting uncoupling of the

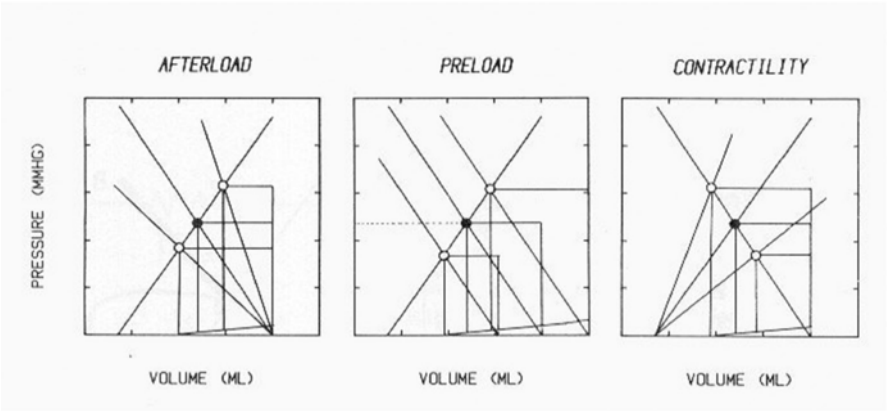

Fig. 7. Calculations of maximum elastance (Emax) and arterial elastance (Ea) on pressure-volume diagrams, with effects of changes in afterload, preload, and contractility [7]

ventricle from its arterial system. Everything else being the same, a decrease in Emax/Ea is necessarily accompanied by a decrease in stroke volume. On the other hand, an isolated increase in preload is associated with an increase in stroke volume with unaltered ventriculo-arterial coupling.

Application to the right ventricle: the single-beat method

The thin-walled right ventricle is sensitive to changes in loading conditions. Right ventricular failure is associated with a poor prognosis whatever the initial aetiology. However, the complex geometry of the right ventricle makes functional evaluations with measurement of instantaneous volume changes technically difficult, and the particular shape of the right ventricular pressure-volume loop makes single beat determinations of Emax unreliable. This latter problem can be overcome by measuring pressure-volume loops at several levels of preload [7, 8], but bedside manipulations of venous return are too invasive to be ethically acceptable. In addition, when applied to intact beings, changes in venous return are associated with reflex sympathetic nervous system activation, which affects the ventricular function that is measured. Accordingly, Brimioulle et al. designed a single beat method to study the coupling of the right ventricle to the pulmonary circulation [14]. The approach had been initially proposed for the left ventricle by Sunagawa et al. [15]. In its principle, the method avoids absolute volume measurements and related technical complexities, to calculate Emax and Ea from instantaneous right ventricular pressure and flow output measurements. As shown in Fig. 8, a Pmax is estimated from a nonlinear extrapolation of the early and late systolic isovolumic portions of the right ventricular pressure curve. This estimated Pmax has been shown to be tightly correlated with Pmax directly measured during a non-ejecting beat [14]. A straight line drawn from Pmax to the right ventricular pressure versus relative change in

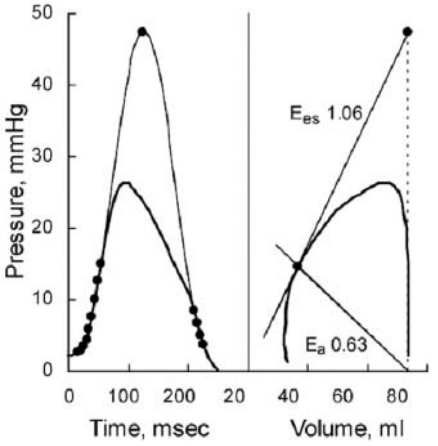

Fig. 8. Determination of ventricular end-systolic elastance (Ees) and arterial effective elastance (Ea). *Left.* The end-systolic pressure of an isovolumic beat is computed by sine wave extrapolation from the ejecting beat, using pressure values recorded before maximal dP/dt and after minimal dP/dt. *Right.* This Pmax value is drawn on the RV pressure-volume diagram. The ESPVR line is drawn from Pmax down and tangent to the pressure-volume curve, i.e., from predicted isovolumic beat end-systole to actual ejecting beat end-systole. The effective arterial elastance line is drawn from end-systole to end-diastole. Ees is the slope of the ESPVR line, and Ea the absolute slope of the arterial elastance line [14].

volume curve allows for determination of Emax. A straight line drawn from the Emax point to the end-diastolic relative volume point allows for determination of Ea.

Brimioulle et al. showed that the Emax/Ea ratio determined by this single-beat method is between 1.5 and 2, which is similar to values reported for left ventricular-aortic coupling, and compatible with an optimal ratio of mechanical work to oxygen consumption [16]. The Emax/Ea ratio was decreased by propranolol and increased by dobutamine, and was maintained in the presence of increased Ea due to hypoxic pulmonary vasoconstriction. In fact, Emax increased adaptedly to increased Ea in hypoxia, even in the presence of adrenergic blockade, which is compatible with the notion of homeometric adaptation of right ventricular contractility [14]. Further studies from the same group showed preserved Emax/Ea ratio in the presence of acutely increased pulmonary artery pressure, in response to hypoxia or pulmonary embolism, but a decoupling of the right ventricle from the pulmonary circulation in the presence of excessive increases in afterload produced by pulmonary arterial banding [17]. Also, the optimal values for the Emax/Ea ratio were found not different in dogs, goats and in pigs [17]. Finally, right ventriculo-arterial coupling as assessed by single-beat determinations of Emax/Ea appeared to be well maintained in piglets with pulmonary arterial hypertension induced by 3 months systemic to pulmonary shunting [18].

Practically, all that is needed to determine single-beat Emax/Ea ratios is instantaneous pulmonary blood flow and right ventricular pressures. This can be done

non-invasively by Doppler echocardiography. Doppler pulmonary flow measurements synchronised to invasively measured pulmonary artery pressures has been reported to allow for realistic pulmonary arterial impedance calculations [19]. Right ventricular pressure can be recalculated from the envelope of tricuspid regurgitant jets and point-by-point application of the simplified form of the Bernoulli equation [20]. More work is needed to see whether this approach is really applicable at the bedside. It will be interesting to correlate the findings to newly-developed tissue Doppler indices of right ventricular contractility. One of the most fascinating aspect of the evolution of ideas on ventricular function since the pioneer experiments of Otto Frank and Ernest Starling is that the basic concepts they put forward remain essentially true, and may at last enter bedside reality thanks to recent technological advances in non-invasive Doppler echocardiography.

References

1. Frank O (1895) Zur Dynamik des Herz Muscles. Z Biol 32:370-447
2. Frank O (1899) Die Grundform des Arteriellen Pulses. Z Biol 37:483-526
3. Patterson SW, Piper H, Starling EH (1914) On the mechanical forces which determine the output of the ventricles. J Physiol 48:357-379
4. Starling EH (1918) The Linacre lecture on the law of the heart. London, Longmans, Green
5. Suga H (1969) Time course of left ventricular pressure-volume relationship under various end-diastolic volumes. Jpn Heart J 10:509-515
6. Suga H (1970) Time course of left ventricular pressure-volume relationship under various extents of aortic occlusion. Jpn Heart J 11:373-378
7. Sagawa K, Maughan L, Suga H et al (1988) Cardiac contraction and the pressure-volume relationship. Oxford University Press, New York, pp 1-480
8. Maughan WL. Shoukas AA, Sagawa K et al (1979) Instantaneous pressure-volume relationship of the canine right ventricle. Circ Res 44:309-315
9. Sarnoff SI, Berglund E (1954) Starling's law of the heart studied by means of simultaneous right and left ventricular function curves in the dog. Circulation 9:706-718
10. Guyton AC (1955) Determination of cardiac output by equating venous return curves with cardiac response curves. Physiol Rev 35:123-129
11. Sarnoff SJ, Mitchell JH, Gilmore JP et al (1960) Homeometric autoregulation of the heart. Circ Res 8:1077-1091
12. Nichols CG, Hanck DA, Jewell BR (1988) The Anrep effect: an intrinsic myocardial mechanism. Can J Physiol Pharmacol 66:924-929
13. Sunagawa K, Sagawa K, Maughan WL (1987) Ventricular interaction with the vascular system. In: Yin FCP (ed) Ventricular/vascular interaction. Springer – Verlag, New York, pp 210-239
14. Brimioulle S, Wauthy P, Ewalenko P et al (2003) Single-beat estimation of right ventricular end-systolic pressure-volume relationship. Am J Physiol Heart Circ Physiol 284:H1625-H1630
15. Sunagawa K, Yamada A, Senda Y et al (1980) Estimation of the hydromotive source pressure from ejecting beats of the left ventricle. IEEE Trans Biomed Eng 57:299-305
16. Burkhoff D, Sagawa K (1986) Ventricular efficiency predicted by an analytical model. Am J Physiol Regul Integr Comp Physiol 250:R1021-R1027
17. Wauthy P, Pagnamenta A, Vassalli F et al (2004) Right ventricular adaptation to

pulmonary hypertension: an interspecies comparison. Am J Physiol Heart Circ Physiol 286:H1441-H1447
18. Rondelet B, Kerbaul F, Motte S et al (2003) Bosentan for the prevention of overcirculation-induced experimental pulmonary arterial hypertension. Circulation 107:1329-1335
19. Huez S, Brimioulle S, Naeije R et al (2004) Feasibility of routine pulmonary arterial impedance measurements in pulmonary hypertension. Chest 125:2121-2128
20. Ensing G, Seward J, Darragh R et al (1994) Feasibility of generating hemodynamic pressure curves from non-invasive Doppler echocardiographic signals. J Am Coll Cardiol 23:434-442

Chapter 41

Pharmacology and selection of inotropic therapy

J.O.C. Auler

General classification

My aim in this paper is to present pharmacological aspects of vasoactive and inotropic drugs and the classification and selection of these agents in clinical use based on the available evidence. Owing to the older classification of vasoactive agents, which was based mainly on the action of peripheral α- or β-adrenoceptors or both, some pharmacological misunderstanding still persists today. The first question relates to the definition of a true inotropic agent. In my view, a pure inotropic agent exerts its action only on the myocardial cell, provoking an increase in contractility without interfering with peripheral receptors or in myocardial oxygen consumption. As we will see, most of the drugs at our disposal for the treatment of sick patients in ICU, operating room, emergency department and ward have mixed actions; nonetheless, they are still presented as inotropic agents.

We can start by defining vasoactive drugs. These agents affect vasomotor tone and can be classified simplistically as vasoconstrictors or vasodilators. Vasoactive drugs can affect vasomotor tone by acting exclusively on peripheral receptor, or even take direct or indirect cardiac effects through peripheral effects, acting by stimulation of α- or β-adrenoceptors, dopaminergic D_{A2}-receptors and arginine vasopressin V_{1a}-receptors. The majority of the best known agents, generally classified as vasoactive drugs, may also have positive inotropic effects, acting on receptors, ion channels or enzymes present on myocardial muscle and enhancing contractility. A pure vasoconstrictor drug promotes contraction of the arterial vessels, increasing vascular resistance. Most of these act by stimulating α-adrenoceptors, e.g. phenylephrine arginine and vasopressin, or V_{1a}-receptors, e.g. vasopressin. On the other hand, β-adrenoceptor-agonistic drugs increase the contractility, but may also provoke some degree of vasoconstriction, e.g. dopamine, or vasodilation, e.g. isoproterenol, depending on the dosage.

The pure vasodilators might be classified according to their effects on the vessels as predominantly arterial or venous, or of mixed action Their action to improve heart performance is based mostly on afterload reduction, as for example in the case of nitroprusside. A summary classification of pure vasodilators follows.

a) Vasodilators acting predominantly on the arterial bed (e.g. hydralazine).
b) Vasodilators acting predominantly on the venous bed (e.g. nitroglycerin).
c) Vasodilators with mixed action (e.g. nitroprusside).

A more recent addition to the pharmacological armamentarium is the concept of the inodilator, an agent that brings about improvements in myocardial contractility and at same time induces peripheral vasodilation, e.g. selective phosphodiesterase (PDE) inhibitors (milrinone) [1].

Depending on their particular mechanisms of action, vasoactive agents can interact directly or indirectly with the principles that maintain the heart function. In general, these drugs can affect afterload, heart rate and the intrinsic contractile state of the myocardium. Three basic mechanisms regulate the contractile strength of the heart in the acute setting. First, muscle force and stroke volume vary directly with sarcomere length and preload, respectively, phenomena that are mostly referred to as the Frank-Starling law of the heart. Second, myocardial force development is heart rate dependent; peak isometric force increases with heart rate in normal mammalian myocardium, including human cardiac muscle. Third, cardiac muscle is under neurohumoral control, including the sympathetic and vagal nervous systems and some polypeptides such as angiotensin and endothelin. The Frank-Starling mechanism is one of the most important physiological principles in regulation of contractile performance [2, 3].

Table 1. Principal vasoactive agents with their corresponding sites of stimulation

Vasoconstrictors	Vasodilators
Peripheral α-adrenoceptors: norepinephrine, phenylephrine, arginine vasopressin V1a, vasopressin	Peripheral β2-adrenoceptors: isoproterenol
Mixed peripheral α- and β-adrenoceptors: epinephrine	Dopaminergic receptors: fenoldopam
	Antagonism: α-adrenoceptors phentolamine
	Inhibition of inward flow of calcium: nicardipine
	Nitric oxide-induced cyclic guanosine-monophosphate: nitroglycerin
	Phosphodiesterase inhibition of breakdown of cyclic AMP: milrinone

The principle of the maximum effectiveness of Frank-Starling mechanism, based on the sarcomere in acute or chronic heart failure strength, should take account of the highest possible efficiency of an inotropic drug. In medical practice, this point is merely correlated to the pulmonary wedge pressure measured, from 12 mmHg, considered normal, to 18 mmHg, considered the highest point of the Starling curve (Fig. 1). Beyond that the heart contractility response to a greater preload might not occur. In their excellent paper, Holubarsch et al. [3] report that the Frank-Starling mechanism is well preserved in failing human myocardium: left ventricular filling pressure is kept high enough to reach the benefit of the length dependence of contractile performance, but low enough to prevent pulmonary congestion in end-stage heart failure. This finding has important clinical implications, assuming that the left ventricle operates near or even beyond the optimal

sarcomere lengths, indicating reduced preload reserve or even none at all. In addition, reduced diastolic compliance has been found in isolated preparations of failing human ventricles. This indicates that higher end-diastolic stresses and pressures are necessary to reach optimal contractile force in failing hearts than in normal hearts.

Thus, there is clear evidence that preload influences ventricular performance in the whole heart. After acute situations, a previously normal heart may show signs of acute deterioration in myocardial contractility, as observed for example after prolonged cardiopulmonary bypass (CPB), sepsis, severe trauma, prolonged shock. In these circumstances, sarcomere fibres are operating over more than normal lengths, while the heart function remains dependent on a shortened but essential preload reserve and requires inotropic support to maintain an acceptable cardiac output.

These findings are consistent with results of earlier clinical studies in patients with chronic heart failure, demonstrating that end-systolic pressure and stroke volume decrease as preload is abruptly curtailed by inferior vena caval occlusion [4].

The final message implies that several observations in addition to the condition of the heart should be used to select a group of inotropic agents for each clinical condition to be treated. At the same time, it is of paramount importance to employ all monitoring tools to ensure the correct preload for each situation before a vasoactive or inotropic agent is used.

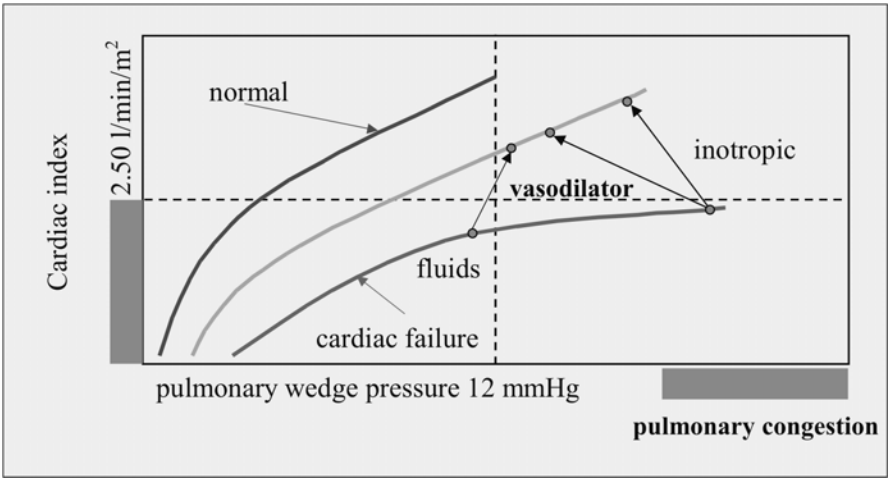

Fig. 1.

Classification of positive inotropic drugs

Parenterally administered positive inotropic agents remain an important component of the treatment of cardiac dysfunction and failure. In general, drugs are classified in a generic sense on the basis of their pharmacological activity, and most classifications have been based on the peripheral adrenoreceptors' action. However, some of the drugs, in parallel with their peripheral actions, have a mixed inotropic mechanism. In attempts to facilitate the comprehension of the mechanisms of action of inotropic drugs, various classifications have been proposed. In the early 1990s Feldman [5] published a useful classification of the inotropic agents in four classes:

I- Agents that increase intracellular cyclic adenosine monophosphate. Beta-adrenergic agonists and phosphodiesterase inhibitors are the main examples of this group.

II- Agents that affect sarcolemmal ions pump, e.g. digoxin.

III- Agents that modulate intracellular calcium mechanism by release of sarcoplasmatic reticulum calcium or increase sensitisation of the contractile proteins to calcium.

IV- Agents that have a multiple mechanism of action. The augmentation of cardiac contractility is based on increasing the affinity of the regulatory site on troponin C for calcium, or even presenting a discrete inhibitory effect on phosphodiesterase III.

Recent investigations suggest that new inotropic agents may be beneficial in the short- and long-term management of chronic cardiac failure. Some of them may be valuable in acute heart failure or even successfully replace catecholamines, which are classically used to support the failing heart.

More recently, owing to the complex pharmacokinetics and pharmacokinetics of new drugs, Lehtonen et al. proposed classifying positive inotropic drugs on the basis of whether or not the inotropic action of the drug is dependent on any increase in the intracellular level of cyclic adenosine monophosphate (cAMP) [6]. This classification is presented in Table 2.

Table 2. Cyclic adenosine monophosphate (*cAMP*)-dependent drugs

Drugs that increase cAMP formation	Nonselective adrenergic drugs (activate both α- and β-receptors, e.g. epinephrine)
	Selective β-adrenergic agonists (e.g. dobutamine)
	Dopaminergic agents (e.g.dopamine)
Drugs that decrease cAMP degradation	Selective PDE III inhibitors(e.g.milrinone)
	Nonselective PDE inhibitors that inhibit several PDE isoenzymes (e.g. papaverine)

Both β-adrenergic receptor agonists and phosphodiesterase inhibitors augment cardiac contractility by raising intracellular levels of the cyclic adenosine monophosphate (AMP). The stimulation of β-adrenergic receptors in the cell ignited

means a regulatory protein and enhanced production of cyclic AMP. The stimulation of cyclic AMP turns on a dependent protein kinase with subsequent phosphorylation of a group of myocardial proteins causing to both improved contraction and relaxation. In the presence of adequate amounts of intracellular cyclic AMP, inhibition of phosphodiesterase can also result in augmentation of intracellular cyclic AMP levels with subsequent improvement of contractility and relaxation.

In summary, drugs in this second group, displayed in Table 3, enhance the cardiac contractility by altering intracellular calcium homeostasis via an action on selective ion pumps and channels within the sarcolemma.

Table 3. cAMP –independent drugs

Drugs that increase cytosolic free calcium	Increase sarcolemmal influx (e.g. digitalis glycosides) Increase release of calcium from sarcoplasmic reticulum (e.g. flosequinan)
Drugs that increase the sensitivity of contractile proteins to calcium (calcium sensitisers)	Increase the calcium affinity of the calcium--binding site of troponin C (e.g. pimobendan, in addition to inhibiting PDE III) Stabilise calcium-induced changes in the troponin complex (e.g. levosimendan, in addition to inhibiting PDE III) Activate myosin ATPASE (e.g. senazodan, in addition to inhibiting PDE III)

Among the drugs that increase cytosolic, free calcium digoxin is the best known. Digoxin inhibits the sarcolemmal sodium potassium adenosine triphosphate, resulting in higher levels of intracellular sodium. The ion sodium is exchanged for calcium by a specific channel and consequently there is an increase in the cardiac contractility because intracellular calcium levels rise.

Among the drugs that increase the sensitivity of contractile proteins to calcium, generically called calcium sensitisers, levosimendan is a prime example. Levosimendan, like other agents used effectively to treat heart failure, has different mechanisms of action. In a simplistic view, the concept of sensitisation means that a calcium concentration dependent on the contractile apparatus is sensitised during systole but not in diastole. The main physiological consequence of a calcium sensitisation is a positive inotropic effect, with no interference in the diastolic relaxation period. At the same time, the absence of cytosolic calcium overload avoids the undesirable effects sometimes seen with catecholamines, such as cardiac myocyte dysfunction, arrhythmogenesis, and cell death [7]. In contrast to levosimendan, pimondan is also a calcium sensitizer. It acts by increasing the affinity of troponin complex for calcium, at the same time causing the inhibition of phosphodiesterase III, an effect that results in enhancement of the contractility leads to a undesirable cytosolic calcium overload [8].

Drugs that inhibit phosphodiesterase (PDE) are also involved in the improvement of the contractility. The PDE isoenzyme group is the most important enzyme

for cAMP degradation in the human heart. PDE inhibitors might increase the calcium sensivity of the contractile apparatus via affecting the phosphorylation status of troponin I [9]. There are three known groups, I, II and III, and some subgroups of phosphodiesterase isoenzymes. The inhibition of PDE in the myocardial enhances contractility, whereas in the vessels the increase in cAMP induces relaxation and reduces arterial pressure. The exact mechanisms of PDE inhibitors in the vascular smooth cells in causing vasodilation has not been completely elucidated, but it probably involves increasing intracellular cGMP levels. Clinically used, PDE inhibitors present differences in their selectivity for several PDE isoenzymes. For instance, milrinone, pimobendan and levosimendan are more selective for PDE III inhibition and consequently for increasing cardiac contractility.

Clinical use

Inotropic agents are widely used in several clinical situations, in most of them to support chronic heart failure, but also in acute cardiac dysfunction, which is now recognised more and more frequently in sepsis, trauma, SIRS linked with high-risk surgery, etc.

Traditional inotropic agents increase cyclic AMP within the myocardium, thus allowing increased admission of calcium ions into the cells, which favours actin–myosin coupling. The two principal mechanisms are activation of β adrenergic receptors on the cell surface or inhibition of specific enzyme phosphodiesterase type III, respectively represented by dobutamine and milrinone. According to Krum and Liew, current therapies have some limitations, which are summarized in Table 4:

Table 4. Disadvantages of current inotropic drugs (β-adrenergic agonists, e.g. dopamine, dobutamine; PDE III inhibitors, e.g. milrinone)

Increased arrhythmogenicity and myocardial oxygen consumption
Increased risk of sudden death after long-term use
Necessity for continuous monitoring
Systemic hypotension
Difficulty in association with newly proposed therapies (e.g. beta blockers)

New drugs for use in severe heart dysfunction

Owing to the alleged limitations of traditional therapies (listed in Table 4) most new drugs have been developed to combat congestive heart failure that is refractory to conventional therapies. Four agents or groups of agents, nesiritide, levosimendan, tezosentan, and vasopressin antagonists (tolvaptan and conivaptan) have been extensively investigated, and the majority of them are in the final phase of clinical trial.

Nesiritide. Has a molecule analogous to that of human B type natriuretic peptide. This agent binds to natriuretic peptide receptors on endothelial and

vascular muscle cells, determining elevation of the levels of intracellular cyclic guanosine monophosphate with successful arterial and venous vasodilation. Although not a true inotropic, the clinical consequence of nesiritide is a reduction of vascular resistance, coronary vasodilation and, due to natriuretic and diuretic effect, a preload reduction. Systemic hypotension is the main side effect of nesiritide, nevertheless several clinical trials have demonstrated a good tolerance and efficacy of this agent [10].

Levosimendan. As mentioned above, levosimendan acts by increasing myocyte sensitivity to calcium, increasing myocardial contractility and producing vasodilatation via ATP-dependent potassium channel opening. Greater efficacy and safety of intravenous levosimendan than of dobutamine in severe low-output heart failure was shown in the LIDO (levosimendan–dobutamine) study, a randomised double-blind trial. In this study, in which patients with severe, low-output heart failure, were enrolled, levosimendan improved haemodynamic performance more effectively than dobutamine. This benefit was accompanied by lower mortality and less arrhythmogenicity in the levosimendan group than in the dobutamine group for up to 180 days [11].

Lochner et al. [12] tested the hypothesis that after coronary artery bypass graft (CABG) operations myocardial contractile function is often very significantly depressed, and inotropic support may be frequently required for resumption of function. With due consideration for the caution required in extrapolating from animal data to humans, the results obtained in this study suggest that the use of calcium sensitisers rather than adrenergic agonists as inotropes after cardioplegic arrest should be seriously considered. A further advantage of levosimendan is its anti-ischaemic properties when administered during ischaemia. In view of this, levosimendan may indeed be regarded as an anti-ischaemic inotrope that also exerts its actions in the presence of calcium and beta blockers.

Tezosentan. This drug is an antagonist of the peptide endothelin (21-aminoacid peptide). Endothelin is a potent vasoconstrictor, but also proinflammatory and implicated in a multiplicity of cardiovascular diseases characterized by vasoconstriction, heart dysfunction and ischemia [13]. The mechanism of tezosentan is a dual endothelin receptor antagonist located on vascular smooth muscle and endothelial cells. The principal effects observed are vasodilatation and a possible anti-inflammatory result. The on-going clinical trials in which patients with severe heart failure are enrolled have shown improvement of cardiac function, but are still inclusive on whether mortality declines [10].

Vasopressin antagonists. AVP is a neurohypophysial peptide hormone released by the posterior pituitary primarily for the maintenance of plasma osmolality through renal free water regulation. AVP may also contribute to the maintenance of vascular tone through its actions on vascular smooth muscle cells. AVP is acutely and transiently activated in response to increases in plasma osmolality and reductions in intravascular pressure. Its synthesis and release are substantially up-regu-

lated during chronic heart failure. The cardiovascular effects of vasopressin are mediated via two major receptors: V_{1A} is located in blood vessels and mediates vasoconstriction; the V2 receptor is involved with water excretion [14]. Selective vasopressin receptor antagonism has been shown to considerably increase free water excretion, and symptoms of severe congestive failure [10]. Several trials are in progress. Recently, a study of tolvaptan has shown that this drug is useful in the treatment of heart failure patients who experience volume overload, with or without hyponatraemia. Tolvaptan appears to produce effective and sustained reductions in congestion without the potential for worsening renal function, potassium depletion or hypotension [14].

Vasopressin in clinical settings

Arginine vasopressin (AVP) is a neurohypophysial peptide hormone that is concerned in a number of physiological activities. Binding of AVP to distinct vasopressin receptor subtypes (V_{1a} and V_2 receptors), is a fundamental function in a variety of physiological processes, including body fluid regulation, vascular tone regulation and cardiovascular contractility. V_{1a} receptors are situated on both vascular smooth muscle cells and cardiomyocytes and have been shown to modulate blood vessel vasoconstriction, whilst myocardial function V_2 receptors are located on renal collecting duct principal cells and regulate volume status through stimulation of free water and urea reabsorption. As well as the response to changes in plasma osmolality, AVP also maintains and regulates vascular tone via V_{1a} receptors. In response to a small decrease in arterial pressure, stimulation of the V_{1a} receptors by AVP results in potent arteriole vasoconstriction with significant increases in systemic vascular resistance (SVR) [14, 15].

Vasopressin in cardiac arrest

Earlier reports provided a great deal of evidence supporting the hypothesis that vasopressin can improve outcomes in cardiac arrest. This assumption was based on studies demonstrating that concentrations of vasopressin were much higher in patients who were successfully resuscitated than in those who were not [16].

Lately, the same research group showed that plasma concentrations of endothelin, catecholamines, arginine vasopressin and adrenocorticotropin rose rapidly in patients with cardiac arrest [17]. Concentrations of the last two hormones were much lower in patients who were not successfully resuscitated. Paradis et al. showed in a canine model of cardiac arrest that arginine vasopressin concentrations increased greatly during resuscitation [18].

Stiell et al. [19] carried out a triple-blind randomised trial in the emergency departments, critical care units, and wards of three Canadian teaching hospitals. They enrolled adults who had suffered cardiac arrest and required drug therapy, who received one dose of vasopressin 40 U or epinephrine 1 mg intravenously as the initial vasopressor. Patients who failed to respond to the study intervention

were given epinephrine as a rescue medication. The primary outcomes were survival to hospital discharge, survival to 1 h, and neurological function. The study assigned 104 patients to vasopressin and 96 to epinephrine. It failed to detect even a modest trend favouring vasopressin, even in the pure subgroups of myocardial ischaemia vs infarction and ventricular fibrillation vs tachycardia. In their excellent study, the authors strongly disagree with the decision of the AHA (American Heart Association) that recommends vasopressin as an alternative to epinephrine. Their ACLS (Advanced Cardiac Life Support) guidelines are used worldwide and will affect the care of millions of patients with cardiac arrest both inside and outside hospitals. Stiell et al. believe that vasopressin cannot be recommended unless further larger clinical trials show evidence of improved survival to hospital discharge [19].

Vasopressin in sepsis

The main characteristic of clinical septic shock is obvious peripheral arteriolar vasodilatation, which results in low systemic vascular resistance, high cardiac output, hypotension and inadequate tissue perfusion. Although the mechanism of the vasodilatation of septic shock has still not been totally clarified, increasing evidence implicates an anomaly of vasomotor regulation. In addition, inappropriately low plasma vasopressin levels have been suggested as the underlying cause of the hypotension in advanced vasodilatory septic shock [20].

The key to septic shock treatment consists in the administration of intravenous fluids, antibiotics and vasopressor agents. It is widely assumed that the development of refractory hypotension is caused by an adrenergic hyposensitivity, with progressive loss of catecholamine pressor responsiveness [21].

Although vasopressor therapy remains a mainstay of the clinical treatment of septic shock, selection of the most appropriate pressor agent continues to be debated. Arginine vasopressin (AVP), a potent endogenous vasoconstrictor, has been proposed as a vasopressor alternative or adjuvant to conventional catecholamine-α adrenoceptor agonists for the treatment of refractory hypotension in septic shock [22].

Guzman et al. [23] conducted a recent comparative animal investigation to evaluate the systemic, splanchnic, and renal haemodynamics and metabolic effects of AVP infusion and norepinephrine (NE) administration during basal conditions and during resuscitation from endotoxic shock. Their data showed that, in contrast to NE, AVP effectively restores renal blood flow and DO_2 with comparable systemic and splanchnic haemodynamic and metabolic effects in endotoxin-induced circulatory shock.

Although more consistent clinical trials are necessary to establish the true role of AVP as a vasopressor in the treatment of refractory hypotension in septic shock, Guzman et al.'s findings suggest that AVP, alone or perhaps in combination with other catecholamines, may enhance renal perfusion and facilitate the clinical management of septic shock.

Postoperative heart failure

Cardiopulmonary bypass surgery has always carried an elevated risk of developing a low-cardiac-output state. The consequence is a reduction of oxygen delivery (DO_2) to vital organs, and if not promptly recognised and treated, low DO_2 can make a large contribution to increasing the morbidity and mortality in the postoperative period. The basis of treatment for low cardiac output is optimisation of cardiac preload and an appropriate increase in myocardial contractility with inotropic drugs, and even a decrease in vascular resistance. Dobutamine, a synthetic directly acting β-adrenoreceptor agonist acting mainly on β1-receptors and with minor activity on β2-receptors, is the drug that is most widely used to treat cardiac dysfunction after CPB. Milrinone, defined as an inodilator, a drug that has both inotropic and vasodilator properties, is a bipyridine methylcarbonitrile that can inhibit the cyclic cAMP-specific phosphodiesterase isoenzyme responsible for the breakdown of cAMP. Milrinone and dobutamine both increase cAMP levels in the myocardium by different means, but the final effect is the same: they increase the concentration of calcium available in the myofibrils and consequently improve myocardial contractility [6].

Feneck et al. [24], in a randomised, open-label, multicentre study (N=120; 60 per group), compared the haemodynamic effects, effectiveness and safety of intravenous milrinone (M), 50 μg/kg over 10 min followed by 0.5 μg kg^{-1} min^{-1}, with intravenous dobutamine (D), 10–20 μg kg^{-1} min^{-1}, in patients with low cardiac output after elective cardiac surgery. The main purpose of this study was to compare the haemodynamic effects of the two drugs, efficacy and safety parameters being assessed as secondary aims.

The data suggest that both drugs effectively reverse a low-cardiac-output state after cardiac surgery, but that there are differences that may make one drug more useful for a given situation. The authors point out some pharmacological differences. When reversal of hypotension and a chronotropic response are required dobutamine appears to be preferable. When more pronounced vasorelaxant effects and avoidance of tachycardia are required, milrinone appears to be the better alternative. It was found that both drugs were equally effective for treating pulmonary hypertension. Although this study was designed to compare and contrast the two drugs, and not to study their combined effects, the authors state that a combination of both drugs would be more effective and logical than combinations of several catecholamine that share the same mechanism of action [24].

Effect of low-dose dopamine in renal function

The objective of a meta-analysis published by Marik [25] was to determine the magnitude of the treatment effect of low-dose dopamine on renal function in patients at risk of renal injury and in early renal injury. The data analysed were collected in 15 randomised controlled studies involving 970 subjects and designed to compare low-dose dopamine with placebo for the prevention or treatment of acute renal dysfunction. The main outcome measure was the absolute change in

serum creatinine. In addition, the number of patients in whom an acute diminution in renal function developed was recorded.

In conclusion, the results of this meta-analysis confirm that low-dose dopamine has no reno-protective effect. In view of the potential side effects of dopamine, this agent should not be used in for the treatment of renal injury [25].

References

1. Priebe HJ (2004) Vasoactive drugs. (IARS Review Course Lectures) Anesth Analg 64-70
2. Holubarsch C, Pieske B, Kretschmann B et al (1995) The functional role of angiotensin and endothelin in failing and nonfailing human myocardium. In: Dhalla NS, Beanish RE, Takeda N, Nagano M (eds) The failing heart. Lippincott-Raven, Philadelphia, pp 295-304
3. Holubarsch C, Ruf T, Goldstein DJ et al (1996) Existence of the Frank-Starling mechanism in the failing human heart: investigations on the organ, tissue, and sarcomere levels. Circulation 94:683-689
4. Kass DA (1992) Clinical evaluation of left heart function by conductance catheter technique. Eur Heart J 13:E57-E64
5. Feldman MA (1993) Classification of positive inotropic agents. J Am Coll Cardiol 22:1223-1227
6. Lehtonen AL, Antilla S, Pentikäinen JP (2004) Pharmacokinetics and pharmacodynamicsm of intravenous inotropic agents. Clin Pharmacokinet 43:187-203
7. Haikala H, Nissinen E, Etemadzadeh E et al (1995) Troponin C mediated calcium sensitization induced by levosimendan does not impair relaxation. J Cardiovasc Pharmacol 25:794-801
8. Haikala H, Linden J (1995) Mechanisms of action of calcium-sensitizing drugs. J Cardiovasc Pharmacol 26 (Suppl 1): S10-S19
9. Lehonen LA (2001) Levosimendan: a parenteral calcium sensitising drug with additional vasodilatatory properties. Expert Opin Investig Drugs 10:955-970
10. Krum H, Liew D (2003). New and emerging drug therapies for the management of acute heart failure. Intern Med J 33:515-520
11. Follath F, Cleland JG, Just H et al (2002) Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. Lancet 360:196-202
12. Lochner A, Colesky F, Genade S (2000) Effect of a calcium-sensitizing agent, levosimendan, on the postcardioplegic inotropic response of the myocardium. Cardiovasc Drugs Ther 14:271-281
13. Greenberg BH (2002) Endothelin and endothelin receptor antagonists in heart failure. Congest Heart Fail 8:257-261
14. Lee CR, Watkins ML, Patterson JH et al (2003) Vasopressin: a new target for the treatment of heart. Am Heart J 146:9-18
15. Schrier RW, Abraham W (1999) Hormones and hemodynamics in heart failure. N Engl J Med 341:577-585
16. Lindner KH, Strohmenger HU, Ensinger H et al (1992) Stress hormone response during and after cardiopulmonary resuscitation. Anesthesiology 77:662-668
17. Lindner KH, Haak T, Keller A et al (1996) Release of endogenous vasopressors during and after cardiopulmonary resuscitation. Heart 75:145-150

18. Paradis NA, Rose MI, Garg U (1993) The effect of global ischemia and reperfusion on the plasma levels of vasoactive peptides: the neuroendocrine response to cardiac arrest and resuscitation. Resuscitation 26:261-269
19. Stiell IG, Hébert PC, Wells GA et al (2001) Vasopressin versus epinephrine for in hospital cardiac arrest: a randomised controlled trial. Lancet 358:105-109
20. Landry DW, Oliver JA (2001) The pathogenesis of vasodilatory shock. N Engl J Med 345:588-595
21. Landry DW, Levin HR, Gallant EM et al (1997) Vasopressin deficiency contributes to the vasodilation of septic shock. Circulation 95:1122-1125
22. Patel BM, Chittock DR, Russell JA et al (2002) Beneficial effects of short-term vasopressin infusion during severe septic shock. Anesthesiology 96:576-582
23. Guzman JA, Rosado AE, Kruse JA (2003) Vasopressin vs. norepinephrine in endotoxic shock: systemic, renal, and splanchnic hemodynamic and oxygen transport effects. J Appl Physiol 95:803-809
24. Feneck RO, Sherry KM, Withington PS et al (2001) Comparison of the hemodynamic effects of milrinone with dobutamine in patients after cardiac surgery. J Cardiothorac Vasc Anesth 15:306-315
25. Marik PE (2002) Low-dose dopamine: a systematic review. Intensive Care Med 28:877-883

Chapter 42

Decision-making in critical care: Cardiac arrhythmias and related topics

J.L. Atlee

This chapter highlights topics to be addressed in cardiovascular perioperative medicine or critical care sessions at APICE 2004 and pertaining to electrocardiographic monitoring or arrhythmias. In addition to an introductory discussion (tolerance of arrhythmias, clinical significance and priorities), topics addressed are: (1) ECG monitoring for ischaemia, imbalance and arrhythmias; (2) selection of antiarrhythmic therapy: drugs vs devices; (3) management of atrial fibrillation; (4) causes and management for the acquired long QT interval syndrome; and (5) amiodarone in life-threatening supraventricular and ventricular arrhythmias. Management of patients with an implanted cardiac rhythm management device is discussed in another chapter.

Tolerance of arrhythmias, clinical significance and priorities

Factors influencing arrhythmia tolerance are: (1) duration; (2) atrial transport function; (3) presence of AV dissociation; (4) tachycardia rate; (5) structural heart disease; and (6) functional status. Untreated, neither ventricular fibrillation nor pulseless electrical activity is compatible with life. Any tachycardia increases O_2 demand and reduces diastolic time. Even sinus tachycardia may be poorly tolerated in patients with structural heart disease. However, in most cases tachycardia with under 150 beats/min does not cause rate-related signs or symptoms [1]. Finally, seemingly benign sinus bradycardia or AV junctional rhythm may not be tolerated by patients with diastolic dysfunction.

When confronted with tachycardias, one must determine whether signs or symptoms are due to tachycardia. If they are, the current ACLS Guidelines advise immediate cardioversion rather than a trial of antiarrhythmic drugs [1]. For patients in whom cardioversion is not indicated (e.g. those with ectopic atrial tachycardia), the Guidelines stress the importance of making a specific diagnosis and identifying patients with impaired cardiac function (ejection fraction (%). Further, the Guidelines play down adenosine for differentiating wide QRS tachycardias, such as ventricular aberration vs ectopy. Its use in the wrong circumstances causes unnecessary exposure of the patients to adenosine's unpleasant side effects, possibly worse arrhythmias, and destabilisation of the heart rate and pressure. Rather

than risking this, more attention should be devoted to explicit diagnoses within the scope of available resources.

Proarrhythmia with antiarrhythmic drugs

Proarrhythmia is the provocation of new or worse arrhythmias by an antiarrhythmic drug (AD). All ADs involve some risk of proarrhythmia, ranging from 1–2% (amiodarone) to 10% or higher (class IC ADs). Torsades de pointes (TDP) (polymorphic VT with QT interval prolongation) and incessant monomorphic VT (absence of QT prolongation) cause most proarrhythmic events. Proarrhythmia is more likely in patients with structural heart disease and functional impairment. ADs alter the electrophysiological properties of normal and diseased myocardium, usually favourably, to modify arrhythmia substrates. Use of two or more ADs exponentially compounds the proarrhythmia potential. Therefore, the ACLS Guidelines advise that one and only one antiarrhythmic drug be used per patient [1, 2].

ECG monitoring for ischaemia, imbalance, and arrhythmias

Surface ECG lead V5 has long been held to be the single best lead for detection of *ischaemia* [3, 4]. Landesberg et al. tested this in a study of patients with high-risk vascular surgery who were continuously monitored with 12-lead ECG during surgery and postoperatively for 48–72 h [5]. Precordial lead V3 or V5 detected 75% and V4, 83% of the ischaemic episodes detected by full 12-lead ECG. Combining two precordial leads increases the sensitivity in detection of ischaemia to 92% (either V4+V5 or V3+V4) or 97% (V3+V5). These findings require confirmation, but do provide an impetus for the use of multiple precordial lead ST-T segment trend monitoring. However, even a 12-lead ECG may fail to detect impending (ischaemia) or evolving myocardial infarction (MI) in some patients (below). While transoesophageal echocardiography (TEE) is more sensitive and allows a more timely diagnosis, it is too subjective and costly for routine ischaemia monitoring [6].

Acute coronary syndromes (ACS) cannot be diagnosed in a timely manner, whether by ECG or by enzymes. Among patients with enzyme-proven MI, the incidence of MI with diagnostic ECG changes declined by 41% and the mortality, by 10% from 1975 to 1997 [7]. With no ECG changes, enzyme-proven MI increased by 211%, while mortality was constant (12%), from 1975 to 1997. Thus, a surface ECG fails to detect MI in many patients. Myocardial enzymes are more sensitive, but irreversible injury has occurred by the time they are elevated; what is more disturbing is that it is possible for MI not to be revealed by either enzymes or ECG. Five million persons undergo chest pain evaluation in emergency rooms (ER) yearly in the U.S. [8]. The MI diagnosis is missed in 2–5% of these during the initial evaluation [9–11]. Thus, more than 100,000 persons each year sustain an MI, which in many cases is fatal.

Why is surface ECG so insensitive? Surface ECG measures the summed cardiac potentials at the body surface [12]. There is no spatial information for the distribution of bioelectric sources contributing to the surface ECG potential. In addition, the potential in any surface lead is inversely proportional to the square of the distance between the cardiac source and the surface lead site (i.e. the cardiac 'inverse problem'). If this applies, small signals from an ischaemic zone may be inundated by bioelectric signals from sources closer to the body surface leads.

Power spectral QRS analysis of surface ECG frequency content has been tested in attempts to improve on sensitivity in the detection of ischaemia [13–15]. Many ECG machines incorporate this technology. Even so, the statistics above suggest that surface ECG lacks sensitivity because of the relative remoteness of the leads. Posterior or inferior ischaemia is the most difficult to detect. One solution may be to record the ECG from closer to the source, and this approach has shown promise in an animal model [16].

Numerous drugs, pathologies and physiological imbalances can affect the ECG [17–19]. Drugs that prolong the QT interval are discussed under "Acquired long QT syndrome." The digitalis effect refers to the scooped appearance of the ST-T segment and short QT interval following reduced duration of the ventricular action potential. Such changes are accentuated by tachycardia, leading to false-positive stress tests. The digitalis effect occurs with therapeutic or toxic doses and is augmented by hypokalaemia.

Beta-adrenergic and nondihydropyridine calcium channel blockers (verapamil; diltiazem) can cause primary or secondary (type 1) AV heart block, an effect augmented by potent inhalation anaesthetics. ECG effects and toxicities of other cardioactive drugs can be anticipated in part by their channel effects. Sodium channel inactivation by class IA and 1C antiarrhythmics can prolong the QRS complex. Class IB antiarrhythmics are less likely to have this effect, except during tachycardia. Tricyclic antidepressants and phenothiazines increase the duration of both the QRS and the Q-T interval. The earliest ECG evidence of acute pericarditis is ST segment elevation in leads facing involved epicardium. Later, ST segments return to baseline and T waves become inverted. These changes can persist for months in the presence of chronic pericarditis. In pericardial effusion, QRS and T wave voltage may be reduced along with electrical alternans. Almost any infectious disease can involve the myocardium. ECG abnormalities include: (1) PR interval prolongation; (2) QRS widening; (3) altered QRS pattern; (4) Q-T prolongation; (5) ST segment depression or T wave inversion in the left chest wall leads; and (6) arrhythmias. Myxoedema causes flattened, inverted or shallow T waves without ST segment changes. Virtually any ECG pattern can be linked with cardiomyopathy. None is specific. The ECG pattern of acute cor pulmonale develops within minutes of a massive pulmonary embolus, or in hours to days with chronic cor pulmonale. This pattern resembles acute inferior wall myocardial infarction. Extreme hypothermia causes intraventricular conduction delay, which is reflected in prominent notching of the terminal QRS complex and ST segment elevation (Osborn waves). Traumatic injury can manifest as arrhythmias, a pattern consistent with pericarditis, myocardial infarction or nonspecific ST-T changes. ECG changes in neuro-

muscular disease include nonspecific ST-T changes, arrhythmias, and P-R prolongation. Subarachnoid haemorrhage or intracerebral bleeding can cause dramatic ECG changes, often with bradycardia. Precordial T waves become wide and prominent and are often inverted (occasionally upright) and continuous with large U waves, extending the T-U segment. Finally, haemodialysis can increase R wave amplitude.

The ECG is the most sensitive and specific marker for arrhythmias. Yet not all bizarre beats are of ventricular origin. They may be atrial beats conducted with ventricular aberration. This can have many causes [17–19]. In a patient with atrial fibrillation, the beat ending a short cycle preceded by one with a long cycle may be conducted with a right bundle branch block pattern aberration (Ashman's phenomenon). If it is conducted with a left bundle branch pattern aberration this signifies severe heart disease.

A few caveats apply to ECG monitoring for arrhythmias: (1) select leads that maximise P waves (inferior leads; V1; oesophageal leads); (2) use a strip-chart recorder to record events; (3) not all wide QRS tachycardia is ventricular tachycardia; (4) capture or fusion beats confirm ventricular tachycardia; and (5) without known structural heart disease, wide QRS tachycardia with Wolff-Parkinson-White syndrome (WPW) is likely to be pre-excited tachycardia. If it is, impulses conducted via accessory pathways cause widened QRS complexes. If the patient is in atrial fibrillation the ECG pattern may be difficult to distinguish from that of polymorphic ventricular tachycardia or fibrillation.[1]

Selection of antiarrhythmic therapy: drugs vs devices

Antiarrhythmic drugs (ADs) take time to produce their effect and have potent effects on cardiac function. They can: (1) depress systolic function; (2) cause venodilatation to reduce preload; (3) alter diastolic function; and (4) cause AV heart block or bradycardia. All ADs block ion channels found in cardiac and vascular smooth muscle and the central nervous system. Chronic use can have other adverse effects (e.g. pulmonary fibrosis with amiodarone; systemic lupus erythematosus-like syndrome with procainamide). In addition, ADs may interact with other drugs, affecting autonomic or neural function. Once they have been given there is no turning back. Finally, interactions between ADs and abnormal myocardium can be complex, leading to inadequate arrhythmia control or proarrhythmia [20].

In contrast to drugs, pacing, cardioversion or defibrillation can be turned on and off at will. Also, the energy needed can easily be titrated to effect, and the effects are immediate. Given the deficiencies of drugs, it is not surprising that 'electricity'

[1] Atrial fibrillation with extremely fast ventricular rates (300 beats/min) is possible, limited only by the refractory period of the accessory pathway. Rapid, widened QRS complexes due to ventricular pre-excitation may be difficult to distinguish from ventricular fibrillation or fast polymorphic ventricular tachycardia and similarly cause profound haemodynamic decompensation. Immediate cardioversion may be necessary.

has assumed a more prominent place in the overall management and prevention of arrhythmias [21, 22]

With reference to the choice between drugs and electricity for arrhythmia management some generalisations can be made [1, 2, 19–24]. First, regardless of its origin or cause, harmful bradycardia is best managed with temporary pacing rather than drugs to accelerate sinus or lower pacemakers. Positive chronotropes may provoke tachyarrhythmias or precipitate ACS. Second, automatic tachyarrhythmias are not amenable to cardioversion. Cardioversion will not affect arrhythmia, or will accelerate it or provoke far worse arrhythmias or even ventricular fibrillation. Third, if destabilising tachycardia is amenable to cardioversion, it should be used. The use of drugs to prevent recurrences should be considered. Fourth, all wide QRS tachycardia is not ventricular in origin. If it is destabilising, the origin does not matter. Early cardioversion or defibrillation is required. For example, pre-excited atrial fibrillation will probably cause severe impairment owing to extremely fast ventricular rates (>300 bpm). Both haemodynamic effects and appearance will be similar to polymorphic ventricular tachycardia or ventricular fibrillation, for both of which the treatment is the same: cardioversion, with drugs to prevent recurrences. Finally, something that is often overlooked is imbalance. It is necessary to identify and correct any contributing imbalance, which will go a long way towards preventing recurrences and facilitating more specific therapy.

Management of atrial fibrillation

Ventricular pacing increases the ventricular rate, relieving bradycardia and symptoms [1, 2, 23, 24]. Prompt cardioversion (100–200 J) is required for haemodynamically unstable atrial fibrillation (AFB), regardless of its duration. Rate control with drugs is the recommended initial treatment for haemodynamically stable AFB (≥120 beats/min), regardless of its duration. Adenosine is not advised for rate control. β-blockers or CCB are reasonable with good LV function, or digitalis or amiodarone in patients with heart failure.

AFB with WPW may cause fast ventricular rates, with early transition to ventricular fibrillation. CCB, adenosine, digitalis and β-blockers (do not affect accessory pathways [AP]), may increase the ventricular rate, destabilising the patient. When this occurs prompt cardioversion is advised. Otherwise, a drug that prolongs AP conduction and refractoriness (e.g. amiodarone, flecainide, procainamide, propafenone) will slow the ventricular rate or even convert some AFB to sinus rhythm.

If DC conversion is not feasible, desirable or successful, patients with preserved LV function may be 'chemically cardioverted' with IV procainamide, amiodarone, flecainide, propafenone, disopyramide or sotolol. In those with LV dysfunction, negative inotropic effects of sotalol, flecainide, propafenone, procainamide or ibutilide, and proarrhythmia make their use less desirable. Pre-excited arrhythmias in patients with impaired LV function are best treated with IV amiodarone. The risk of thromboembolism is highest in patients with a previous history of such

events, mitral stenosis, enlarged left atrium, chronic AFB, hypertension or diabetes. Three weeks of anticoagulation is advised before elective cardioversion of AFB. Finally, drugs that can be used for prophylaxis against AFB in cardiac and noncardiac surgery include β-blockers, amiodarone and sotalol. Digoxin and verapamil are not effective.

Causes and management of acquired long QT syndrome

QT prolongation predisposes patients to possibly fatal torsades de points (TdP) [25–27]. While long-QT syndrome (LQTS) is often regarded as congenital (C-LQTS) or acquired, a gene–environment interaction is probably involved [25]. 'Pure' C-LQTS is rare, but carries a high risk of sudden death. Several forms are known (LQT1, LQT2, LQT3), each with different clinical manifestations and outcomes, including factors that trigger arrhythmias to cause sudden death or syncope [25, 26]. Physical activity triggers events in LQT1, auditory stimuli in LQT2 and rest or sleep in LQT3. Each form involves mutations of genes that encode cardiac ion channels involved in depolarisation (LQT3) or depolarisation (LQT1 and LQT2). While the risk of cardiac events is significantly higher with LQT1 or LQT2, that for lethal events is higher with LQT3. Finally, there can be incomplete penetrance of gene defects in C-LQTS [27]. Thus, close relatives of persons with C-LQTS can have gene mutations but have near-normal QT intervals and lack any predisposition to lethal arrhythmias.

Drugs that prolong the QT interval and represent a proven risk of TdP are listed in Table 1. A more extensive listing, including drugs with lower risk, can be found at http://www.torsades.org. When there is baseline QTc prolongation (men > 450 ms; women >460 ms) but no interventricular conduction defects, all QT-prolonging medications should be avoided (Table 1) [25]. When QT-prolonging antiarrhythmic drugs are given, the risk of TdP is highest in patients with structural heart disease within the first few days of beginning therapy [25]. For this reason, it is recommended that such patients be hospitalised so that they can be monitored for warning signs of TdP (QTc >500–520 ms[2]) [25].

When exposed to QT-prolonging drugs or imbalance (e.g. hypokalaemia), individuals without life-threatening QT prolongation may develop it with or without TdP, or not develop it at all [25, 27]. Current evidence suggests that 5–10% of persons in whom TdP develop on exposure to QT-prolonging drugs have gene mutations associated with LQTS, and these are viewed as having a subclinical form of the congenital syndrome [27]. Another explanation is that common gene polymorphisms cause subtle variations in ion channels generating cardiac action potentials. These defects become apparent only when the person concerned is exposed to drugs

[2] There is no clear consensus on the degree of drug-induced QT prolongation that should require discontinuation of a drug that prolongs the QT interval, although respondents to a survey [25] were more likely to stop a QT-prolonging medication for a QT of 520 ms than for one of 500 ms.

Table 1. Drugs that prolong the QT interval and involve a recognised risk of torsades de points (TdP)

Generic name	Trade name	Clinical indication(s)/use	Risk of TdP; comments
Amiodarone	Cordarone, Pacerone	Antiarrhythmic	Low (<1–2%)
Arsenic trioxide	Trisenox	Antineoplastic; leukaemia	
Bepridil	Vasocor	Antianginal	Female > male
Chloroquine	Arelan	Antimalarial	
Clorpromazine	Thorazine	Antipsychotic; antiemetic; schizophrenia; nausea	
Cisapride	Propulsid	Prokinetic; reduce gastric secretions	Female > male; restricted use (U.S.)
Clarithromycin	Biaxin	Antibiotic	High (≤10%)[a]
Disopyramide	Norpace	Antiarrhythmic (class 1A)	
Dofetilide	Tikosyn	Antiarrhythmic (class III)	
Domperidone	Motilium	Antiemetic/nausea	
Droperidol	Inapsine	Antiemetic/nausea	
Erythromycin	Erythrocin; E.E.S.	Antibiotic; prokinetic	
Halofantrine	Halfan	Antimalarial	Female > male
Haloperidol	Haldol	Antipsychotic; schizophrenia; agitation	
Ibutilide	Corvert	Antiarrhythmic (class III)	High (≤10%)[a] female > male
Levomethadyl	Orlaam	Opiate agonist; pain control; narcotic dependence	
Mesoridazine	Serentil	Antipsychotic; schizophrenia	
Methadone	Dolophine	Opiate agonist; pain control; narcotic dependence	Female > male
Pentamidine	NebuPent	Antimicrobial; pneumocystis pneumonia	Female > male
Pimozide	Orap	Antipsychotic/ Tourette's tics	Female > male
Procainamide	Pronestyl	Antiarrhythmic (class 1A)	
Sotolol	Betapace	Antiarrhythmic (class III)	Female > male
Sparfloxacin	Zagam	Antibiotic	
Thioridazine	Mellaril	Antipsychotic	

[a] Highest in patients with structural heart disease. Source: http://www.torsades.org; also, class II

that block K-channels (sotalol, ibutilide, dofetilde, amiodarone) or some other form of stress (e.g. hypokalaemia or heart failure) [27]. Such variants can be frequent (~15% in some populations) and they vary among ethnic groups [27].

Factors in predisposition to acquired QT prolongation (A-LQTS) and TdP are older age, female sex and reduced left ventricular ejection fraction (associated remodelling provides the substrate for TdP[3]). Management of TdP requires urgent suppressive measures. Magnesium may suppress it, but fails to shorten the QT interval [26]. Increasing the heart rate with atropine or isoproterenol, or *preferably* in a more controlled fashion with temporary atrial or ventricular pacing, often suppresses TdP. Fast pacing shortens action potential duration and the QT interval and suppresses EAD. In addition, any electrolyte abnormalities must be corrected and QT-interval-prolonging drugs, discontinued. Finally, K-channel openers (pinacidil, cromakalim) can be useful in both C-LQTS and A-LQTS [23].

Amiodarone for life-threatening supraventricular and ventricular arrhythmias

Amiodarone has all four Vaughan-Williams class actions [2], but has a lower proarrhythmia potential (2–4%) than other antiarrhythmics (5–10%). IV amiodarone is useful (1) for ventricular rate control of rapid atrial arrhythmias with severely impaired ventricular function when digitalis has proved ineffective; (2) for control of haemodynamically stable wide-QRS complex tachycardia of uncertain origin; (3) as an adjunct to cardioversion of drug-refractory paroxysmal supraventricular tachycardia, atrial tachycardia and pharmacological conversion of atrial fibrillation or flutter; and (4) to control rapid ventricular rates with pre-excited atrial tachyarrhythmias [2]. When heart function is severely impaired, IV amiodarone is preferable to other IV drugs for atrial and ventricular arrhythmias, because its efficacy is high and it causes less proarrhythmia than any of the others [2]. Amiodarone is indicated after defibrillation, and epinephrine or vasopressin for persisting ventricular tachycardia (VT) or fibrillation (VF) [2, 27-32]. It may suppress AV junctional tachycardia, especially in children who have undergone open heart surgery. Withdrawal of any inciting factors (digitalis, catecholamines or theophylline [2]) is also necessary. Junctional tachycardia is not amenable to electrical cardioversion. It may be overdriven by temporary atrial pacing, with gradual 'weaning' from pacing thereafter.

References

1. Anonymous (2000) Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. 6. Advanced cardiovascular life support. Section 7D: The tachycardia algorithms. (Issued by the American Heart Association in collaboration with the International Liaison Committee on Resuscitation) Circulation 102:I-158–I-165
2. Anonymous (2000) Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. 6. Advanced cardiovascular life support. Section 5: Pharmacology II: Agents for arrhythmias. (Issued by the American Heart Association in collaboration with the International Liaison Committee on Resuscitation) Circulation 102:I-112–I-128
3. Blackburn H, Katigbak R (1964) What electrocardiographic lead to take after exercise? Am Heart J 67:184-185
4. London MJ, Hollenberg M, Wong MG et al (1988) Intraoperative myocardial ischemia: localization by continuous 12-lead electrocardiography. Anesthesiology 69:232-241
5. Landesberg G, Mosseri M, Wolf Y et al (2002) Perioperative myocardial ischemia and infarction: Identification by continuous 12-lead electrocardiogram with online ST-segment monitoring. Anesthesiology 96:264-270
6. Fleisher LA, Weiskopf RB (2000) Real-time intraoperative monitoring of myocardial ischemia in noncardiac surgery. Anesthesiology 92:1183-1188
7. Furman MI, Dauerman HL, Goldberg RJ et al (1997) Twenty-two year (1975-1997) trends in the incidence, in-hospital and long-term case fatality rates from initial Q-wave and non-Q-wave myocardial infarction: a multi-hospital, community wide perspective. J Am Coll Cardiol 37:1571-1580
8. Nourjah P (1999) National Hospital Ambulatory Medical Care Survey: 1997 emergency department summary. Advance data from Vital and Health Statistics. National Center for Health Statistics, Hyattsville, Md, p 304
9. Welch RD, Zalenski RJ, Frederick RD et al (2001) Prognostic value of a normal or nonspecific initial electrocardiogram in acute myocardial infarction. JAMA 286:1977-1984
10. Jesse RL, Kontos MC (1997) Evaluation of chest pain in the emergency department. Curr Probl Cardiol 22:149-236
11. Pope HJ, Aufderheide TP, Ruthazer R et al (2000) Missed diagnosis of acute cardiac ischemia in the emergency department. N Engl J Med 342:1163-1170
12. Cohen RJ (2000) T wave alternans and laplacian imaging. In: Zipes DP, Jalife J (eds) Cardiac electrophysiology, 3rd edn. Saunders, Philadelphia, pp 781-789
13. Mor-Avi V, Shargorodsky B, Abboud S et al (1987) Effects of coronary occlusion on high-frequency content of the epicardial electrogram and body surface electrocardiogram. Circulation 76:237-243
14. Abboud S, Belhassen B, Miller HI et al (1986) High frequency electrocardiography using an advanced method of signal averaging for non-invasive detection of coronary artery disease in patients with normal conventional electrocardiogram. J Electrocardiol 19:371-380
15. Abboud S, Cohen RJ, Selwyn A et al (1987) Detection of transient myocardial ischemia by computer analysis of standard and signal-averaged high-frequency electrocardiograms in patients undergoing percutaneous transluminal coronary angioplasty. Circulation 76:585-596
16. Mächler HE, Lueger A, Rehak P et al (1998) A new high-resolution esophageal electrocardiography recording technique: an experimental approach for the detection of myocardial ischemia. Anesth Analg 86:34-39

17. Mirvus DM, Goldberger AL (2001) Electrocardiography. In: Braunwald E, Zipes DP, Libby P (eds) Heart disease, 6th edn. Saunders, Philadelphia, pp 82-128
18. Wagner GS (1994) Marriott's Practical electrocardiography, 9th edn. Williams & Wilkins, Baltimore
19. Alee JL (1996) Arrhythmias and pacemakers. Saunders, Philadelphia, p 465
20. Zipes DP, Wellens HJJ (2000) What have we learned about cardiac arrhythmias? Circulation 102: IV-52–IV-57
21. Crystal E, Connolly SJ, Dorian P (2003) Prevention and treatment of life-threatening ventricular arrhythmia and sudden death. In: Yusef S, Cairns JA, Camm AJ, Fallen EL, Gersch BJ (eds) Evidence-based cardiology, 2nd edn. BMJ Books, London, pp 577-786
22. Toff WD, Camm AJ (2003) Impact of pacemakers: when and what kind? In: Yusef S, Cairns JA, Camm AJ, Fallen EL, Gersch BJ (eds) Evidence-based cardiology, 2nd edn. BMJ Books, London, pp 587-618
23. Olgin JE, Zipes DP (2001) Specific arrhythmias: diagnosis and treatment. In: Braunwald E, Zipes DP, Libby P (eds) Heart disease, 6th edn. Saunders, Philadelphia, pp 815-889
24. Crijns H JGM, Van Gelder IC, Savelieva I, Camm AJ (2003) Atrial fibrillation: antiarrhythmic therapy. In: Yusef S, Cairns JA, Camm AJ, Fallen EL, Gersch BJ (eds) Evidence-based cardiology, 2nd edn. BMJ Books, London, pp 519-547
25. Al-Khatib SM, LaPointe NMA, Kramer JM, Califf RM (2003) What clinicians should know about the QT interval. JAMA 289:2120-2127
26. El-Sherif N, Trritto G (1999) The long QT syndrome and torsades de pointes. Pacing Clin Electrophysiol 22:91-110
27. Roden DM (2004) Drug-induced prolongation of the QT interval. N Engl J Med 350:1013-1022
28. Levine JH, Massumi A, Scheinman M et al (1996) Intravenous amiodarone for recurrent sustained hypotensive ventricular tachyarrhythmias. J Am Coll Cardiol 27:67-75
29. Scheimann MM, Levine JH, Cannom DS et al (1995) Dose-ranging study of intravenous amiodarone in patients with life-threatening ventricular tachyarrhythmias. Circulation 92:3264-272
30. Kowey PR, Levine JH, Herre JM et al (1995) Randomized, double-blind comparison of intravenous amiodarone and bretylium in the treatment of patients with recurrent, hemodynamically destabilizing ventricular tachycardia or fibrillation. Circulation 92:3255-3263
31. Kudenchuk PJ, Cobb LA, Copass MK et al (1999) Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. N Engl J Med 341:871-878
32. Dorian P, Cass D, Schwartz B et al (2002) Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation. N Engl J Med 346:884-890

Chapter 43

Management for the patient with an implanted cardiac rhythm management device

J.L. Atlee

A cardiac rhythm management device (CRMD) is an implanted pacemaker (PM) or cardioverter-defibrillator (ICD). All present-day ICDs provide pacing and shock therapies for bradyarrhythmias and tachyarrhythmias. In addition, some CRMDs provide cardiac resynchronisation therapy (CRT). CRT is left- or biventricular pacing to synchronise ventricular contractions in patients with heart failure and left bundle branch block or intraventricular conduction delay. CRT improves haemodynamic profiles and quality of life in these patients [1–7]. Furthermore, CRT reduces the risk of the combined end-points of death and hospitalisation for heart failure (34% for CRT; 40% for CRT/ICD) [8].

In this paper the following aspects are discussed: (1) indications; (2) device design, function and malfunction; (3) mechanical and electromagnetic interference (EMI); and (4) management of patients with CRMD[1] [9, 10].

Indications

Indications for temporary pacing are: (1) sinus bradycardia or escape rhythms with haemodynamic compromise attributable to reversible causes; (2) advanced secondary or tertiary atrioventricular (AV) heart block, as a bridge to permanent pacing; (3) asystole, new bifascicular block with primary AV heart block, alternating bundle branch block, symptomatic or disadvantageous bradycardia not responsive to drugs, or type II secondary AV heart block in acute myocardial infarction; (4) bradycardia-dependent tachycardia (e.g., torsades de pointes with congenital or acquired long QT interval syndrome).

Patients with sinus node dysfunction or AV heart block may have symptoms caused by bradycardia, ventricular arrhythmias, or both. The decision to implant a permanent pacemaker is supported by the presence of symptoms attributable to

[1] At the time of this writing (May 2004), a draft version of a CRMD Practice Advisory prepared by a Task Force commissioned by the American Society of Anesthesiologists (ASA) in 2003, of which this author was a member, was in the final stages of preparation. If approved by the ASA House of Delegates at the 2004 Annual Meeting, this document should be available in the Journal *Anesthesiology* and/or posted on the ASA website (www.asawebapps.org) by Spring 2005.

bradycardia or arrhythmias. Many indications for pacing have evolved over more than 30 years on the basis of experience rather than of prospective randomised trials, because there was no alternative treatment (e.g. secondary or tertiary AV heart block with bradycardia and symptoms). Pacing may be indicated for asymptomatic tertiary AV heart block with rates below 40 bpm or asymptomatic type I or II AV block below the bundle of His, or primary AV block with heart failure or symptoms of low cardiac output relieved by temporary pacing. Sinus node dysfunction or chronotropic incompetence can be acquired or due to drugs for which no alternative is available.

Indications for pacing in children and adolescents are similar to those in adults. However, they are based more on whether there is any correlation between symptoms and bradycardia and, if so how close this is, than on arbitrary rate criteria. In addition, permanent pacing for bradycardia is indicated only after exclusion of other causes (e.g. seizures, breath-holding, apnoea, neurally mediated causes). Finally, permanent pacing may be indicated for syncope caused by hypersensitive carotid sinus or neurally mediated syndromes.

Indications for insertion of an ICD are: (1) cardiac arrest due to ventricular tachycardia or fibrillation (VT, VF) not due to transient or reversible causes; (2) sustained VT; (3) syncope of undetermined origin, haemodynamically significant sustained VT or VF induced during a cardiac electrophysiological (EP) study when drug therapy is not effective, tolerated or preferred; and (4) nonsustained VT (lasting =15 s) with coronary artery disease (CAD), old myocardial infarction (MI), LVEF =40%) and inducible VF/VT on EP study not suppressed by a class I antiarrhythmic drug. Other indications are: (1) cardiac arrest presumed to be secondary to VT/VF when other medical conditions preclude cardiac EP study; (2) severely symptomatic VT before heart transplantation; (3) long QT interval syndrome, hypertrophic cardiomyopathy and other familial conditions involving a high risk of life-threatening ventricular arrhythmias; (4) inducible, sustained VT/VF in patients with nonsustained VT, CAD, old MI and LV dysfunction; and (5) recurrent syncope of unknown aetiology with LVEF ≤40% and inducible ventricular arrhythmias on EP study if other causes of syncope are excluded.

Device design and function

Most pacemakers (PMs) in current use are conventional or adaptive-rate devices. They are powered by lithium-iodide batteries, with an expected service life of 5–12 years, depending on capabilities. Most PMs employ bipolar leads. These reduce (but do not eliminate) susceptibility to electromagnetic inference (EMI)-related malfunction. PMs sense atrial or ventricular depolarisation and respond to events sensed by triggering or inhibition of pacing in the appropriate chamber. Coding is used to designate CRMD function [11]. 'O' in the first or second position means none. The letter 'A', 'V' or 'D' in one of these positions means atrium, ventricle and dual, respectively. The character in the third position indicates the response (stimulation) to sensing ('O' = none; 'T' = triggered; 'I' = inhibited) in

one or the other chamber. If stimulation is inhibited in one chamber and triggered in the other by a sensed event, as in atrial-inhibited, ventricular-triggered pacing, then 'D' in the third position designates dual. For example, a CRMD programmed VDD stimulates only in the ventricle, but senses in both chambers. In addition, a sensed atrial event will trigger ventricular stimulation if no spontaneous ventricular event is sensed before the A-V interval is timed out. If programmed DDD, the CRMD paces the atria as well as all VDD functions. Either a sensed or a paced atrial event can trigger ventricular stimulation, provided the A-V interval has not timed out first as the result of a sensed spontaneous event. 'O' or 'R' in the fourth position designates none or rate modulation, respectively. Thus, DDDR designates a dual-chamber CRMD with pacing and sensing in both chambers; triggering or inhibition of pacing in the ventricle; inhibition only in the atria; and adaptive rate pacing. The fifth position is for multisite pacing. 'O' designates none, and 'A', 'V' or 'D' 'atrium', 'ventricle' or 'dual', respectively. A DDD, adaptive rate PM with biventricular pacing for CRT would be designated DDDRV.

An ICD consists of a pulse generator and leads for detection and diagnosis of tachyarrhythmias and bradyarrhythmias, with provision for antibradycardia or antitachycardia pacing in response to sensed events. In addition, there could be cardioversion or defibrillation shocks if required [12]. In addition, ICDs provide telemetry for stored electrograms and event logs. Expected service life is shorter than for PMs (5–8 years). Tachycardia detection and diagnosis differ for VT and VF, and algorithms must distinguish atrial fibrillation from VT or VF. Thus, algorithms are complex, and vary for different manufacturers [9, 12]. The risk of spurious shocks for misdiagnosed arrhythmias is now very low compared with earlier devices. Since most monomorphic VT (≥90%) is terminated by a critical antitachycardia pacing (ATP) sequence, provision for ATP greatly reduces the need for painful shocks. ATP is programmed during EP study. While ATP terminates most VT, there is some risk that it will not do so or that it will only accelerate its rate. In addition, if ATP is applied during a misdiagnosed supraventricular tachycardia it may induce VT or VF in some patients.

Device malfunction

Primary pacing malfunction can occur with PMs or ICDs, since all ICDs in current use have at least single-chamber pacing capability and most also have the full antibradycardia, antitachycardia and adaptive rate capabilities. Primary PM function is rare, accounting for less than 2% of device-related problems. Some PM have programmed behaviour simulating malfunction (pseudomal function); for example with rate hysteresis.[2] True malfunction includes failure to pace, failure to capture, pacing at an abnormal rate, undersensing, oversensing and malfunction unique to dual-chamber PMs. Causes of malfunction are listed in Table 1 and causes of failure to capture in Table 2.

[2] The pacing interval after a sensed spontaneous beat is longer than after paced beats to encourage the emergence of intrinsic rhythm.

Table 1. Pacemaker malfunction common to single- and dual-chamber pacemakers

Failure to pace	No pacing artefacts in either or both of the chambers. Intrinsic rate below lower rate interval (from patient's records; device interrogation). Easily misdiagnosed if device inhibited by intrinsic cardiac events not apparent in surface ECG or with impending battery depletion (elective replacement indicator rate is not the same as the nominally programmed rate). Often due to oversensing. Other causes include system component failure or problems with lead–tissue interface.
Failure to capture	Visible pacing artefacts (one or both chambers) but no or intermittent atrial or ventricular depolarisations. Confirmation requires device interrogation to examine event markers and other parameters (lead impedance; pacing and sensing thresholds). Drugs or imbalance that increase pacing thresholds can be a cause (Table 2).
Pacing at abnormal rate (PAR)	PAR can be intended or nonintended CRMD function. PAR can correspond to the elective replacement indicator, or output is not visible during bipolar pacing due to low amplitude of bipolar pacing artefacts.[a] Upper rate behaviour is normal device function if it occurs in response to an adaptive rate sensor. In rare cases, very rapid ventricular pacing may be due to PMr runaway, which can occur with a single- or dual-chamber PM, requires at least two system component failures, and can trigger lethal arrhythmias.
Undersensing	Cardiac electrograms must have adequate amplitude slew rate to be sensed properly. Attenuation of either may cause undersensing, and drugs and other factors that affect pacing thresholds can also be the cause of undersensing (Table 2). Undersensing occurring shortly after implantation may be due to lead dislodgement or malposition, or to cardiac perforation. Later undersensing could be due to battery depletion or system component failure. Undersensing can also be due to altered cardiac signal morphology (e.g. myocardial ischaemia or infarction; cardiac remodelling; new intraventricular conduction block; transient imbalance; or preceding external cardioversion or defibrillation).

[a] Many current ECG monitors incorporate a feature that can be selected for amplification of bipolar pacing artefacts on the monitor screen or strip-chart recordings

Table 2. Drugs and other factors that can affect pacing thresholds

Effect	Drugs	Imbalance
Increases threshold	Bretylium; sotolol; class 1C antiarrhythmics (flecainide)	Myocardial ischaemia and infarction; hyperkalaemia; severe acidosis/alkalosis; after ICD shocks or external cardioversion/defibrillation
Possibly increases threshold	Beta blockers; class 1A and 1B antiarrhythmics; verapamil	Myxoedema; hyperglycaemia
Possibly decreases threshold	Atropine and similar drugs; catecholamines; steroids	Phaeochromocytoma; hypermetabolic states (e.g. thyroid disease, sepsis)
No known effect on threshold	Inhalation and IV anaesthetics; amiodarone	

Crosstalk inhibition and PM-mediated tachycardia are types of malfunction specific to devices with dual-chamber pacing and sensing. Crosstalk is the appearance in the atrial or ventricular sense channel or circuit of unwanted electrical signals present in the other, leading to inhibition of pacing stimuli in the other channel. Crosstalk inhibition of ventricular pacing can be prevented by using bipolar atrial stimulation (creates a smaller artefact), increasing the ventricular sensing threshold, decreasing current for atrial stimulation, or programming a longer ventricular blanking period (i.e. ventricular sensing is disabled to avoid overloading the sense amplifier by voltages generated by atrial pacing stimulation).

Pacemaker-mediated tachycardia (PMT) is unnecessary rapid pacing caused by the device or interactions with the patient. PMT includes PM runaway, sensor driven tachycardia, tachycardia during magnetic resonance imaging (MRI), tachycardia due to the tracking of myopotentials or atrial tachyarrhythmias, and pacemaker re-entry tachycardia. Adaptive rate (AR) devices that sense vibration, impedance changes or the QT interval may sense physiological or mechanical interference to cause inappropriately high-rate pacing (sensor-driven tachycardia). AR pacing should be disabled in patients exposed to such interference. Pacemaker runaway was common earlier, but is now limited by upper rate cut-offs. There are several possible causes of tachycardia during MRI. Static magnetic fields can produce a torque effect on the PG or close the magnetic reed switch to cause asynchronous pacing (unlikely these days because CRMDs contain little ferromagnetic material). CRMD leads may serve as antennae for radiofrequency energy. This may generate sufficient current in the leads to produce pacing at the frequency of the pulsed energy (60–300 bpm). Gradient magnetic fields may induce enough voltage in the circuitry to inhibit a demand PM, but are unlikely to cause pacing. The atrial channel of a unipolar, dual-chamber PM that tracks P-waves may sense and track myopotentials from muscle beneath the PG, with triggered pacing up to the programmed maximum tracking rate. Similarly, atrial tachyarrhythmias may be tracked by ventricular pacing at or near the upper rate interval. Algorithms now

discriminate nonphysiological atrial tachycardia and automatically switch to a nontracking mode (automatic mode-switching). Finally, pacemaker re-entry tachycardia (PRT) incorporates the CRMD into the re-entry circuit. There must be intact retrograde (VA) conduction via an accessory AV pathway or the AV node, and the device must be programmed to an atrial-tracking mode.[3] PRT is initiated by a premature ventricular beat that is conducted back to the atria and sensed, then initiating the PM's AV interval. This times out with delivery of ventricular stimulation, and the process self-repeats. One way to prevent PRT is to programme a longer postventricular atrial refractory period. Also, magnet application4 over the pulse generator (PG) will terminate most PRT by disabling sensing and producing asynchronous, dual-chamber pacing (DOO).

In addition to any conceivable PM malfunction, specific ICD malfunction includes inappropriate shocks, failure to deliver antitachycardia pacing (ATP) or shock therapy, ineffective shocks and interactions between drugs or devices[5] affecting efficacy of therapy. Inappropriate shocks can be due to a sensed artefact or to misdiagnosed supraventricular tachycardia or nonsustained VT. The failure to deliver therapy or ineffective shocks may be due to magnet-disabled sensing or undersensing of VT/VF. Neither X-rays nor computer tomography affect shock delivery. Lead problems may also cause failure to deliver ATP or shocks. Physiological imbalance or MI may increase thresholds for shocks or the ability to detect or discriminate tachyarrhythmias. Antiarrhythmic drugs may affect the efficacy of ICD therapy by changing the morphology or rate of VT. They may also cause proarrhythmia (increase the need for shocks), or increase defibrillation thresholds. For the rare patient with both PM and ICD, sensed pacing artefact may be diagnosed as VT or VF, triggering unnecessary therapies. Finally, magnet application may disable tachycardia sensing and delivery of therapy. Except for Guidant devices, sensing is inhibited only while a magnet is directly over the PG. With Guidant ICDs, magnet application for <30 s will disable sensing temporarily. Application for >30 s requires subsequent magnet application for >30 s to re-enable sensing.

Electromagnetic and mechanical interference

CRMDs are well shielded against most EMI [10]. The use of bipolar sensing has further reduced the problem. EMI frequencies above 10^9 Hz (i.e., infrared, visible

[3] About 80% of sick sinus syndrome patients and 35% of those with AV heart block have VA conduction. Thus, more than 50% of patients with DDD devices are susceptible to PRT [9].

[4] Most pulse generators respond to a magnet with asynchronous pacing in a device-specific single-chamber (SOO) or dual-chamber mode (DOO) [9]. However, in some, the magnet response may have been programmed off. In others, a variety of responses may have been programmed, some of which do not confer immunity to sensing. In still others, the device will continue to pace SOO or DOO, or pacing will cease after a programmed number of intervals.

[5] Such interactions are now rare because there are few patients with implanted PM and ICD.

and UV light, X-rays and gamma rays) do not interfere with CRMDs, since the wavelengths are shorter than the device or lead dimensions. High-intensity therapeutic X-rays and irradiation can directly damage circuitry. EMI enters a CRMD by radiation or conduction, which depends on whether or not there is direct contact with the source or whether the leads act as antennae. Shielding and filtering exclude noncardiac signals. If EMI does enter the device, noise protection algorithms reduce its effect. EMI between 5 and 100 Hz is not filtered (these frequencies overlap those of cardiac signals) and may give rise to anomalous behaviour. Possible responses are: (1) inhibition or triggering of pacing; (2) asynchronous pacing; (3) mode resetting; (4) damage to circuitry; and (5) triggering of spurious ICD shocks.

Specific interference

In hospital, EMI includes surgical electrocautery, external cardioversion–defibrillation (CV/DF) shocks, MRI, therapeutic radiation, lithotripsy, radiofrequency arrhythmia ablation (RFA), electroconvulsive therapy (ECT) and transcutaneous electric nerve stimulation (TENS) [10]. Bone hammers/saws and mechanical ventilators may interfere with vibration, acceleration or minute-ventilation adaptive-rate CRMDs.

Surgical electrocautery

Current generated by unipolar electrocautery in CRMD is related to the distance and orientation of the cautery tool and grounding plate to the PG and leads. As this increases, a smaller voltage difference is measured in the PG. High current is generated in the PG if the cautery tool is close to it, and even higher current if the PG is between the cautery tool and grounding plate. Bipolar cautery produces the least voltage differences in PG circuitry. Anomalous behaviour with cautery EMI is mentioned above. Further, cautery may overwhelm the impedance-measuring circuit of minute ventilation adaptive-rate CRMD, causing pacing at the upper rate limit. Finally, induced currents in the CRMDs leads may cause heating at the electrode–tissue interface, leading to tissue damage and elevated pacing or sensing thresholds. Fortunately, these are usually transient.

External cardioversion and defibrillation shocks

CV/DF produces sufficient energy near a CRMD to damage the PG or electrode–tissue interface. Transient elevation of pacing and sensing thresholds is not uncommon after external or internal defibrillation. Unipolar systems are most susceptible. ICDs deliver less energy, but can interfere with PM function. It is likely that ICD shocks will activate the back-up or reset modes, or the elective replacement indicator. However, for ICD with programmable lead configuration, unipolar pacing will be delivered in the back-up or reset modes. Since unipolar stimuli are likely to be detected by ICD, it was formerly necessary to implant a dedicated PM in patients

with ICD, to programme a bipolar configuration, or to test unipolar stimulation to assure no malfunction occurred.

Other sources of EMI

It is advised that patients with CRMDs do not undergo *MRI*. While a few descriptive studies and case reports suggest otherwise, there are restrictions. These include: (1) reprogramming the device to an asynchronous pacing mode; (2) disabling antitachycardia pacing or shock therapies; and (3) not placing the PG or leads within the magnet bore [13].[6] If the patient has adequate intrinsic rhythm, the device must be programmed to its lowest voltage and pulse width or OOO. Otherwise, it must be programmed to SOO or DOO. The pulse waveform should be closely monitored in any PM-dependent patient. Also, inactivate antitachycardia pacing/shock therapies, and have an external cardioverter-defibrillator at hand. CRMD function must be checked after any *MRI*.

Diagnostic radiation has no effect on CRMDs. Therapeutic radiation therapy (RT) can cause PG failure in modern CRMDs. RT produces leakage currents between insulated circuitry parts, causing inappropriate charge accumulation in the silicon oxide layers, leading to eventual circuit failure. RT involves cumulative doses up to 70 Gy, and devices may fail with as little as 10 Gy. Failure is unpredictable, possibly involving changes in sensing thresholds, or pulse amplitude or width. Also, loss of telemetry, output failure or PM runaway rates may occur. Replacement of the device may be necessary. While some changes may resolve in a matter of hours, long-term reliability of the device is suspect. Therefore, before the start of any course of RT, the CRMD must be identified and its function evaluated. RT to any part of the body far removed from the PG site should not cause problems, but the PG must still be shielded to avoid potential damage from scatter. If this is not possible the PG should be removed and reimplanted as far as possible from the ionising beams of RT. The cumulative doses of RT energy to which the PG is exposed must be recorded for each session. Finally, CRMD function must be evaluated during and after the course of RT.

Vibration or acceleration adaptive-rate (AR) CRMD may malfunction during orthopaedic surgery [14]. Positive-pressure ventilation may affect minute ventilation AR [15]. *ECT* appears to be safe with CRMDs, since little current flows within the heart owing to high body tissue impedance [14] However, ECT may generate sufficient myopotentials for inhibition of pacing stimuli (unipolar CRMD) or cause rapid pacing (AR devices) [14]. Extracorporeal shock wave lithotripsy (ESWL) appears to be safe, provided shocks are synchronised to ECG R or S waves and DDD devices have their crosstalk management feature enabled [14, 16]. Activity-sensing AR PMs may increase their rate after ESWL shocks. If detrimental, AR pacing should be disabled.

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[6] Additional references will be available in the ASA CRMD Advisory (refer to footnote 1).

Programming a DDD device to VVI, VOO or DOO is advised to avoid irregularities in pacing rate, tracking of ESWL-induced supraventricular tachycardia, or triggering of ventricular output by sensed shocks [14]. For ICD, disable tachycardia detection, and confirm function after ESWL [14]. TENS appears to be safe in the presence of CRMD with bipolar lead polarity [10]. However, the device's function must be monitored during initial TENS use. PM-mediated tachycardia may be induced by somatosensory evoked potentials [10]. Finally, the effects of radiofrequency catheter ablation for arrhythmias are similar to those of electrocautery EMI [10].

Management of the patient with a CRMD in the hospital environment

Determination of CRMD type, indications for therapy, and dependence on the device

The objective is to reduce the risk of haemodynamic instability due to inhibition or triggering of pacing or antitachycardia therapies, or upper rate behaviour [10]. First, establish that the patient has a CRMD. If this is truly so, define the type and the indications for its implantation from the manufacturer's ID card or other sources, such as medical records, 12-lead ECG, monitored ECG rhythm strips, the radiographic signature (chest X-ray) or manufacturer's databases. Once this has been done, it is necessary to determine that these are dependent on CRMD pacing function. Clues to this are a history of symptomatic bradyarrhythmias, successful AV nodal ablation or inadequate escape rhythm if programmed to the lower rate interval. To confirm the intended CRMD function interrogation of the device may be necessary (by the cardiologist, a CRMD service, a manufacturer's representative).

Determining likelihood of exposure to EMI and advised management for specific EMI

It is necessary to determine whether EMI is likely during the planned procedure and whether reprogramming to an asynchronous pacing mode or disabling adaptive rate pacing is required. Antitachycardia pacing or shock therapies should be disabled if present. If surgery is to be performed, the surgeon should be advised to consider the use of a bipolar cautery or an ultrasonic (harmonic) scalpel. Equipment for temporary pacing and cardioversion or defibrillation should be readily available.

Surgical electrocautery. Care must be taken to ensure that the cautery groundplate (GP) is positioned in such a way that current does not pass through or near the PG or leads. In some circumstances, the GP must be positioned elsewhere than in the thigh or buttocks (e.g. at the posterior apex of the shoulder on the opposite side to the PG for head and neck surgery). The surgeon must be advised to avoid proximity of the cautery's electrical field to the PG or leads; to use short, intermittent or irregular cautery bursts at the lowest possible energy levels; and, finally, to consider

the use of bipolar cautery or an ultrasonic (harmonic) scalpel in preference to a monopolar cautery whenever possible.

Emergency direct current CV/DF. Before emergency CV/DF in a patient with an ICD and magnet-disabled therapies, all EMI sources should be removed and the magnet removed to re-enable ICD therapies. Then the patient must be monitored to determine the appropriate ICD therapy. For the patient with ICD and antiarrhythmic therapies that have been disabled by programming, it is necessary to consider re-enabling therapies by programming. If these measures fail to restore function the next step is to proceed to emergency external CV/DF. There are guidelines for energy level and paddle placement, and these should be followed. It is also advisable for current flowing through the PG and leads to be minimised by: (1) positioning the CV/DF pads or paddles as far as possible from the PG; (2) positioning the CV/DF pads or paddles perpendicular to the major axis of the PG and the leads as far as possible (e.g., anterior–posterior); and (3) using appropriate (the lowest possible) CV/DF energy levels.

Magnetic resonance imaging. While some case reports and descriptive studies suggest that MRI can be performed without adverse effects in specific circumstances (e.g. disabling ICD therapies; programming an asynchronous pacing mode; limiting MRI to extremities), others advise against MRI.[8] Therefore, it is advised that MRI is generally contraindicated for all CRMD patients.[9] However, if MRI is absolutely necessary, the referring physician and the patient's cardiologist, the diagnostic radiologist, and the CRMD manufacturer should be consulted before it is implemented.

Radiation therapy and lithotripsy. It is usually possible to perform RT safely in patients with CRMDs [17]. The PG must be outside the RT field. If this is not so, some PGs will require relocation before a course of RT. Most manufacturers recommend confirmation of PG function during and after completion of RT. Potential malfunction includes sudden output loss and PM runaway. For LT, the operator should be advised not to focus the LT beam near the PG. If the LT triggers on the R wave, disablement of atrial pacing should be considered, to avoid triggering LT shocks by stimulus artefacts.

Transcutaneous electric nerve stimulation and radiofrequency ablation. Use of TENS appears to be safe in patients with CRMD with bipolar lead polarity [10]. Nonetheless, it is advisable for PM- or ICD-dependent patients to be monitored during the initial session of TENS therapy.

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[7] Citations will be found in the American Society of Anesthesiologists (ASA) CRMD Practice Advisory, expected to become available in Spring 2005.

[8] As of late May 2004, about 75% of ASA CRMD Practice Advisory Task Force members, consultants and surveyed ASA members agreed with this recommendation. Others were of the opinion that MRI was contraindicated for some, but not all, CRMD patients (restrictions in text).

During any RF ablative procedure, any concerns regarding the proximity of the RF ablation catheter to the CRMD leads should be discussed with the cardiac electrophysiologist, who should be advised to avoid direct contact between the RF ablation catheter and the PG or leads and to ensure that the RF current path will be as far removed from the PG and leads as possible.

Electroconvulsive therapy. Although transient or long-term myocardial and CNS effects can be associated with ECT, it is believed[9] that ECT can be performed in patients with CRMDs without significant damage to the device provided it is disabled. If it is necessary for ECT to be performed, consultation with the referring physician and the patient's cardiologist is needed, both of whom should assist in planning the first and subsequent procedures. All CRMDs should undergo comprehensive interrogation before a course of ECT. Functions should be disabled during ECT shock therapy. However, one must be prepared for the ventricular arrhythmias that can occur secondary to ECT. CRMD-dependent patients may require a temporary pacing system to preserve cardiac rate and rhythm during ECT shock therapy.

Postprocedural management

It is strongly advised that postprocedural management of CRMD patients include interrogation and restoration of all CRMD functions in the postanaesthetic or intensive care units, or in any other hospital or ambulatory setting, as the case may be.[10]

References

1. Atlee JL (2004) Cardiac resynchronization therapy. In: Gullo G (ed) Anaesthesia, pain, intensive care and emergency medicine, 18th edn. Springer, Milan, pp 3–16
2. Abraham WT, Hayes DL (2003) Cardiac resynchronization therapy for heart failure. Circulation 108:2596–2603
3. Sundell J, Engblom E, Koistinen J et al (2004) The effects of cardiac resynchronization therapy on left ventricular function, myocardial energetics, and metabolic reserve in patients with dilated cardiomyopathy and heart failure. J Am Coll Cardiol 43:1027–1033
4. Kerwin WF, Paz O (2003) Cardiac resynchronization therapy: overcoming ventricular dyssynchrony in dilated heart failure. Cardiol Rev 11:221–239
5. Bradley DJ, Bradley EA, Baughman KL et al (2003) Cardiac resynchronization and death from progressive heart failure: a meta-analysis of randomized controlled trials. JAMA 289:730–740
6. Abraham WT, Fisher WG, Smith AL et al (2002) Multicenter InSync randomized clinical, evaluation cardiac resynchronization in chronic heart failure. N Engl J Med 346:1845–1853
7. Young JB, Abraham WT, Smith AL et al (2003) Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. JAMA 289:2685–2694

[10] ASA CRMD Advisory Task Force members and consultants as of late May 2004.
[11] Ibidem.

8. Bristow MR, Saxon LA, Boehmer J (2004) Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 350:2140–2150
9. Atlee JL, Bernstein AD (2001) Cardiac rhythm management devices. 1. Indications, device selection and function. Anesthesiology 95:1265–1280
10. Atlee JL, Bernstein AD (2001) Cardiac rhythm management devices. 2. Perioperative management. Anesthesiology 95:1492–1506
11. Bernstein AD, Daubert J-C, Fletcher RD, et al (2002) The revised NASPE/BPEG generic code for antibradycardia, adaptive-rate, and multisite pacing. Pacing Clin Electrophysiol 25:260–264
12. DiMarco JP (2003) Implantable cardioverter-defibrillators. N Engl J Med 349:1836–1847
13. Gimbel JR, Johnson D, Levine PA et al (1996) Safe performance of magnetic resonance imaging on five patients with permanent cardiac pacemakers. Pacing Clin Electrophysiol 19:913–919
14. Hayes DL, Strathmore NF (2000) Electromagnetic interference with implantable devices. In: Ellenbogen KA, Kay GN, Wilkhoff BL (eds) Clinical cardiac pacing and defibrillation, 2nd edn. Saunders, Philadelphia, pp 939–952
15. Andersen C, Madsen GM (1990) Rate-responsive pacemakers and anaesthesia. A consideration of possible implications. Anaesthesia 45:472–476
16. Strathmore NF (1995) Interference in cardiac pacemakers. In: Ellenbogen KA, Kay GN, Wilkoff BL (eds) Clinical cardiac pacing. Saunders, Philadelphia, pp 770–779
17. Rozner MA (2003) Untitled letter. Pacing Clin Electrophyiol 26:1–3

Chapter 44

Hypothermia in cardiac surgery

J.O.C. Auler

The aim of this paper is to review physiological aspects of human body thermoregulation and the rationale for using hypothermia as a therapeutic agent in cardiac surgery. Core body temperature is one of the most closely regulated human physiological parameters. The thermoregulatory system usually maintains core body temperature within 0.2–0.4°C of 'normal'. Nonetheless, hypothermia, defined as a core temperature lower than 36.8°C, commonly develops in patients during anaesthesia and surgery because anaesthetics inhibit central thermoregulation and patients are exposed to a cold operating-room environment [1].

Hypothermia can be intentionally induced during anaesthesia as a therapeutic tool or it may occur inadvertently as a combination of anaesthetic-induced impairment of thermoregulatory control, a cool operating room setting and factors peculiar to surgery that determine excessive heat loss from the body.

The body produces heat according to the metabolic activity. During anaesthesia the metabolic rate declines as a direct consequence of a reduction in oxygen consumption. The heat needed to maintain core temperature is produced by the combustion of glucose (4.1 kcal/kg), protein (4.1 kcal/ kg) and fat (9.3 kcal/kg), which are the major substrates for human metabolism. Almost all of this energy originating from chemical reactions is ultimately converted to heat. At rest, and this includes the anaesthetised status, brain, liver and heart are the tissues that are metabolically most active and are responsible for most of the energy produced and its conversion to heat. In contrast, heat production by skeletal muscle, e.g. by postanaesthetic shivering, can sometimes exceed the basal metabolic rate [2].

To facilitate the comprehension of heat distribution inside the body it is important to define the thermal compartments. Simplistically, the human body can be divided in a core or central heat compartment and a peripheral heat compartment. The core thermal compartment is composed of very well-perfused tissues whose temperature is uniform and is higher than in the rest of the body. It consists of the head, the neck and the trunk, without the outer layer that consists of skin and subcutaneous fatty tissue, while the legs and arms represent the peripheral compartment. The main difference between the two compartments is that the central compartment produces all the energy that is heat converted, so that its temperature is almost constant [3]. In contrast, temperatures in the peripheral compartment are lower, usually 4°C less than the core temperature, in moderate environments. However, this difference might become greater or smaller during extreme thermal conditions, in very cold or warm environments [4] or in pathologic conditions [5].

Core-to-peripheral temperature gradients result from the environmental temperature, body metabolism, haemodynamic conditions or the setting of brain thermoregulatory mechanisms. When thermoregulatory mechanisms are compromised, as they are during anaesthesia, vasodilatation permits the transference of central heat to the periphery. Conversely, vasoconstriction confines metabolic heat to the core, making the core-to-peripheral temperature gradient steeper [3]. General anaesthesia reduces the vasoconstriction threshold via inhibition of centrally mediated thermoregulatory vasoconstriction, with the result that the thermoregulatory defence mechanisms are impaired and responses to a reduction in core temperature, normally evidenced by vasoconstriction and shivering, will be triggered at much lower body temperature than in a nonanaesthetised individual [1].

In summary, thermoregulatory imbalance is characterised by a profound inhibition of arteriovenous shunt vasoconstriction, nonshivering thermogenesis and shivering; sweating and vasodilatation may also be inhibited. Peripheral vasodilatation that contributes to the heat losses is also incremented locally, since most anaesthetic agents cause direct vasodilation [6].

Vasodilatation flattens the peripheral–core thermal gradient, allowing transference of central heat to the peripheral regions. This transference of heat to the peripheral compartment does not necessarily mean losses of energy to the environment. However, owing to the systemic cooling that occurs at the same time, it will augment the chance of core hypothermia. Heat loss during surgery occurs mostly by way of radiation as a result of the cold operating theatre and of convection from the skin, and also through evaporation from surgical incisions and conductive cooling caused by the administration of cold intravenous fluids.

This means that about 90% of metabolic heat is lost through the skin surface. To be effective, any warming system must therefore reduce cutaneous heat loss.

Hypothermia is usually used during cardiac surgery because it is believed to give additional protection against cardiac and cerebral ischaemia [7].

During cardiopulmonary bypass, a two-compartment model of body heat distribution may break down; according to Sessler, it is therefore sometimes helpful to define a third 'intermediate' compartment [3]. To this third compartment are allocated tissues such as the rectum and bladder, which are regularly considered to be part of the core during cardiopulmonary bypass (CPB), but are not so well perfused as to remain homogeneous during the huge and rapid heat fluxes associated with CPB As a result, it is common for temperatures in such sites to insulate several degrees behind core sites [8, 9]. Otherwise, the temperatures in those third compartments remain much closer to core temperature than do those in more peripheral tissues.

Temperature Monitoring

Core temperature should be monitored in all patients who are under a general anaesthetic for longer than 30 min, and unless hypothermia is specifically indicated core temperature should be maintained above 36.8°C. This is because, except in the case of intentional therapeutic hypothermia, a large amount of evidence had documented harmful effects of hypothermia [10]. In Table 1, as proposed by Lenhardt, the sites where the temperature can be monitored are demonstrated. The choice of body site for measurements depends on the surgical procedure. Unless hypothermia is specifically indicated, efforts should be made to maintain intraoperative core temperatures above 36.8°C. The ideal site is the tympanic membrane, where the temperature is close to core temperature. In open heart and thoracic surgery, owing to the possibility that ambient temperature will have an effect in the open cavity and to enhance the accuracy of the measurements, the oesophageal site should be avoided in favour of the tympanic membrane or nasopharynx. During the rewarming phase after a bypass, the temperature obtained via the pulmonary catheter could be much higher than the real core temperature, owing to the proximity of warmed blood. In a liver transplantation, the proximity of the cold donor liver to the diaphragmatic muscle may cause some interference with the oesophageal temperature. In this particular situation, the sites chosen should be the pulmonary catheter, nasopharynx or even tympanic membrane.

Table 1. Thermal compartments and temperature sites

Compartment	Temperature site	Use indicated for	Accuracy[a]
Outside core	Bladder	Liver transplant	Reasonable
	Rectum		Use with caution
	Axilla		Reasonable
	Skin		Use with caution
Inside core	Tympanic membrane	Liver transplant, open heart + thoracic surgery	High
	Pulmonary artery	Liver transplant	High
	Nasopharynx	Open heart + thoracic surgery	High
	Distal oesophagus		High

[a]Oral temperature also gives a reasonably accurate reflection of core temperature

Induction of therapeutic hypothermia

Brain protection

There are a great many surgical procedures during which the brain is at risk of ischaemia, including neurosurgery, carotid endarterectomy and cardiopulmonary

bypass. In addition, haemodynamically unstable patients are at risk of cerebral hypoperfusion. The outcome of cerebral ischaemic events can be catastrophic. This explains the renewed interest in the use of hypothermia for cerebral protection [11].

Traditionally, induced hypothermia has been extensively used in cardiac surgery with cardiopulmonary bypass. Hypothermia is not considered therapeutic, but it is believed that mild to deep hypothermia may act as a brain protector during the low-blood-flow periods of surgery. The classic mechanism proposed for neuronal protection by hypothermia is the reduction of oxygen and glucose consumption caused in turn by a reduction in the rates of enzymatic reactions. Experimentally, focal and global cerebral ischaemia are markedly affected by small changes in brain temperature; mild hypothermia diminishes, and mild hyperthermia intensifies, ischaemia-induced neuronal injury [12].

With the advent of off-pump cardiac surgery, the debate about whether or not hypothermia should be used during surgery has intensified, and most of the arguments against its use are based on the harmful effects of hypothermia.

Traditionally used during CPB, hypothermia has gained increasing popularity as a therapeutic adjunct in patients with stroke or myocardial infarction and after resuscitation. The animal evidence for cerebral protection by mild hypothermia is convincing [13]. In head trauma patients, the results of different studies employing mild hypothermia for brain protection have been inconclusive. Some results favour the use of hypothermia [14], while others have questioned its beneficial effects [15]. The outcome of cerebral ischaemic events after high-risk surgery can be devastating. This explains the enormous interest in mild hypothermia as a therapeutic resource to reduce brain injury after stroke and aneurysmal subarachnoid haemorrhage. However, no satisfactorily large prospective randomised trials in patients support this procedure [16, 17].

Recently, induced hypothermia after cardiac arrest has attracted renewed interest. Two randomised clinical trials have lately shown a neurological benefit of mild therapeutic hypothermia in survivors of out-of-hospital cardiac arrest. Although much large clinical trials are necessary, both studies showed that in patients successfully resuscitated following out-of-hospital cardiac arrest due to ventricular fibrillation, therapeutic mild hypothermia increased the rate of favourable neurological outcome and reduced mortality [18–20].

Nowadays, cardiac surgery requiring CPB still carries a significant risk of neurological complications. As mentioned in the literature, stroke (1–9%), neurocognitive disorders (10–60%) immediately after surgery and 5–20% remained at hospital discharge still represent higher markers [21–23]. This emphasises the validity of using mild to moderate core hypothermia (35–33°C) during the majority of CPB procedures.

Although the incidence of brain injury is very high after cardiac surgery because a variety of neurological risks are concentrated in this surgical population, and it is possible that this cannot be modified, interventions with the potential capability to reduce neurological morbidity might be considered. According to Arrowsmith et al., neuroprotective interventions can be summarised in two categories: physical and pharmacological [24].

Physical neuroprotective interventions can be defined as interventions during surgery, the most important besides prompt and efficient surgery and CPB, being management of temperature, mean arterial pressure, glucose and carbon dioxide. The role of temperature in neurological outcome came to the fore after several studies, all of which indicated that hypothermia during CPB might confer some degree of 'brain protection'. The question is whether normothermic (warm) bypass techniques can improve myocardial outcomes without interfering with the brain's tolerance of the ischaemic insults that accompany all cardiac procedures. A study reported by Martin et al. in 1994, although not recent, remains one of the most illuminating. A large cohort of patients undergoing CPB were assigned to two groups, one with temperatures of 35°C or higher and one with temperatures of 28°C or lower: the incidence of neurological morbidity in the 'warm' group was threefold that in the 'cold' group [25].

In 1996, Mora et al. investigated the effect of CPB temperature on central nervous system outcomes in patients undergoing coronary artery bypass grafting (CABG), having randomly assigned 138 patients to two treatments: hypothermia (n=70), with patients cooled to a temperature of less than 28°C during CPB, and normothermia (n=68), with patients remaining warm at a temperature of at least 35°C. They found a significantly higher incidence of perioperative neurological risk in patients who were warmed (kept at a minimum of 35°C) during CPB [26].

Rasmussen et al. compared normothermic CPB versus hypothermic CPB in 20 paediatric patients undergoing repair of congenital heart defects. They used specific cerebral biochemical markers, neuron-specific enolase (NSE) and S-100 β protein as indicators of lesion. In this investigation the authors showed that the serum level of S-100 β protein was significantly elevated in both groups, whereas no significant difference was found in serum levels of NSE. Except for considerably greater total blood loss in the normothermic group no difference was observed between patients undergoing hypothermic and normothermic CPB [27]. Another point that gives rise to controversy is related to the perfusion pressure during CPB. Although there is a general consensus that during cold CPB a mean arterial pressure of 50 mmHg (MAP) could be enough, some groups advise mean arterial pressure higher than 70 mmHg. Gold et al. compared cardiac and neurological outcomes in two groups of patients assigned randomly to either lower (50–60 mmHg) or higher (above 80 mmHg) MAP. Later follow-up (6 months) showed low levels of significant neurological and cardiac complications in the group managed with higher arterial pressure. Nevertheless, not all data agree, but in view of the fact that the surgical population is becoming older and is at high neurological risk, it seems cautious that patients will benefit from maintenance of their mean arterial pressure at values corresponding to the autoregulatory brain perfusion range during CPB, together with hypothermia.

Myocardial protection

Myocardial infarction is one of the most important causes of unexpected perioperative morbidity and mortality in patients with coronary heart disease who undergo noncardiac surgery. It has long been suggested that patients with cardiopulmonary disease may not tolerate the increased metabolic demands associated with postoperative shivering and may have adverse outcomes for this reason [28, 29].

The hypothesis that mild core hypothermia might cause an elevation in blood catecholamine levels and consequently stress the cardiovascular system through tachycardia, hypertension and systemic vasoconstriction has been confirmed by some studies. The resulting cardiac morbidity and mortality may prejudice the outcome of these patients very seriously [30]. Evidence to support this hypothesis was given by Frank et al., who conducted a randomised controlled trial in 300 high-risk patients to find whether mild perioperative hypothermia increased the incidence of morbid cardiac events [31]. Patients were randomised to routine thermal care or active warming. Perioperative myocardial ischaemia and ventricular tachycardia were more common in hypothermic than in normothermic patients. The authors deduce that the maintenance of normothermia is associated with a reduced incidence of morbid cardiac events in the perioperative period.

A high cardiovascular complication rate in major vascular surgery is documented in the literature. The postoperative period is characterised by an increase in sympathetic nervous activation associated with an increase in vascular resistance, a marked increase in the global body oxygen consumption and a higher incidence of myocardial infarction [28].

During the postoperative period, global body oxygen consumption increases. This is caused by resetting of the core temperature triggered by thermogenesis mechanisms. The period of high risk falls during rewarming and is coincident with the resumption of spontaneous ventilation and perception of postoperative pain. Postoperative management will be aimed at controlling metabolic stress by preventing hypothermia, warming the patient in a convenient manner and providing adequate sedation and effective analgesia. When extubation is performed in a hypothermic patient after vascular surgery, this drastically increases the risk of acute myocardial ischaemia [32].

In patients undergoing cardiac surgery, it is currently believed that mild to moderate core and local myocardial hypothermia can be protective. Specifically in the myocardial muscle, it is assumed that hypothermia acts to prevent myocardial damage by reducing oxygen consumption and the ischaemic lesions that can otherwise be induced by blood reperfusion after an ischaemic period [33].

Aortic cross-clamping during graft anastomosis can induce different degrees of myocardial ischaemia otherwise the use of cold cardioplegic solutions. Consequently, this type of ischaemia can provoke dysregulation of the cellular metabolism and may contribute to myocardial injury and cell death in addition to reperfusion injury.

The precise mechanisms by which hypothermia provides protection during myocardial ischaemia–reperfusion are not well defined. One possible explanation

is that hypothermia reduces metabolic demand in the myocardium at risk as a result of down-regulation of cardiac myocyte metabolism, thus limiting the area of myocardium at risk. Experimental data show that hypothermia acts to preserve myocardial ATP stores during ischaemia [34].

The present techniques for reduction of global myocardial ischaemia during cardiac surgery with CPB include mild to moderate hypothermia, various types of cardioplegic solutions and different approaches for infusion of this solution into the coronary circulation.

The reason for providing myocardial protection for patients undergoing a CABG is that they are more at risk for myocardial damage than any other group undergoing any other major surgery. Aside from the underlying coronary artery disease, CABG is thought to decrease the tolerance of the hypoperfused heart to stress and increased afterload. Additionally, CPB induces a range of harmful effects related to systemic and local myocardial neutrophil activation, interleukin production and free-radical generation that may contribute to aggravation of the coronary endothelial deregulation imposed by surgical vessel manipulation [35]. The consequence is the augmented chance that the myocardium will be damaged during the postoperative period in all patients undergoing cardiac surgery, but especially in those undergoing CABG.

The main question is whether the higher level of serum norepinephrine concentrations provoked by systemic hypothermia might contribute to jeopardising a vulnerable myocardium in the postoperative period. Some authors argue that whilst core hypothermia may be an adjuvant acting as an 'additional myocardial protector', its adverse effects may be worse than those of normothermia maintained during the surgery [30].

Nesher et al. assessed the cardioprotective effects of perioperative maintenance of normothermia by determining the perioperative profile of troponin I, a highly cardiac-specific protein important in risk stratification of patients with acute ischaemic events. The patients enrolled underwent primary CABG and were randomised to a new thermoregulation system group, Allon™ thermoregulation (AT; n=30), and a routine thermal care (RTC; n=30) group. The Allon™ technology used in the AT study group consists of a microprocessor-controlled heating/cooling unit, body temperature sensors (core [i.e., rectal]) and skin thermistors, and a specially designed garment that is wrapped around the patient. Continuous monitoring of the patient's rectal and skin temperature is performed via the thermistors.

Anaesthetic and operative techniques were similar in both groups. Intraoperative warming was applied before and after CPB and up to 4 h after surgery. Both groups behaved almost identically. Cardioplegia was established through antegrade priming followed by intermittent, tepid-blood, retrograde intervals. Rectal temperature was allowed to decline to 33–34°C during bypass.

The authors showed that the maintenance of normothermia throughout cardiac surgery could attenuate ischaemic injury to the myocardium, as demonstrated by improved haemodynamic variables and reduced levels of serum cTnI, a sensitive marker of intraoperative myocardial ischaemia [36].

However, there is some polemic about whether myocardial and cerebral pro-

tection results hypothermia is induced and maintained during cardiac surgery. An interesting paper investigating the effects on the splanchnic circulation has recently been published. Nobuhiro et al. tested the hypothesis that there are changes in hepatic venous oxygen saturation (ShvO2), hepatosplanchnic blood flow and oxygen delivery during mild hypothermic and normothermic CPB. They randomly allocated 14 otherwise healthy patients undergoing elective CABG to the normothermic (group I, n=7) or the mild hypothermic (group II, n=7) group. Hepatic blood flow was determined by a primed (6 mg), continuous infusion (1 mg min^{-1}) of indocyanine green (ICG) [5] via a central venous catheter (1) after the induction of anaesthesia; (2) during the steady state of CPB; and (3) after cessation of the CPB. Arterial and hepatic venous ICG concentrations were at steady state plateaus at each measurement. The authors consider that although liver dysfunction does not constitute a major cause of morbidity after CPB, despite the presence of severe hepatic venous oxygen desaturation, postoperative liver function tests did not reveal any major abnormalities in either group. Possible explanations include a very transient decrease in $ShvO_2$, the limited number of patients studied and their relatively low level of risk, preservation of hepatosplanchnic blood flow during CPB, and fully developed compensation mechanisms in the liver. Although no sound clinical results were achieved, this study shows that hepatosplanchnic oxygenation is better preserved during mild hypothermic than that during normothermic CPB [37].

Hypothermia was an independent predictor of morbid cardiac events according to multivariate analysis, indicating a 55% reduction in risk when normothermia was maintained. Evidence for an adverse effect of postoperative mild core hypothermia on mortality and major morbidity outcomes was provided by Insler et al. through a retrospective database analysis of 5701 CABG surgery patients requiring CPB [38].

In conclusion, the literature, although not yet conclusive, suggests that hypothermia may provide myocardial protection without exposing the patient to the risks of systemic hypothermia.

Implications of perioperative hypothermia

In his excellent review, Doufas summarises the consequences of hypothermia. Of course, the negative consequence should be balanced against the possible benefits in specific conditions, as discussed above. We will emphasise just some points that may have some impact on the outcome of patients undergoing cardiac surgery.

Cardiovascular System

The rewarming process triggered by thermoregulatory mechanisms activates both the sympathoneural (noradrenalin; norepinephrine) and the adrenomedullary (adrenalin; epinephrine) systems. The cardiovascular response involves an increase in the various indices of cardiac work, tachycardia and sometimes hypertension.

However, even in the absence of vasoconstriction, increased myocardial metabolic requirements in the presence of flow-limiting coronary lesions may predispose patients to myocardial ischaemia [40]. Finally, several studies indicate that perioperative myocardial ischaemia is not directly related to shivering, but rather to the haemodynamic stress caused by a cold-provoked sympathoadrenal activation [40].

Coagulation

As demonstrated by the literature, hypothermia produces a coagulopathy and increases perioperative blood loss. This has been demonstrated after orthopaedic surgery, such as hip replacement [41]. In this study, patients were randomly allocated to normothermia or mild hypothermia during elective primary hip arthroplasty. A reduction of just 1.6°C in core temperature increased blood loss by 500 ml (30%) and significantly increased the number of blood bank transfusions required. Three general mechanisms contribute to temperature-related coagulation disorders: platelet function, clotting factor enzyme function and fibrinolytic activity. Kestin et al. have shown that prolongation of the bleeding time in patients after CPB is probably the result of a lack of available platelet activators rather than an intrinsic platelet defect [42].

The suggestion that hypothermia might promote pathologic platelet aggregation in the presence of platelet activators may have clinical relevance in conditions in which hypothermic blood is exposed to platelet activators such as extracorporeal circuits or diseased endothelium.

During cardiac surgery, this effect may be maximised by CPB itself and haemodilution. However, the widespread practice of using antifibrinolytics during CPB may balance out the harmful effect of hypothermia. The message derived from the studies can be summarised as follows: hypothermia should be used during part of the surgery, but after that, all available procedures for rewarming the patient and keeping core temperature near normal must be implemented.

Wound Infection

Several studies that have appeared in the literature are in agreement that perioperative hypothermia may make a negative contribution to surgical wound infections even though the infections are usually not detected until some days after surgery [43, 44].

This statement is based in part on studies that have demonstrated that bacterial fixation is more intensive while unwarmed patients remain hypothermic. Hypothermia can prejudice neutrophil function directly or impair it indirectly by triggering subcutaneous vasoconstriction and subsequent tissue hypoxia. Hypothermia may also intensify postoperative protein wasting interfering with healing. Haemostatic reactions, particularly platelet plug formation, that play a primary role in initiating the first and perhaps the second stage of wound healing are affected by hypothermia. In summary, disturbances of haemostasis are frequently detected

during hypothermia and may also slow down wound healing, which leaves an open gate for the acquisition of infections [45, 46].

In summary, inadvertent hypothermia may hardly affect the outcome in high-risk patients, but except in patients undergoing cardiac surgery, perioperative hypothermia strongly increases the incidence of adverse myocardial ischaemia.

Mild hypothermia may also significantly increase blood loss and increase the likelihood that an allogeneic transfusion will be required and the amount needed. Related to postoperative infection, core hypothermia seems to triples the incidence of surgical wound infection in any kind of surgery. Hypothermia alters the pharmacokinetics and pharmacodynamics of various anaesthetic and paralysing agents, significantly altering the anaesthesia due to patients' delayed postanaesthetic recovery [39].

References

1. Sessler DI (1997) Perioperative hypothermia. N Engl J Med 336:1730-1737
2. Fagher B, Monti M, Thulin T (1988) Selective b1-andrenoceptor blockade and muscle thermogenesis. Acta Med Scand 223:139-145
3. Sessler DI (2000) Perioperative heat balance. Anesthesiology 92:578-596
4. Bristow GK, Biesbrecht GG, Sessler DI (1994) Leg temperature and heat content in humans during immersion hypothermia and rewarming. Aviat Space Environ Med 65:220-226
5. Buck SH, Zaritsky AL (1989) Occult core hyperthermia complicating cardiogenic shock. Pediatrics 83:782-784
6. Weiskopf RB (1995) Cardiovascular effects of desflurane in experimental animals and volunteers. Anaesthesia 50:S14-S27
7. Neubauer RA, James P (1998) Cerebral oxygenation and the recoverable brain. Neurol Res 20:S33-S36
8. Webb GE (1973) Comparison of esophageal and tympanic temperature monitoring during cardiopulmonary bypass. Anesth Analg 52:729-733
9. Horrow JC, Rosenberg H (1988) Does urinary catheter temperature reflect core temperature during cardiac surgery? Anesthesiology 69:986-989
10. Lenhardt R (2003) Monitoring and thermal management. Best Pract Res Clin Anaesthesiol 17:569-581
11. Sessler DI (2003) Cerebral protection perioperative hypothermia in the high-risk surgical patient. Best Pract Res Clin Anaesthesiol 17:485-498
12. Minamisawa H, Nordstrom CH, Smith ML et al (1990) The influence of mild body and brain hypothermia on ischemic brain damage. J Cereb Blood Flow Metab 10:365-374
13. Busto R, Dietrich WD, Globus MY-T et al (1987) Small differences in intraischemic brain temperature critically determine the extent of ischemic neuronal injury. J Cereb Blood Flow Metab 7:729-738
14. Marion DW, Penrod LE, Kelsey SF et al (1997) Treatment of traumatic brain injury with moderate hypothermia. N Engl J Med 336:540-546
15. Hartung J, Cottrell J (1998) Statistics and hypothermia (editorial). J Neurosurg Anesth 10:1-4
16. Hindman BJ, Todd MM, Gelb AW et al (1999) Mild hypothermia as a protective therapy during intracranial aneurysm surgery: a randomized prospective pilot trial. Neurosurgery 44:23-32

17. Krieger DW, De Georgia MA, Abou-Chebl A et al (2001) Cooling for acute ischemic brain damage (cool aid): an open pilot study of induced hypothermia in acute ischemic stroke. Stroke 32:1847-1854
18. Steiner T, Ringleb P, Hacke W (2001) Treatment options for large hemispheric stroke. Neurology 57 (Suppl 2):S61-S68
19. Bernard SA, Gray TW, Buist MD et al (2002) Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 346:557-563
20. Safar PJ, Kochanek PM (2002) Therapeutic hypothermia after cardiac arrest. N Engl J Med 346:612-613
21. David JC (2000) Neurologic effects. In: Gravllee PG, Davis FR, Kursz M, Utley RJ (eds) Cardiopulmonary bypass: principles and practice, 2nd edn. Lippincott–Williams & Wilkins, Philadelphia, pp 404-424
22. Wolman RL, Nussmeier NA, Aggarwal A et al (1999) Cerebral injury after cardiac surgery: identification of a group of extraordinary risk. Stroke 30:514-552
23. Taggart DP, Browne SM, Halligan PW et al (1999) Is cardiopulmonary bypass still the cause of cognitive dysfunction after cardiac operations. J Thorac Cardiovasc Surg 118:414-420
24. Arrowsmith JE, Grocott HP, Reves JG (2000) Central nervous system complications of cardiac surgery. Br J Anaesth 84:378-393
25. Martin TD, Craver JM, Gott JP et al (1994) Prospective, randomized trial of retrograde warm cardioplegia: myocardial benefit and neurologic threat. Ann Thorac Surg 57:298-304
26. Mora TC, Henson BM, Weintraub WS et al (1996) The effect of temperature management during cardiopulmonary bypass on neurologic and neuropsychologic outcomes in patients undergoing coronary revascularization. J Thorac Cardiovasc Surg 112:514-522
27. Rasmussen L S, Sztuk F, Christiansen M, Elliot MJN (2001) Normothermic versus hypothermic cardiopulmonary bypass during repair of congenital heart disease. J Cardiothorac Vasc Anesth 15:563-566
28. Mangano DT (1990) Perioperative cardiac morbidity. Anesthesiology 72:153-184
29. Macintyre PE, Pavlin EG, Dwersteg JF (1987) Effect of meperidine on oxygen consumption, carbon dioxide production, and respiratory gas exchange in postanesthesia shivering. Anesth Analg 66:751-755
30. Frank SM, Higgins MS, Breslow MJ et al (1995) The catecholamine, cortisol, and hemodynamic responses to mild perioperative hypothermia. Anesthesiology 82:83-93
31. Frank SM, Fleisher LA, Breslow MJ et al (1997) Perioperative maintenance of normothermia reduces the incidence of morbid cardiac events: a randomized clinical trial. JAMA 277:1127-1134
32. Franck SM, Beatties C, Christopherson R et al (1993) Unintentional hypothermia is associated with postoperative myocardial ischemia. Anesthesiology 78:468-476
33. Hayashida N, Ikonomidis JS, Weisel RD et al (1994) The optimal cardioplegic temperature. Ann Thorac Surg 58:961-971
34. Carrier M, Tourigny A, Thoribe N et al (1994) Effects of cold and warm blood cardioplegia assessed by myocardial pH and release of metabolic markers. Ann Thorac Surg 58:764-767
35. Hall RI, Smith MS, Rocker G (1997) The systemic inflammatory response to cardiopulmonary bypass: pathophysiological, therapeutic, pharmacological considerations. Anesth Analg 85: 766-782
36. Nesher N, Zisman E, Wolf T et al (2003) Strict thermoregulation attenuates myocardial injury during coronary artery bypass graft surgery as reflected by reduced levels of cardiac-specific troponin I. Anesth Analg 96:328-335

37. Okano N, Hiraoka H, Owada R et al (2001) Hepatosplanchnic oxygenation is better preserved during mild hypothermic than during normothermic cardiopulmonary bypass. Can J Anaesth 48:1011-1014
38. Insler SR, O'Connor MS, Leventhal MJ et al (2000) Association between postoperative hypothermia and adverse outcome after coronary artery bypass surgery. Ann Thorac Surg 70:175-181
39. Doufas AG (2003) Consequences of inadvertent perioperative hypothermia. Best Pract Res Clin Anaesthesiol 17:535-549
40. Frank SM, Satitpunwaycha P, Bruce SR et al (2003) Increased myocardial perfusion and sympathoadrenal activation during mild core hypothermia in awake humans. Clin Sci (Lond) 104:503-508
41. Schmied H, Kurz A, Sessler DI et al (1996) Mild intraoperative hypothermia increases blood loss and allogeneic transfusion requirements during total hip arthroplasty. Lancet 347:289-292
42. Kestin AS, Valeri CR, Khuri SF et al (1993) The platelet function defect of cardiopulmonary bypass. Blood 82:107-117
43. Sessler DI, Kurz A, Lenhardt R (1999) Hypothermia reduces resistance to surgical wound infections (letter). Am Surg 65:1193-1196
44. Melling AC, Ali B, Scott EM et al (2001) Effects of preoperative warming on the incidence of wound infection after clean surgery: a randomized controlled trial. Lancet 358:876-880
45. Carli F, Emery PW, Freemantle CAJ (1989) Effect of peroperative normothermia on postoperative protein metabolism in elderly patients undergoing hip arthroplasty. Br J Anaesth 63:276-282
46. Deuel TF, Kawahara RS, Mustoe TA et al (1991) Growth factors and wound healing: platelet-derived growth factor as a model cytokine. Annu Rev Med 42:567-584

CARDIOPULMONARY RESUSCITATION

Chapter 45

Pharmacological management of cardiopulmonary resuscitation

T. Pellis

Pathophysiology of cardiac arrest

The current International Liaison Committee on Resuscitation (ILCOR) guidelines recommends rhythm-based therapies during cardiac arrest [1]. However, these treatment algorithms are static in the sense that they do not consider the passage of time. Emerging data suggest that this approach is not optimal for all patients, particularly as the duration of cardiac arrest increases and the pathophysiology of ischemia/reperfusion progresses over time. Given these premises, Weisfeld and Becker [2] recently proposed a 3-phase model for cardiopulmonary resuscitation (CPR) to reflect the time-sensitive progression of resuscitation physiology. The model applies to cardiac arrest of cardiac origin and is divided in:

1. The *electrical phase*, which extends from the time of cardiac arrest to approximately 4 min following the arrest.
2. The *circulatory phase*, from approximately 4 min to approximately 10 min after cardiac arrest.
3. The *metabolic phase*, extending beyond approximately 10 min after cardiac arrest.

The authors suggest that each time-phase corresponds to a maximally effective and most critical initial therapy. However, the time boundaries between phases are approximate and not precisely defined in the current literature. Another limitation of this model is that it addresses only ventricular fibrillation (VF)-mediated cardiac arrest.

Electrical shocks are highly effective in restoring spontaneous circulation (ROSC) if the interval of untreated VF was short, i.e. still in the electrical phase [3]. Whereas, defibrillation provided after longer periods of untreated VF (>4 min) is less effective in restoring an organized rhythm and may result in asystoly or pulseless electrical activity (PEA) [4].

During the circulatory phase, priority should be given to interventions that promote oxygen delivery, minimising myocardial ischemia, including cardiac massage and vasopressor agents. Even if reduced compared to normal cardiac output, external chest compressions generate blood flow, hence maintaining the heart and the brain viable. The rationale for the administration of vasopressor agents during CPR is to restore threshold levels of coronary perfusion pressure

(CPP) and, therefore, myocardial blood flow since. Coronary perfusion pressure is the resultant of diastolic aortic pressure minus right atrium pressure determining therefore the pressure gradient that promotes blood flow to the myocardium. Restoration of threshold levels of CPP is the single overriding determinant of the success of the resuscitation effort, especially when the duration of untreated cardiac arrest exceeds 4 min [5]. Anti-arrhythmic therapy is also used during this phase with the intent of reducing the defibrillation threshold and thereby improving defibrillation efficacy of shock-resistant VF and for prevention of recurrent VF.

After a time lapse of approximately 10 min of cardiac arrest, the effectiveness of both immediate defibrillation and CPR followed by defibrillation decreases rapidly, and survival rates appear poor. The underlying mechanisms involved are not completely defined; either irreversible injury occurs or the current therapeutic approaches fail to correct important imbalances in this phase. Global ischaemia involving the whole body has far worse consequences than does regional ischaemia. Peripheral vasoconstrictors, which are helpful during the circulatory phase, may worsen organ ischaemia and may lead to decrease survival during the metabolic phase. Particularly promising interventions currently under investigation include controlled reperfusion after treatment with apoptosis inhibitors and external cooling.

Considering cardiac arrest and resuscitation efforts from a broader prospective, Weil et al. [6] perceived the importance of different stages of resuscitation and introduced the following classification:

1. *Pre-arrest* phase: prevention of impending cardiac arrest being the goal, e.g. by use of vasoconstrictors during hypotension from anaphylaxis or no-reflow post PCI.
2. *Cardiac arrest* phase: during which priority is given to restoration of spontaneous circulation by use of vasoconstrictors to raise CPP in order to enhance myocardial blood flow, hence resuscitation success.
3. *Post-resuscitation* phase: when substantial impairment of ventricular function occurs. The aim during this phase is to improve longer-term survival by minimising post-resuscitation myocardial dysfunction (PRMD). Both electrical and pharmacological interventions capable of initially restoring spontaneous circulation may worsen PRMD, hence ultimately compromising survival.

Vasopressor agents

Epinephrine has been used during CPR for more than 100 years [7] but has become controversial because it is associated with increased myocardial oxygen consumption, ventricular arrhythmias, and myocardial dysfunction during the period after resuscitation [8]. In particular, two studies investigating the use of high-dose epinephrine for out-of-cardiac arrest showed no benefit over low dose (1 mg); on the contrary, PRMD, presenting as arterial hypotension and fatal ventricular arrhythmias, was magnified [9, 10]. Accordingly, high-dose epinephrine is no longer recommended [11, 12]. However, the current *International Guidelines on Emergen-*

cy Cardiac Care cite both epinephrine (low-dose) and vasopressin as acceptable vasopressor drugs for treatment of refractory VF, although neither drug is acknowledged to be of proven benefit [11, 12]. Epinephrine received a class indeterminate recommendation because a randomised, controlled clinical trial has not been conducted to prove the superiority of epinephrine over placebo [11].

Interest in vasopressin was intially raised by the observation that, in successfully resuscitated patients, vasopressin levels are significantly higher, and epinephrine and norepinephrine levels are lower than in patients who die [13]. In a prospective, randomised study, 40 patients with out-of-hospital VF refractory to three countershocks were randomized to receive 1 mg epinephrine or 40 U vasopressin [14]. Significantly more patients treated with vasopressin were successfully resuscitated and survived to 24 h compared with those treated with epinephrine. Based on these data, vasopressin received a class IIb recommendation for the treatment of shock-resistant VF [11,12]. The results of a randomised, multicentre study comparing vasopressin and epinephrine in out-of-hospital cardiac arrest of 1200 patients have recently been published [15]. There were no differences both in the rates of hospital adminssion and discharg either among patients with VF (46.2% vs. 43.0%, P=0.48) or among those with PEA (33.7% vs. 30.5%, P=0.65). Among patients with asystole, however, vasopressin use was associated with significantly higher rates of hospital admission and discharge (4.7% vs. 1.5%, P=0.04). Among patients in whom spontaneous circulation was not restored with two injections of the study drug, additional treatment with epinephrine resulted in significant improvement in the rates of survival to hospital admission and hospital discharge in the vasopressin group, but not in the epinephrine group (hospital admission rate, 25.7% vs. 16.4%, P=0.002; hospital discharge rate, 6.2% vs. 1.7%; P=0.002). However, the study was not powered to detect differences within subgroups and the authors had to conclude that the effects of vasopressin are similar to those of epinephrine in the management of VF and PEA, whereas vasopressin is superior to epinephrine in patients with asystole [15].

Antiarrhythmic agents

Traditionally, lidocaine or bretylium has been used, but no randomised, controlled data have proven efficacy with either drug. Since 1999, two randomised, controlled clinical studies have been carried out with amiodarone in shock-resistant patients and in those with recurrent VF [16, 17].

Amiodarone

The Amiodarone in the Resuscitation of Refractory Sustained Ventricular Tachyarrhythmias (ARREST) trial randomised 504 patients with out-of-hospital cardiac arrest owing to VF to receive 300 mg intravenous amiodarone or diluent as placebo in a double-blinded manner [16]. Patients were eligible if VF or pulseless ventricular tachycardia was present after receiving three or more precordial shocks at any

time during resuscitation. Approximately 20% of the patients had recovery of spontaneous circulation before study-drug administration, indicating that they had recurrent VF. The study drug was given on average 21 min from dispatch and 12 min after the first defibrillation shock. The primary end-point was survival to hospital admission, which was achieved in 44% of the patients in the amiodarone group versus 34% in the placebo group ($P = 0.03$). Significantly more patients in the amiodarone group had hypotension, defined as the need for vasopressor infusion, or bradycardia, defined as the need for chronotropic therapy. The proportion of patients who survived to hospital discharge did not differ in the two treatment groups: 13.4% in the amiodarone group and 13.2% in the placebo group. The investigators concluded that amiodarone acted primarily by preventing the recurrence of VF.

The Amiodarone versus Lidocaine in Prehospital Ventricular Fibrillation Evaluation (ALIVE) trial was a double-blinded, randomised study comparing 5 mg intravenous amiodarone/kg with 1.5 mg intravenous lidocaine/kg in 347 patients with out-of-hospital VF [17]. Patients were eligible if VF was present after receiving three or more precordial shocks, at least one dose of intravenous epinephrine, and a fourth defibrillation shock. The study drug was given, on average, 25 min from dispatch and 17 min after the first defibrillation shock. The primary end-point was survival to hospital admission. After treatment with amiodarone, 22.8% survived to hospital admission compared with 12% in the lidocaine group. Among the patients who were treated earlier (less than the median of 24 min from dispatch to study drug administration), 28% survived to admission compared with 18% of those who were treated after more than 24 min delay. There were no differences between the treatment groups in the proportion of patients who needed therapy for hypotension or bradycardia. The proportion of patients who survived until hospital discharge was 5% in the amiodarone group and 3% in the placebo group ($P = 0.34$). The findings of this study are consistent with those of the ARREST trial, suggesting that intravenous amiodarone is effective and superior to lidocaine in the treatment of shock-resistant, out-of-hospital VF.

Amiodarone was administered relatively late in the course of advanced cardiac life support in both trials, when prolonged hypoperfusion had probably already caused significant end-organ damage, and neither trial had sufficient power bydesign to adequately assess a survival benefit with respect to hospital discharge [16–18]. Despite a few limitations, the ARREST and ALIVE studies represented the first instance of any proven benefit from a pharmacologic anti-arrhythmic intervention in randomised trials of cardiac arrest. The guidelines currently recommend amiodarone, 300-mg intravenous bolus, after the third shock in the treatment of refractory VF, with a class IIb indication [11].

Lidocaine

Although lidocaine has been used for more than 50 years, there has been little evidence supporting any benefit with lidocaine treatment in cardiac arrest [18]; rather, lidocaine increases the defibrillation threshold [19–21]. Meta-analyses of

randomised trials of prophylactic lidocaine administration in patients with acute myocardial infarction showed a statistically significant 62% increase in mortality rate over placebo [22, 23]. A randomised, prospective, out-of-hospital VF trial compared lidocaine with a standard dose of epinephrine. This study showed that there was no short or long-term benefit with lidocaine, and a higher incidence of asystole was observed in the lidocaine group [24]. Lidocaine received a class indeterminate recommendation in the current guidelines [11]. Available data suggest that lidocaine is probably not effective and may be harmful in shock-resistant VF.

Magnesium

Magnesium has also been used, without strong evidence, for decades to treat arrhythmias. Previous anecdotal reports supported its use in shock-refractory VF. Recently, however, two randomised, double blind, placebo-controlled studies tested its efficacy in out-of-hospital VF refractory to three countershocks [25, 26]. In the first, 116 patients were randomised to epinephrine and either 2 g magnesium sulfate or placebo. The study failed to demonstrate any short- or long-term benefit of the administration of magnesium sulfate [25]. In the second trial as well, there was no significant difference observed between the treatment groups with respect to recovery of spontaneous circulation or survival [26]. Based on these data, magnesium sulfate is no longer recommended routinely in refractory VF [11]. Based on observational studies, magnesium sulfate is still recommended (class indeterminate) in the guidelines for cardiac arrest presumably caused by low magnesium levels or torsade de pointes [11].

Bretylium

The evidence favoring the efficacy of bretylium in shock-resistant VF is poor [27–29]. In 2000, bretylium was removed from the guidelines because of concern about its efficacy, the high occurrence of side effects, the availability of safer agents and its limited supply because of the shortage of raw material [11, 18].

Procainamide

Procainamide is effective in the treatment of haemodynamically stable monomorphic ventricular tachycardia [11, 30]. However, its use in cardiac arrest is only supported by a retrospective comparison study involving 20 patients [18, 31]. Bolus administration of intravenous procainamide can result in toxic concentrations and significant hypotension [11]. The use of the drug in refractory VF is limited by the need to infuse it slowly. In the guidelines, it received an indeterminate recommendation [11].

A glance into the future

The association of ephinephrine and vasopressin might be superior over the single agent, as suggested by a recently concluded trial [15], and is currently under investigation in an out-of-hospital randomised study in France. Concerns with the use of vasopressin have been expressed because of its prolonged action, which accounts for the increased afterload faced by the resuscitated heart. Greater postresuscitation arterial pressures in association with lower cardiac output may incflict additional myocardial injury and compromise resuscitability. In this setting the use of a V_1 receptor antagonist appears promising (Kern K, personal communication).

Efforts are currently directed at understanding the underlying mechanisms of myocardial injury associated with current resuscitation methods, with the purpose of developing alternative approaches that are safer and more effective. These new approaches include the use of vasopressor agents devoid of β-agonist effects and/or the use of β-blockers to minimise myocardial oxygen consumption [32].

There is also interest in understanding the role of intracellular calcium overload following ischemia and reperfusion injury. To this end, activation of the sarcolemmal sodium-hydrogen exchanger isoform 1 (NHE-1) seems to play an important role. The impact has been documented in animal models and is currently under investigation in an out-of-hospital randomised trial. Other potentially important pathways of ischemic and reperfusion injury involve adenosine metabolism, activation of potassium ATP channels, and generation of oxygen radical species. These pathways may all become novel pharmacologic targets for cardiac resuscitation.

Finally, the use of thrombolysis during and after CPR appears to be particularly promising. While thrombolysis is a first-line treatment option in massive pulmonary embolism and acute myocardial infarction, CPR has been regarded as a relative contraindication for thrombolysis. However, current available data do not suggest a significant increase in bleeding complications when thrombolysis is administered during CPR [33]. Once again the issue is a matter of current randomised multicentre investigation.

References

1. Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care (2000) Circulation. 8(Suppl):I-1-403
2. Weisfeldt ML, Becker LB (2002)Resucitation after cardiac arrest – A 3 phase time-sensitive model. JAMA 288:3035-3038
3. Valenzuela TD, Roe DJ, Nichol G et al (2000) Outcomes of rapid defibrillation by security officers after cardiac arrest in casinos. N Engl J Med 343:1206-1209
4. Niemann JT, Burian D, Garner D et al (2000) Monophasic versus biphasic transthoracic countershock after prolonged ventricular fibrillation in a swine model. J Am Coll Cardiol 36:932-938
5. Cobb LA, Fahrenbruch CE, Walsh TR, et al (1999) Influence of cardiopulmonary resuscitation prior to defibrillation in patients with out-of-hospital ventricular fibrillation. JAMA 281:1182-1188

6. Weil MH et al (1995) Circulation 92:3089
7. Gottlieb R (1896-1897) Ueber die Wirkung der Nebennieren Extracte auf Herz und Blutdruck. Arch Exp Path Pharmakol 38:99-112
8. Paradis NA, Wenzel V, Southall J (2002) Pressor drugs in the treatment of cardiac arrest. Cardiol Clin 20:61-78
9. Brown CG, Martin DR, Pepe PE (1992) A comparison of standard-dose and high-dose epinephrine in cardiac arrest outside the hospital. N Engl J Med 327:1051-1055
10. Stiell IG, Herbert PC, Weitzman BN (1992) High-dose epinephrine in adult cardiac arrest. N Engl J Med 327:1045-1050
11. The American Heart Association in collaboration with the International Liaison Committee on Resuscitation (2000) Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 8(Suppl):I-90-193
12. The European Resuscitation Council. Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care (2000) Resuscitation. 46:155-162
13. Lindner KH, Strohmenger HU, Ensinger H et al (1992) Stress hormone response during and after CPR. Anesthesiology 77:662–668
14. Lindner KH, Dirks B, Strohmenger HU et al (1997) A randomized comparison of epinephrine and vasopressin in patients with out-of-hospital ventricular fibrillation. Lancet , 349:535–537
15. Wenzel V, Krismer AC, Arntz RH, Sitter H, Stadlbauer KH, Lindner KH (2004) A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. N Engl J Med 350:105-13
16. Kudenchuk PJ, Cobb LA, Copass MK et al (1999) Amiodarone for resuscitation after out of hospital cardiac arrest due to ventricular fibrillation. N Engl J Med 341:871–878
17. Dorian P, Cass D, Schwartz B et al (2002) Amiodarone as compared with lidocaina for shock-resistant ventricular fibrillation. N Engl J Med 346:884–890
18. Kudenchuk PJ (2002) Advanced cardiac life support antiarrhythmic drugs. Cardiol Clin 20:79–87
19. Dorian P, Fain ES, Davy JM et al (1986) Lidocaine causes a reversible, concentration dependent increase in defibrillation energy requirements. J Am Coll Cardiol 8:327–332
20. Kerber RE, Pandian NG, Jensen SR et al (1986) Effect of lidocaine and bretylium on energy requirements for transthoracic defibrillation: experimental studies. J Am Coll Cardiol 7:397–405
21. Echt DS, Black JN, Barbey JT et al (1989) Elevation of antiarrhythmic drugs on defibrillation energy requirements in dogs: sodium channel block and action potential prolongation. Circulation 76:1106–1117
22. MacMahon S, Collins R, Peto R et al (1988) Effects of prophylactic lidocaine in suspected acute myocardial infarction. An overview of results from randomized controlled trials. JAMA 260:1910–1916
23. Hine LK, Laird N, Hewitt P, et al (1989) Meta-analytic evidence against prophylactic use of lidocaine in acute myocardial infarction. Arch Intern Med 149:2694–2698
24. Weaver WD, Fahrenbruch DCE, Johnson DD et al (1990) Effect of epinephrine and lidocaine therapy on outcome after cardiac arrest due to ventricular fibrillation. Circulation 82:2027–2034
25. Allegra J, Lavery R, Cody R et al (2001) Magnesium sulfate in the treatment of refractory ventricular fibrillation in the prehospital setting. Resuscitation 49:245–249
26. Hassan TB, Jagger C, Barnett DB (2002) A randomized trial to investigate the efficacy of magnesium sulphate for refractory ventricular fibrillation. Emerg Med J 19:57–62
27. Nowak RM, Bodnar TJ, Dronen S et al (1981) Bretylium tosylate as initial treatment for

cardiopulmonary arrest: randomized comparison with placebo. Ann Emerg Med 10:404–407
28. Haynes RE, Chinn TL, Copass MK et al (1981) Comparison of bretylium and lidocaina in management of out-of-hospital ventricular fibrillation. Am J Cardiol 48:353–356
29. Olson DW, Thompson BM, Darin JC et al (1984) A randomized comparison study of bretylium tosylate and lidocaine in resuscitation of patients from out-of-hospital ventricular fibrillation in a paramedic system. Ann Emerg Med 13:807–810
30. Atkins DL, Dorian P, Gonzalez ER et al (2001) Treatment of tachyarrhythmias. Ann Emerg Med 37:S91–S109
31. Stiell IG, Wells GA, Hebert PC et al (1995) Association of drug therapy with survival in cardiac arrest. Acad Emerg Med 2:264–273
32. Pellis T, Weil MH, Tang W et al (2003) Evidence favoring the use of an α_2-selective vasopressor agent for cardiopulmonary resuscitation. Circulation 108:2716-2721
33. Spohr F, Bottiger BW (2003) Safety of thrombolysis during cardiopulmonary resuscitation. Drug Safety 26:367-379

Chapter 46

Myocardial preservation, reperfusion injury, and postresuscitation myocardial dysfunction

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Cessation of blood flow after cardiac arrest is characterised by rapid development of profound tissue ischaemia in proportion to the metabolic needs of individual tissue beds [1]. Remarkably, very little cell injury is demonstrable during the interval of ischaemia when there is no blood flow. Injury, however, becomes evident upon reperfusion subsequent to the reintroduction of oxygen, generation of reactive oxygen species (ROS), and activation of a myriad of pathogenic pathways [2]. This phenomenon has been termed "reperfusion injury" and is now recognised as a major player of ischaemic injury. After ischaemia and reperfusion, a more protracted (post-ischaemic) phase begins, which manifests by varying degrees of cell dysfunction and cell death, as a result of apoptosis and cell necrosis. These processes have been well characterised in various cell systems and models of acute ischaemic injury, with the exclusion of cardiac arrest models. Yet, growing evidence points to a major role in the cardiac arrest setting, probably determining initial capability for re-establishing spontaneous circulation and subsequent capability for restoring organ function.

Although cardiac arrest and resuscitation set the conditions for all tissues to suffer ischaemia and reperfusion injury, the most susceptible ones are also the most vital; namely, the heart and brain. There is a very narrow time-windows within which no flow or partial flow can be tolerated before irreversible injury develops. Current resuscitation protocols provide for interventions aimed at reversing the precipitating cause of cardiac arrest (i.e., terminating ventricular fibrillation, or correcting severe hypoxaemia) and artificially promoting blood flow across the coronary and cerebral circuits. However, no specific interventions are currently available that could target pathogenic pathways responsible for ischaemic and reperfusion injury. Yet, there is substantial interest and various research laboratories have begun to examine pharmacological interventions aimed at cell protection.

In this chapter, we address primarily the myocardial effects of ischaemia and reperfusion, with emphasis on its functional consequences, mechanisms, and potential therapeutic implications.

Myocardial effects of global ischaemia and reperfusion

The immediate goal of cardiopulmonary resuscitation is to re-establish a competent electrical and mechanical cardiac activity. However, varying degrees of electrical and mechanical dysfunction challenge this goal and account for a substantial number of deaths that occur during the early post-resuscitation phase [3-5]. Approximately one-third of victims of out-of-hospital cardiac arrest who are initially resuscitated die before hospital admission, presumably as a result of cardiac events. Of those who survive to hospital admission, approximately two-thirds die before discharge. These late deaths are likely to reflect cardiac and cerebral ischaemic injury along with intercurrent complications.

These functional myocardial abnormalities can be grouped into those that manifest during the resuscitation effort and those that manifest after the return of spontaneous circulation. The former includes ischaemic contracture and increased resistance to electrical defibrillation; the latter includes reperfusion arrhythmias and myocardial dysfunction. In addition, important changes occur in the coronary circuit that parallel these myocardial changes and include maximal coronary dilation during cardiac arrest, and reactive hyperaemia during the post-resuscitation interval. Discussion on abnormalities in coronary blood flow is beyond the scope of this chapter. However, the reader should be aware that impairments in these coronary responses may affect myocardial function and the resuscitation outcome.

Ischaemic contracture

Ischaemic contracture is characterised by progressive left ventricular wall thickening, and reductions in cavity size, which may compromise the preload required for chest compression to effectively promote forward blood flow [6, 7]. Ischaemic contracture is in part responsible for the characteristic time-dependent reduction in haemodynamic efficacy of closed-chest resuscitation. Studies in models of closed-chest resuscitation have shown that ischaemic contracture begins to develop coincident with the start of chest compression, suggesting that it is a manifestation of reperfusion injury [7]. In the absence of reperfusion, the time to onset of ischaemic contracture is markedly delayed. The extreme manifestation of ischaemic contracture is known as "stony heart", and is typically associated with irreversible injury. The severity of ischaemic contracture is in part proportional to the duration of untreated ventricular fibrillation [6]. In humans, ischaemic contracture has been reported during open-chest resuscitation after failure of closed-chest resuscitation, and described as myocardial "firmness" and associated with decreased resuscitability [8]. Given the importance of adequate preload for haemodynamically effective closed-chest resuscitation [9], preservation of cavity size represents a critical therapeutic goal. Our studies have shown that inhibition of the sodium-hydrogen exchanger isoform-1 (NHE-1) can ameliorate ischaemic contracture and enable haemodynamically more-effective resuscitation (see below).

Resistance to defibrillation

Electrical shocks delivered immediately after onset of ventricular fibrillation are consistently effective in re-establishing sinus activity. Even short delays in shock delivery (i.e., up to 3 minutes) are acceptable, and associated with more than 50% likelihood of successfully re-establishing spontaneous circulation [10]. However, after longer intervals of untreated ventricular fibrillation – as is usually the case in out-of-hospital settings – electrical shocks alone are less effective, and often fail to reverse ventricular fibrillation or may precipitate asystole or pulseless electrical activity [11]. Under these conditions, additional resuscitation interventions are usually required to restore myocardial conditions favourable for successful defibrillation. Untimely and repetitive delivery of electrical shocks may cause myocardial injury and worsen post-resuscitation electrical and mechanical dysfunction [12, 13]. New approaches are being developed to optimise the effectiveness of electrical defibrillation by identifying the proper timing for shock delivery and by using safer and more effective defibrillation waveforms [14, 15].

Post-resuscitation ventricular arrhythmias

Electrical instability typically follows the return of spontaneous circulation. This is characterised by frequent premature ventricular beats, episodes of ventricular tachycardia, and episodes of refibrillation which may become refractory to subsequent defibrillation attempts. In fact, refibrillation has been associated with worse outcomes [16]. The underlying mechanism of these arrhythmias is complex and probably involves cytosolic Ca^{2+} overload with afterdepolarisations triggering ventricular ectopic activity [17]. Maximal arrhythmic activity occurs immediately after the return of spontaneous circulation and is temporally related to shortening of the action potential duration [7]. Experimentally, both of these abnormalities gradually subside within approximately 15 minutes after resuscitation.

Post-resuscitation myocardial function

Systolic and diastolic myocardial dysfunction typically occur after resuscitation from cardiac arrest [18-22]. Systolic dysfunction is a manifestation of global decreases in contractility, which can be documented by using load-independent indices of contractility [19] as well as indices of overall ventricular performance such as ejection fraction, left ventricular stroke work, and cardiac index [20, 22, 23]. Diastolic dysfunction is probably the extension of ischaemic contracture into the post-resuscitation period [24] and is characterised by myocardial wall thickening, with reductions in end-diastolic volume and impaired relaxation [7]. Diastolic dysfunction is important because it may preclude ventricular dilatation as required – according to the Frank-Starling mechanism – to compensate for decreases in contractility. Diastolic dysfunction is more prominent during the early post-resuscitation interval and typically subsides before resolution of systolic dysfunction.

The phenomenon of post-resuscitation myocardial dysfunction has also been

documented in humans [18, 22]. Recently, Laurent and colleagues studied 165 victims of out-of-hospital cardiac arrest and documented protracted post-resuscitation haemodynamic dysfunction in patients who had longer resuscitation times, need for greater number of electrical shocks, and had received larger amounts of epinephrine [23].

Underlying pathogenic injury: the pivotal role of mitochondria

Discussion on the multiple cell mechanisms responsible for ischaemia and reperfusion injury is beyond the scope of this chapter. However, it is pertinent to discuss the growing evidence pointing to the mitochondria for its critical role in myocardial preservation, reperfusion injury, and post-ischaemic dysfunction [25-30].

The mitochondria are best known for their function as energy-producing organelles in the form of ATP in response to metabolic needs. The mechanism of ATP production involves first the generation of a large H^+ gradient across the inner mitochondrial membrane following the transport of electrons through the electron transport chain from NADH and $FADH_2$ to their final acceptor oxygen. As the electrons flow through a series of protein complexes, protons are pumped into the intermembrane space of the mitochondria, generating a proton motive force which is used by ATP synthase to form ATP from ADP + Pi. However, this H^+ gradient may collapse during ischaemia and reperfusion, subsequent to the formation of a large pore across the inner and outer mitochondrial membrane uncoupling electron transport from oxidative phosphorylation [27, 28]. This process is known as mitochondria permeability transition (MPT) and is central to the paradigm of ischaemia and reperfusion injury. In addition, opening of the transition pore causes mitochondrial swelling and disrupting of its outer membrane prompting the release of pro-apoptotic factors constitutively present in the intermembrane space and matrix [25]. One prominent pro-apoptotic mechanism encompasses the release of cytochrome-c into the cytosol. Once in the cytosol, cytochrome-c binds to the apoptotic protease activating factor 1 (Apaf-1) in the presence of dATP/ATP inducing a conformational change in Apaf-1 which exposes a caspase recruiting domain (CARD) and forms a heptamer known as the apoptosome complex [25]. The apoptosome, in turn, recruits procaspase-9 and becomes active leading to the cleavage and activation of executioner caspases 3, 6 and 7. Accordingly, the mitochondria respond to ischaemia by uncoupling its ATP formation from the electron transport and by initiating the process of programmed cell death. It is believed that some ATP needs to be generated in order for apoptosis – which is an energy requiring process – to proceed. In instances of more-severe ischaemia with complete disruption of ATP production, cell death by necrosis occurs [28].

Post-resuscitation myocardial dysfunction is largely a reversible process, and thus points to cell dysfunction rather than cell death. However, it is less clear whether dysfunction may represent part of the same but less-severe process in a continuum of ischaemia and reperfusion injury. It is worth noticing that cytochrome-*c* (discussed before as a pro-apoptotic factor) is also required for electron

transport. Thus, translocation of cytochrome-*c* to the cytosol could potentially lessen the mitochondrial capability for energy production. We have in fact shown reductions in myocardial ATP levels to approximately 50% of baseline following resuscitation from cardiac arrest in rat and pig models (unpublished). Whether this represents decreased capability for ATP production or loss of the adenine pool is not completely clear. In addition, recent studies have suggested the development of "partial apoptosis" with disruption of contractile proteins but without loss of cell viability [31]. Much work remains before we can fully elucidate the process of ischaemic injury and post-ischaemic dysfunction. Meanwhile, understanding the mechanisms that affect mitochondrial function and its signalling of apoptosis is providing opportunity for developing new therapies for cardiac resuscitation.

Along the lines of recent discoveries a novel paradigm – centered on the MPT – has emerged, providing a unifying landscape upon which various myocardial protective mechanisms are beginning to be understood [29]. The essence of protection seems to be the prevention of MPT. It has been shown experimentally that ROS can induce MPT. The presence of hypoxia and reoxygenation, however, lowers the threshold at which ROS induce MPT. Thus, protection can be assessed by documenting increases in the threshold for ROS-induced MPT.

When examining agents with demonstrable protective myocardial effects, two distinct behaviours are evident [29]. A group of protective agents exert their effect with a lasting memory defined as protection that persists for more than one hour after the agent has been removed. These agents also have in common that they induce mitochondrial swelling. Mitochondrial swelling appears to represent a key signalling step for protection. Swelling increases electron transport leading to increased ROS production. ROS, in turn, activates protein kinase C (PKC), which phosphorylates the glycogen synthase kinase 3β (GSK-3β). GSK-3β has recently emerged as a key enzyme, which is immediately proximal to the mitochondrial permeability pore [29]. By mechanisms not yet fully defined, inhibition of this enzyme by phosphorylation or other mechanisms limits MPT during period of oxidant stress, and protects the cell from ischaemia and reperfusion injury. Mutant mice that express a constitutively active GSK-3β- in which serine 9 is replaced by alanine (the phosphorylation site) do not exhibit protection to preconditioning, diazoxide, sodium-hydrogen exchange inhibition, insulin, or GSK inhibitors (see below) [29]. The importance of ROS generation for this mechanism is illustrated by the fact that protection is precluded by use of ROS scavengers, and this is perhaps the reason why antioxidants have not been clearly shown to be beneficial in humans. Mitochondrial swelling may occur by opening of the mitochondrial K_{ATP} channels, inhibition of the mitochondrial K^+/H^+ exchanger, activation of bradykinin B_2 and δ-opioid receptors, and cyclosporin A (by mechanisms not yet well defined). This group of agents has been dubbed "swellers" and their behaviour mimics ischaemic preconditioning.

Another group of agents exerts protection without induction of mitochondrial swelling or memory (effects last less than 15 minutes). Some of these agents act directly on PKC, signalling its activation and the subsequent phosphorylation of GSK-3β. Examples include receptor tyrosine kinase activation by insulin and

insulin-like growth factor-1 (IGF-1) and G protein-coupled receptor activation by adenosine A_1 receptors signalling through phosphoinositide-3 kinase/protein kinase B. In addition, GSK-3β may be directly inhibited by lithium and novel compounds recently developed [32, 33]. The myocardial protective effects of the glucose-insulin-potassium (GIK) solution may in fact operate through GSK-3β inhibition.

Treatment

Our laboratory has reported prominent myocardial protective effects by selective inhibition of the sodium-hydrogen exchanger isoform-1 (NHE-1) during resuscitation from ventricular fibrillation (see below). In the light of the new findings suggesting that protection converges via GSK-3β- on the mitochondria, it is conceivable that similar benefits may derive from other known myocardial protective agents. In fact, studies in animal models of cardiac arrest and resuscitation provide support for potential beneficial effects of adenosine [34], δ-opioid receptor agonists [35], mitochondria K_{ATP} openers [36], and sodium-calcium exchanger inhibitors [37]. In addition, protection can also be attained by limiting injury associated with the resuscitation process itself. To this end, especial attention should be paid to defibrillation strategies that limit the number of shock and use newer defibrillation waveforms; the use of vasopressor agents devoid of adrenergic actions; and new resuscitation devices that can enhance the amount of blood flow beeing generated. Once myocardial dysfunction occurs, partial reversal may be accomplished by inotropic stimulation using epinephrine [38] and dobutamine [39]. However, these agents induce tachycardia and have the potential for inducing ischaemia, especially in patients with underlying coronary artery disease. Our experience with NHE-1 inhibitors during resuscitation from ventricular fibrillation is discussed in the following section.

Sarcolemmal sodium-hydrogen exchange

NHE-1 activation in response to the intense intramyocardial acidosis that develops during ischaemia initiates an electro -neutral Na^+ and H^+ exchange across the cell membrane. This exchange brings Na^+ into the cell; however, because the capability of the Na^+-K^+ pump to extrude Na^+ is concurrently diminished [40-42], Na^+ accumulates in the cytosol becoming a "substrate" for reperfusion injury [43]. Intracellular Na^+ overload, in turn, induces sarcolemmal Ca^{2+} entry through the Na^+-Ca^{2+} exchanger acting in its reverse mode [44]. The end-result is Na^+-induced cytosolic Ca^{2+} overload, which in conjunction with ATP depletion and oxidative stress can cause MPT (as described above) [45]. Na^+ overload may also contribute to cell injury through Ca^{2+}-independent effects on mitochondrial function [46] and facilitate reperfusion arrhythmias by maintaining reentry as a result of decreased phase o (conduction velocity) of the action potential [47].

The conditions that develop during cardiac arrest and resuscitation are uniquely poised to activate and sustain NHE-1 activity. The initial trigger for NHE-1

activation is the intense intracellular acidosis of cardiac arrest. The subsequent resuscitation attempt, using closed-chest techniques, promotes reperfusion with coronary flows that rarely exceed 20% of normal. These low blood-flow levels are not sufficient to reverse ischaemia [48], but sufficient to supply the coronary circuit with normo-acidic blood, hence, washing out the excess of extracellular protons but failing to reverse ischaemia. These conditions favour NHE-1 to remain active throughout the resuscitation effort and probably the initial minutes after restoration of spontaneous circulation.

Work in our laboratory using the selective NHE-1 inhibitor cariporide has shown amelioration of functional manifestations of myocardial ischaemia and reperfusion [49, 50]. In an intact pig model, cariporide reduced ischaemic contracture during chest compression such that there was less ventricular wall thickening and better preservation of cavity size. This effect enabled chest compression to generate and maintain a coronary perfusion pressure above resuscitability thresholds throughout the resuscitation effort [7]. Cariporide also ameliorated post-resuscitation ventricular ectopic activity and fully prevented episodes of recurrent ventricular fibrillation [7, 50]. This effect was associated with preservation of the action potential duration [7]. Moreover, cariporide ameliorated post-resuscitation diastolic dysfunction promoting earlier recovery of haemodynamic function. More recently, we have reported that cariporide allows the effects of epinephrine and vasopressin to last longer, hence, allowing reduction in doses of vasopressor agents required to reestablish cardiac activity [51]. The evidence suggests that this effect is not mediated through vascular responses but results from improved forward blood flow subsequent to preserved ventricular preload during chest compression. In a separate series of experiments in which systemic and organ blood flow were measured using fluorescent microspheres, we reported that cariporide improved the relationship between depth of compression and forward blood flow, such that higher flows were generated for a given depth of compression [52]. Although cariporide inhibits sarcolemmal NHE-1 and ameliorate cytosolic Na^+ ands Ca^{2+} overload, recent evidence suggest that protection may also involve direct effects on the mitochondria by preserving the inner membrane H^+ gradient and delaying ATP depletion [53].

Conclusions

The current scientific knowledge related to ischaemia and reperfusion is expanding at a fast pace, providing unprecedented levels of understanding and paving the way for novel therapeutic approaches to emerge. We anticipate that an era of novel pharmacological treatments for cardiac arrest is about to commence.

References

1. Kette F, Weil MH, Gazmuri RJ et al (1993) Intramyocardial hypercarbic acidosis during cardiac arrest and resuscitation. Crit Care Med 21:901-906
2. Vanden Hoek TL, Qin Y, Wojcik K et al (2003) Reperfusion, not simulated ischemia, initiates intrinsic apoptosis injury in chick cardiomyocytes. Am J Physiol 284:H141-H150
3. Brown CG, Martin DR, Pepe PE et al (1992) A comparison of standard-dose and high-dose epinephrine in cardiac arrest outside the hospital. N Engl J Med 327:1051-1055
4. Kellermann AL, Hackman BB, Somes G (1993) Predicting the outcome of unsuccessful prehospital advanced cardiac life support. JAMA 270:1433-1436
5. Lombardi G, Gallagher J, Gennis P (1994) Outcome of out-of-hospital cardiac arrest in New York City. The pre-hospital arrest survival evaluation (PHASE) study. JAMA 271:678-683
6. Klouche K, Weil MH, Sun S et al (2002) Evolution of the stone heart after prolonged cardiac arrest. Chest 122:1006-1011
7. Ayoub IM, Kolarova JD, Yi Z et al (2003) Sodium-hydrogen exchange inhibition during ventricular fibrillation: Beneficial effects on ischemic contracture, action potential duration, reperfusion arrhythmias, myocardial function, and resuscitability. Circulation 107:1804-1809
8. Takino M, Okada Y (1996) Firm myocardium in cardiopulmonary resuscitation. Resuscitation 33:101-106
9. Sigurdsson G, Yannopoulos D, McKnite SH et al (2003) Cardiorespiratory interactions and blood flow generation during cardiac arrest and other states of low blood flow. Curr Opin Crit Care 9:183-188
10. Valenzuela TD, Roe DJ, Nichol G et al (2000) Outcomes of rapid defibrillation by security officers after cardiac arrest in casinos. N Engl J Med 343:1206-1209
11. Niemann JT, Burian D, Garner D, Lewis RJ (2000) Monophasic versus biphasic transthoracic countershock after prolonged ventricular fibrillation in a swine model. J Am Coll Cardiol 36:932-938
12. Mehta J, Runge W, Cohn JN, Carlyle P (1978) Myocardial damage after repetitive direct current shock in the dog: correlation between left ventricular end-diastolic pressure and extent of myocardial necrosis. J Lab Clin Med 91:272-289
13. Gazmuri RJ, Deshmukh S, Shah PR (2000) Myocardial effects of repeated electrical defibrillations in the isolated fibrillating rat heart (feature article). Crit Care Med 28:2690-2696
14. Kolarova J, Ayoub IM, Yi Z, Gazmuri RJ (2003) Optimal timing for electrical defibrillation after prolonged untreated ventricular fibrillation. Crit Care Med 31:2022-2028
15. Tang W, Weil MH, Sun S et al (2004) The effects of biphasic waveform design on post-resuscitation myocardial function. J Am Coll Cardiol 43:1228-1235
16. van Alem AP, Post J, Koster RW (2003) VF recurrence: characteristics and patient outcome in out-of-hospital cardiac arrest. Resuscitation 59:181-188
17. Koretsune Y, Marban E (1989) Cell calcium in the pathophysiology of ventricular fibrillation and in the pathogenesis of postarrhythmic contractile dysfunction. Circulation 80:369-379
18. Deantonio HJ, Kaul S, Lerman BB (1990) Reversible myocardial depression in survivors of cardiac arrest. PACE 13:982-985
19. Gazmuri RJ, Weil MH, Bisera J et al (1996) Myocardial dysfunction after successful resuscitation from cardiac arrest . Crit Care Med 24:992-1000

20. Kern KB, Hilwig RW, Rhee KH, Berg RA (1996) Myocardial dysfunction after resuscitation from cardiac arrest: An example of global myocardial stunning. J Am Coll Cardiol 28:232-240
21. Kern KB (2002) Postresuscitation myocardial dysfunction. Cardiol Clin 20:89-101
22. Mullner M, Domanovits H, Sterz F et al (1998) Measurement of myocardial contractility following successful resuscitation: quantitated left ventricular systolic function utilising non-invasive wall stress analysis. Resuscitation 39:51-59
23. Laurent I, Monchi M, Chiche JD et al (2002) Reversible myocardial dysfunction in survivors of out-of-hospital cardiac arrest. J Am Coll Cardiol 40:2110-2116
24. Gazmuri RJ (2000) Effects of repetitive electrical shocks on postresuscitation myocardial function. Crit Care Med 28:N228-N232
25. Green DR, Reed JC (1998) Mitochondria and apoptosis. Science 281:1309-1312
26. Crompton M (1999) The mitochondrial permeability transition pore and its role in cell death. Biochem J 341(Pt 2):233-249
27. Weiss JN, Korge P, Honda HM, Ping P (2003) Role of the mitochondrial permeability transition in myocardial disease. Circ Res 93:292-301
28. Halestrap AP, Clarke SJ, Javadov SA (2004) Mitochondrial permeability transition pore opening during myocardial reperfusion--a target for cardioprotection. Cardiovasc Res 61:372-385
29. Juhaszova M, Zorov DB, Kim SH et al (2004) Glycogen synthase kinase-3beta mediates convergence of protection signaling to inhibit the mitochondrial permeability transition pore. J Clin Invest 113:1535-1549
30. Murphy E (2004) Primary and secondary signaling pathways in early preconditioning that converge on the mitochondria to produce cardioprotection. Circ Res 94:7-16
31. Communal C, Sumandea M, de Tombe P et al (2002) Functional consequences of caspase activation in cardiac myocytes. Proc Natl Acad Sci U S A 99:6252-6256
32. Meijer L, Skaltsounis AL, Magiatis P et al (2003) GSK-3-selective inhibitors derived from Tyrian purple indirubins. Chem Biol 10:1255-1266
33. Polychronopoulos P, Magiatis P, Skaltsounis AL et al (2004) Structural basis for the synthesis of indirubins as potent and selective inhibitors of glycogen synthase kinase-3 and cyclin-dependent kinases. J Med Chem 47:935-946
34. von Planta M, von Planta I, Wagner O, Scheidegger D (1992) Adenosine during cardiac arrest and cardiopulmonary resuscitation: a placebo-controlled, randomized trial. Crit Care Med 20:645-649
35. Sun S, Weil MH, Tang W et al (2004) Delta-opioid receptor agonist reduces severity of postresuscitation myocardial dysfunction. Am J Physiol 287:H969-H974
36. Tang W, Weil MH, Sun S et al (2000) K(ATP) channel activation reduces the severity of postresuscitation myocardial dysfunction. Am J Physiol 279:H1609-H1615
37. Sehgal MA, Kolarova JD, Ayoub IM et al (2003) Reverse mode inhibition of the Na^+-Ca^{2+} exchanger protects the myocardium during resuscitation from ventricular fibrillation. Circulation 108:IV-380
38. Gazmuri RJ, Weil MH, von Planta M et al (1991) Cardiac resuscitation by extracorporeal circulation after failure of conventional CPR. J Lab Clin Med 118:65-73
39. Kern KB, Hilwig RW, Berg RA et al (1997) Postresuscitation left ventricular systolic and diastolic dysfunction. Treatment with dobutamine. Circulation 95:2610-2613
40. Karmazyn M (1988) Amiloride enhances postischemic ventricular recovery: Possible role of Na^+/H^+ exchange. Am J Physiol 255:H608-H615
41. Lazdunski M, Frelin C, Vigne P (1985) The sodium/hydrogen exchange system in cardiac cells: its biochemical and pharmacological properties and its role in regulating

internal concentrations of sodium and internal pH. J Mol Cell Cardiol 17:1029-1042
42. Avkiran M (1999) Rational basis for use of sodium-hydrogen exchange inhibitors in myocardial ischemia. Am J Cardiol 83:10G-17G
43. Imahashi K, Kusuoka H, Hashimoto K et al (1999) Intracellular sodium accumulation during ischemia as the substrate for reperfusion injury. Circ Res 84:1401-1406
44. Mosca SM, Cingolani HE (2001) [The Na+/Ca2+ exchanger as responsible for myocardial stunning]. Medicina (B Aires) 61:167-173
45. Halestrap AP, Connern CP, Griffiths EJ, Kerr PM (1997) Cyclosporin A binding to mitochondrial cyclophilin inhibits the permeability transition pore and protects hearts from ischaemia/reperfusion injury. Mol Cell Biochem 174:167-172
46. Iwai T, Tanonaka K, Inoue R et al (2002) Mitochondrial damage during ischemia determines post-ischemic contractile dysfunction in perfused rat heart. J Mol Cell Cardiol 34:725-738
47. Faber GM, Rudy Y (2000) Action potential and contractility changes in [Na(+)](i) overloaded cardiac myocytes: a simulation study. Biophys J 78:2392-2404
48. Ditchey RV, Horwitz LD (1985) Metabolic evidence of inadequate coronary blood flow during closed-chest resuscitation in dogs. Cardiovasc Res 19:419-425
49. Gazmuri RJ, Hoffner E, Kalcheim J et al (2001) Myocardial protection during ventricular fibrillation by reduction of proton-driven sarcolemmal sodium influx. J Lab Clin Med 137:43-55
50. Gazmuri RJ, Ayoub IM, Hoffner E, Kolarova JD (2001) Successful ventricular defibrillation by the selective sodium-hydrogen exchanger isoform-1 inhibitor cariporide. Circulation 104:234-239
51. Kolarova JD, Ayoub IM, Gazmuri RJ (2002) NHE-1 inhibition enhances the pressor responses to epinephrine and vasopressin during chest compression. Crit Care Med 30:A3
52. Kolarova JD, Ayoub IM, Hoda Z et al (2003) NHE-1 inhibition improves the depth/flow relationship of chest compression. Crit Care Med 31:A10
53. Ruiz-Meana M, Garcia-Dorado D, Pina P et al (2003) Cariporide preserves mitochondrial proton gradient and delays ATP depletion in cardiomyocytes during ischemic conditions. Am J Physiol 285:H999-1006

MICROCIRCULATION AND SHOCK

Chapter 47

Regional blood flow distribution in septic, cardiogenic and haemorrhagic shock

D. De Backer

Shock, or acute circulatory failure, is characterised by profound haemodynamic alterations. In addition to global haemodynamic alterations, regional haemodynamic alterations are commonly observed. In many cases, mesenteric vasoconstriction occurs in an attempt to preserve organ blood flow to vital organs, but other factors, such as loss of vasoregulatory processes, local metabolic alterations and therapeutic interventions, may also play a part. This may lead to an imbalance between demand and supply at the regional level, which may be involved in the development of multiple organ failure. Even though regional blood alterations are observed in most types of shock, these may differ slightly according to the type of shock as different pathophysiological mechanisms are involved (Table 1).

Table 1. Effects of haemorrhagic, cardiogenic and septic shock on the splanchnic circulation (*BF* blood flow, *PCO_2 gap* difference between gastric mucosal and arterial PCO_2)

	Haemorrhagic shock	Cardiogenic shock	Septic shock
Mesenteric BF	Decreased	Decreased	Variable
PCO_2 gap	Increased	Increased	Increased
Liver BF	Decreased	Decreased	Increased
Liver metabolism	Decreased	Decreased	Increased

Low-flow states

In hypovolaemic, haemorrhagic and cardiogenic shock, blood flow is redistributed in an attempt to preserve blood flow to vital organs (the brain and myocardium) at the expense of skin, renal and splanchnic blood flow. The splanchnic venous system acts as a capacitance bed, which may be acutely mobilised in haemorrhagic conditions. In a first phase, the mesenteric response to shock is characterised by severe vasoconstriction of mesenteric venules and veins, resulting in a blood autotransfusion corresponding to up to 30% of the total circulating volume [1]. This venous constriction occurs at the postcapillary level and thus does not affect gut nutrient blood flow. Theoretically, hepatic blood flow may have been impaired with the decrease in portal blood flow, but the compensatory increase in hepatic arterial

blood flow through the arterial buffer response [2] maintains total hepatic blood flow at a constant level. When blood losses (or hypovolaemia or the decrease in cardiac output) are even greater, selective vasoconstriction of the afferent mesenteric arterioles will promote blood flow redistribution to more vital organs and allow the maintenance of systemic arterial pressure. This markedly disproportionate response of the mesenteric resistance vessels is largely independent of the sympathetic nervous system and is variably related to vasopressin, but is mediated primarily by the renin–angiotensin axis. It will of course result in global hypoperfusion of the splanchnic organs (gut, liver, pancreas) and kidneys.

Distributive states

In addition, in distributive shock (septic shock, anaphylactic shock, pancreatitis) the loss of vascular tone impairs the normal distribution of blood flow toward the different vascular beds, resulting in regional blood flow redistribution. Ischaemia reperfusion injury, which may occur after hypovolaemic, haemorrhagic and cardiogenic shock, may result in similar alterations under the influence of the release of inflammatory mediators.

Experimental models have reported that mesenteric/portal blood flow can be either decreased, normal or increased, depending on the animal model and, especially, on the adequacy of fluid resuscitation. Even in experimental models in which mesenteric blood flow has been increased, alterations in the gut mucosal permeability, gut mucosal acidosis and histological lesions can be observed [3]. Several studies [4, 5] have shown that perfusion of the villi is markedly decreased and heterogeneous, In addition, Tugetkin et al. [5] were able to ascribe the increase in gut mucosal PCO_2 and the increased portal lactate/pyruvate ratio to these alterations in mucosal blood flow. In humans, gut mucosal acidosis can also be observed, and this is associated with a poor outcome [6–8].

In humans splanchnic blood flow has usually been reported to be either normal or elevated in patients with fluid-resuscitated severe sepsis and septic shock [9]. Nevertheless, even when elevated, splanchnic blood flow may be insufficient in view of the tremendous increase in oxygen demand. [10, 11]. This increase in metabolism is due to a combination of factors, including increased neoglucogenesis, protein synthesis and cytokine turnover, all of which are involved in the increased VO_2 [11, 12]. In comparison with trauma patients, patients with severe sepsis have higher splanchnic VO_2, so that the gradient between SvO_2 and ShO_2 is increased, ranging between 20% and 40% [13]. Importantly, a gradient that is steeper than 10% is associated with covariance of hepatosplanchnic VO_2 and hepatosplanchnic O_2 delivery, suggesting flow limitation of the liver metabolism in septic patients [14].

In addition, sepsis also induces specific microcirculatory alterations. In the bowel, endotoxin induces a decrease in gut microvascular blood flow, especially in the mucosa [4]. Capillary density decreases and, more importantly, heterogeneity (over time as well as between areas) of microvascular blood flow increases [5, 15].

This is associated with signs of bowel hypoxia, as reflected in the increased gut lactate release [16] and the increased lactate-to-pyruvate ratio [5]. In the liver, endotoxin administration decreases the number of perfused sinusoids and promotes leucocyte adhesions. These alterations have been linked with endothelin [17, 18], while nitric oxide seems to have a protective role [19–21].

In addition, oxygen extraction capabilities are impaired by endotoxin, both in the liver and in the gut, and this could possibly be related to increased blood flow heterogeneity [15]. In septic patients, Temmesfeld-Wollbrück et al. [22] report that the heterogeneity of gut O_2 saturation is increased, ranging from 0 to 70%.

Effect of therapeutic interventions

In addition to the effects of the disease itself, many of the therapeutic interventions applied can affect splanchnic perfusion and metabolism. The usual effects of common interventions are summarised in Table 2.

Table 2. Usual effects of various therapeutic interventions on the splanchnic blood flow in haemorrhagic, cardiogenic and septic shock

Interventions	Haemorrhagic	Cardiogenic	Septic
Mechanical ventilation	Decreased	Decreased	Decreased
PEEP	Decreased	Variable	Variable
Fluids	Increased	Unchanged	Unchanged or increased
Transfusions	Increased	Unchanged	Unchanged
Alpha-adrenergic stimulation	Decreased	Decreased	Unchanged or increased
Beta-adrenergic stimulation	Increased	Increased	Increased

Mechanical ventilation decreases splanchnic blood flow, but these effects are usually reversed by fluid administration [23]. Similarly, the application of positive end-expiratory pressure (PEEP) can also decrease splanchnic blood flow, but these effects depend on the level of PEEP, baseline cardiac index and volume status.

The effects of fluids are quite variable. Fluids increase splanchnic blood flow in hypovolaemic shock but do not affect it in cardiogenic shock. In septic shock, the effects of fluids can be quite variable [24, 25]. Interestingly, the regional response to fluid administration may be independent of its systemic effects [24, 25]. The effects of red blood cell transfusions are also quite variable, and especially their effects on gastric mucosal PCO_2 [26–28].

Vasoactive agents can also markedly affect splanchnic blood flow and metabolism. In physiological conditions, hepatosplanchnic blood flow is increased by β-adrenergic and dopaminergic stimulation and decreased by α-adrenergic stimulation. The various adrenergic agents usually combine α-adrenergic, β-adrenergic

and sometimes dopaminergic actions, so that their effects on hepatosplanchnic blood flow are likely to differ. In hypovolaemic shock, α-adrenergic stimulation decreases renal and portal blood flow while hepatic arterial blood flow increases, so that liver perfusion may be somewhat preserved, in contrast to perfusion of the gut and kidneys [29]. In contrast, in septic shock α-adrenergic stimulation with dopamine or norepinephrine may preserve [30] or even increase splanchnic blood flow [9]. β-adrenergic stimulation usually increases splanchnic blood flow in hypovolaemic, cardiogenic and septic conditions [14, 30, 31]. However, β-adrenergic agents also influence metabolic demand, so that this effect may overcome the beneficial effects on splanchnic blood flow. Although calibrated stimulation such as is obtained with dobutamine or dopexamine seems to have a favourable influence on splanchnic blood flow [14], uncalibrated and excessive stimulation such as is obtained with high doses of epinephrine can result in an imbalance between flow and metabolism [30, 32]. Hence, the combination of dobutamine and norepinephrine is usually preferred to epinephrine.

Finally, the effects of dopaminergic stimulation have been challenged. In contrast to healthy conditions, in which dopaminergic stimulation increases splanchnic and renal blood flow, low-dose dopamine does not improve renal or splanchnic blood flow in hypovolaemia, cardiogenic shock or septic shock.

Consequences

The decrease in splanchnic blood flow in hypovolaemic and cardiogenic shock can lead to gastric stress erosion, nonocclusive mesenteric ischaemia, ischaemic colitis, ischaemic hepatitis, ischaemic cholecystitis and/or ischaemic pancreatitis. Septic shock is associated with severe splanchnic alterations that can result in liver dysfunction. In addition, the mesenteric organ injury resulting from ischaemia/reperfusion consequent on any form of shock can trigger a systemic inflammatory response syndrome, and it promotes translocation of bacterial by-products and bacteria. Ultimately this can lead to multiple organ dysfunction syndrome. The mesenteric vasculature is therefore a major target and a primary determinant of the systemic response to circulatory shock.

Conclusions

Hepatosplanchnic haemodynamics can be significantly altered in patients with haemorrhagic, cardiogenic or septic shock. The effects of the different interventions on hepatosplanchnic blood flow may improve or further increase these alterations and cannot be inferred from evaluation of global haemodynamic parameters.

References

1. Reilly PM, Wilkins KB, Fuh KC et al (2001) The mesenteric hemodynamic response to circulatory shock: an overview. Shock 15:329-343
2. Lautt WW, Legare DJ, Ezzat WR (1990) Quantification of the hepatic arterial buffer response to graded changes in portal blood flow. Gastroenterology 98:1024-1028
3. Sautner T, Wessely C, Riegler M et al (1998) Early effects of catecholamine therapy on mucosal integrity, intestinal blood flow, and oxygen metabolism in porcine endotoxin shock. Ann Surg 228:239-248
4. Nakajima Y, Baudry N, Duranteau J et al (2001) Microcirculation in intestinal villi. A comparison between hemorrhagic and endotoxin shock. Am J Respir Crit Care Med 164:1526-1530
5. Tugtekin I, Radermacher P, Theisen M et al (2001) Increased ileal-mucosal-arterial PCO_2 gap is associated with impaired villus microcirculation in endotoxic pigs. Intensive Care Med 27:757-766
6. Marik PE (1993) Gastric intramucosal pH: a better predictor of multiorgan dysfunction syndrome and death than oxygen-derived variables in patients with sepsis. Chest 104:225-229
7. Levy B, Gawalkiewicz P, Vallet B et al (2003) Gastric capnometry with air-automated tonometry predicts outcome in critically ill patients. Crit Care Med 31:474-480
8. Gomersall CD, Joynt GM, Freebairn RC et al (2000) Resuscitation of critically ill patients based on the results of gastric tonometry: a prospective, randomized, controlled trial. Crit Care Med 28:607-614
9. Meier-Hellmann A, Specht M, Hannemann L et al (1996) Splanchnic blood flow is greater in septic shock treated with norepinephrine than in severe sepsis. Intensive Care Med 22:1354-1359
10. Dahn MS, Lange P, Lobdell K et al (1987) Splanchnic and total body oxygen consumption differences in septic and injured patients. Surgery 101:69-80
11. Dahn MS, Mitchell RA, Lange MP et al (1995) Hepatic metabolic response to injury and sepsis. Surgery 117:520-530
12. Dahn MS, Lange MP, McCurdy B et al (1995) Metabolic function of the isolated perfused rat liver in chronic sepsis. J Surg Res 59:287-291
13. Ruokonen E, Takala J, Uusaro A (1991) Effect of vasoactive treatment on the relationship between mixed venous and regional oxygen saturation. Crit Care Med 19:1365-1369
14. De Backer D, Creteur J, Noordally O et al (1998) Does hepato-splanchnic VO_2/DO_2 dependency exist in critically ill septic patients? Am J Respir Crit Care Med 157:1219-1225
15. Madorin WS, Martin CM, Sibbald WJ (1999) Dopexamine attenuates flow motion in ileal mucosal arterioles in normotensive sepsis. Crit Care Med 27:394-400
16. Lobo SM, De Backer D, Sun Q et al (2003) Gut mucosal damage during endotoxic shock is due to mechanisms other than gut ischemia. J Appl Physiol 95:2047-2054
17. Pannen BHJ, Bauer M, Zhang JX et al (1996) A time-dependent balance between endothelins and nitric oxide regulating protal resistance after endotoxin. Am J Physiol 271:H1953-H1961
18. Baveja R, Yokoyama Y, Korneszczuk K et al (2002) Endothelin 1 impairs oxygen delivery in livers from LPS-primed animals. Shock 17:383-388
19. Nishida J, McCuskey RS, McDonnell D et al (1994) Protective role of NO in hepatic microcirculatory dysfunction during endotoxemia. Am J Physiol 267:G1135-G1141
20. Corso CO, Gundersen Y, Dörger M et al (1998) Effects of nitric oxide synthase inhibitors N^G-nitro-l-arginine methyl ester and aminoethyl-isothiourea on the liver microcirculation in rat endotoxemia. J Hepatol 28:61-69

21. Gundersen Y, Corso CO, Leiderer R et al (1998) The nitric oxide donor sodium nitroprusside protects against hepatic microcirculatory dysfunction in early endotoxaemia. Intensive Care Med 24:1257-1263
22. Temmesfeld-Wollbrück B, Szalay A, Mayer K et al (1998) Abnormalities of gastric mucosal oxygenation in septic shock. Am J Respir Crit Care Med 157:1586-1592
23. Matuschak GM, Pinsky MR, Rogers RM (1987) Effects of positive end-expiratory pressure on hepatic blood flow and performance. J Appl Physiol 62:1377-1383
24. Sakka SG, Meier-Hellmann A, Reinhart K (2000) Do fluid administration and reduction in norepinephrine dose improve global and splanchnic haemodynamics? Br J Anaesth 84:758-762
25. Silva E, De Backer D, Creteur J et al (2004) Effects of fluid challenge on gastric mucosal $PCO_{(2)}$ in septic patients. Intensive Care Med 30:423-429
26. Steffes CP, Dahn MS, Lange MP (1994) Oxygen transport-dependent splanchnic metabolism in the sepsis syndrome. Arch Surg 129:46-52
27. Marik PE, Sibbald WJ (1993) Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. JAMA 269:3024-3029
28. Fernandes CJJ, Akamine N, De Marco FV et al (2001) Red blood cell transfusion does not increase oxygen consumption in critically ill septic patients. Crit Care 5:362-367
29. Corday E, Williams JH (1960) Effect of shock and vasopressor drugs on the regional circulation of the brain, heart, kidney, and liver. Am J Med 228:241-245
30. De Backer D, Creteur J, Silva E et al (2003) Effects of dopamine, norepinephrine, and epinephrine on the splanchnic circulation in septic shock: which is best? Crit Care Med 31:1659-1667
31. Reinelt H, Radermacher P, Kiefer P et al (1999) Impact of exogenous beta-adrenergic receptor stimulation on hepatosplanchnic oxygen kinetics and metabolic activity in septic shock. Crit Care Med 27:325-331
32. Meier-Hellmann A, Reinhart K, Bredle DL et al (1997) Epinephrine impairs splanchnic perfusion in septic shock. Crit Care Med 25:399-404

Chapter 48

Orthogonal polarisation spectral imaging: principles, techniques, human studies

D. De Backer

In addition to global and regional haemodynamic alterations, alterations in microcirculatory blood flow can frequently occur in shock states. Curiously, the microcirculation is often neglected, even though it is where most of the exchanges of oxygen and nutrients between the blood and the tissues occur. The microcirculation differs from the systemic circulation in many aspects. First, capillary PO_2 and haematocrit are much lower than arterial ones and may even behave differently. Second, the control of microvascular blood flow is complex and depends both on local metabolic control and on systemic, humoral controls but capillary perfusion is relatively independent of systemic blood flow and pressure. Finally, the architecture of the microvessels differs among organs so that some organs may be more vulnerable.

The study of the microcirculation has long been nearly impossible in critically ill patients. However, recent development of orthogonal polarisation spectral (OPS) imaging techniques has allowed direct visualisation of the microcirculation in critically ill patients, opening the door to monitoring of the microcirculation.

Microcirculatory blood flow is altered in experimental studies

Numerous experimental studies have observed a decrease in capillary density and the presence of stopped flow capillaries in close vicinity of well perfused capillaries (blood flow heterogeneity) [1-3]. Although these alterations can be observed in various conditions, including haemorrhagic shock [1], ischaemia/reperfusion injury [4], and sepsis [2, 3, 5-7], these alterations are more severe in septic than in other insults [8, 9]. In addition, these microcirculatory alterations clearly differ from macrocirculatory haemodynamic alterations of sepsis, with vasoconstriction in the microcirculation in contrast to the vasodilatory state with high cardiac output.

Focal vasoconstriction, microthrombi and impairment of red and white blood cell deformability are likely to concur in these microvascular alterations. In view of the severe vasoconstriction observed in some vessels, inflammatory and vasoactive mediators, such as tumour necrosis factor (TNF) [10] and endothelin [11], may aggravate the problem, while nitric oxide may have a protective role [12].

Microvascular alterations have major physiopathological implications. The juxtaposition of well perfused and non-perfused capillaries may be responsible for

the sepsis-induced decrease in oxygen extraction capabilities [13-15]. In addition, stopped flow capillaries are associated with zones of tissue hypoxia, as suggested by the decreased intravascular PO_2 [16, 17]. Finally, the transient flow observed in some capillaries may lead to focal areas with ischaemia/reperfusion injury.

The OPS imaging technique

Intravital microscopy is the gold standard technique for studying the microcirculation but, unfortunately, this technique cannot be used in humans, as a large microscope is needed in order to examine fixed tissue preparation while fluorescent dyes are infused. Alternative methods that have been used in humans include phlethysmography, videomicroscopy of the nailfold area and laser-Doppler technique [18]. Nailfold videomicroscopy uses microscopes applied on a finger that is fixed under its focus. Unfortunately, the nailfold area is very sensitive to changes in temperature, and ambient but not body temperature can be controlled. Peripheral vasoconstriction can also occur during chills and acute circulatory failure and can even be promoted by the use of vasopressor agents. Hence, this area is of limited interest in critically ill patients; instead, laser-Doppler techniques have been frequently used in these patients. The advantage of this technique is that it can be applied on various tissues and can even be inserted in the upper digestive tract through a nasogastric tube. Laser-Doppler provides measurements of blood flow in relative units (mV); accordingly, only relative changes to baseline can be assessed. However, the major limitation of this technique is that it does not take into account the heterogeneity of microvascular blood flow, the measured parameter representing the average of the velocities in all the vessels included in the investigated volume (~1 mm^3). Plethysmographic techniques have similar limitations, the sampling volume being even larger.

Orthogonal polarisation spectral (OPS) imaging is a non-invasive technique that allows direct visualisation of the microcirculation [19]. The device is composed of a small camera and several lenses, is small and can easily be used at the bedside. Polarised light illuminates the area of interest, the light is scattered by the tissue and collected by the objective lens. A polarisation filter (analyser), oriented orthogonal to the initial plane of the illumination light, is placed in front of the imaging camera and eliminates the reflected light scattered at or near the surface of the tissue, which retains its original polarisation [20]. Depolarised light scattered deeper within the tissues passes through the analyser. High-contrast images of the microcirculation are formed by absorbing structures (e.g. red blood cells) close to the surface that are illuminated by the depolarised light coming from deeper structures. Due to its specific characteristics, this device can be used to visualise the microcirculation in tissues protected by a thin epithelial layer, such as the mucosal surface. In critically ill patients, the sublingual area is the most easily investigated mucosal surface. Other mucosal surfaces include rectal and vaginal surfaces, which are of limited accessibility, and ileal or colic mucosa in patients with enterostomies. Images can also be generated in eyelids and in the nailfold [21].

The use of OPS imaging techniques to visualise the microcirculation has been validated against standard techniques. Vessel diameters, functional capillary density and vessel blood flow were found to be similar with OPS imaging and standard intravital fluorescence videomicroscopy in various animal models [19, 22-24]. In human healthy volunteers, the agreement in the measurement of capillary density and red blood cell velocity in the nailfold area was excellent between OPS imaging and capillaroscopy [21]. Unfortunately, a quantitative approach cannot be used for observations of the sublingual microcirculation in critically ill patients, due to small movements of the probe (especially respiratory movements). Accordingly, we [25] have developed a semi-quantitative method to determine capillary density and the proportion of perfused capillaries. In addition, the investigation of the sublingual microcirculation requires a cooperative or sedated patient, and the absence of bloody secretions in the mouth.

Microvascular blood flow is altered in critically ill patients

Using the OPS technique in the sublingual area of patients in circulatory failure, we [25, 26] observed that microcirculatory alterations are frequent in shock states. Fifty patients with severe sepsis ($n = 8$) and septic shock ($n = 42$) were investigated within 48 h of the onset of sepsis [25]. Compared to controls, septic patients presented a decrease in capillary density (vessels containing no red blood cells cannot be visualised) and a decrease in the proportion of the perfused capillaries (Fig. 1). These alterations were more pronounced in non-survivors than in survi-

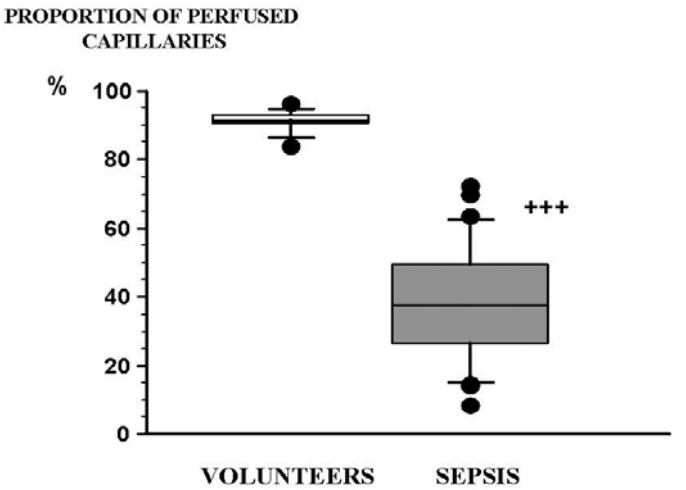


Fig. 1. Proportion of perfused capillaries in patients with sepsis. Volunteers *open rectangles*, patients with sepsis *gray rectangles*. Redrawn from [25]

vors. In a second cohort of 49 patients with septic shock [27], the sublingual microcirculation was investigated daily, up to shock resolution or death. It was observed that microvascular blood flow rapidly improved (but did not totally resolve) in survivors but remained altered in non-survivors, whether these patients died from shock or from multiple organ failure after shock had resolved (Fig. 2). In survivors, microcirculatory alterations improved even though these patients were still on vasopressors for several days. In addition, the finding that microvascular alterations improved by more than 7.5% within the first 24 h of observation was an excellent predictor of outcome (71% survival rate above this cut-off value versus only 19% below it). Perhaps more importantly, microvascular alterations were the most powerful predictor of outcome in these patients, well before changes APACHE II score or changes in global haemodynamics or SOFA score occurred. These data suggest that microvascular blood flow alterations are implicated in the pathophysiological process involved in the development of multiple organ failure and death in septic patients.

These alterations were fully reversible after topical application of a high dose of acetylcholine [25, 26], suggesting that vasodilators may be of value [28]. This was further corroborated by Spronk et al. [29], who reported that nitroglycerin improved the sublingual microcirculation; unfortunately, it also induced a marked hypotension. Furthermore, as the potential cytotoxic effects of NO donors should not be neglected, further studies are needed before this intervention can be translated into clinical practice. Other interventions are currently under investigation.

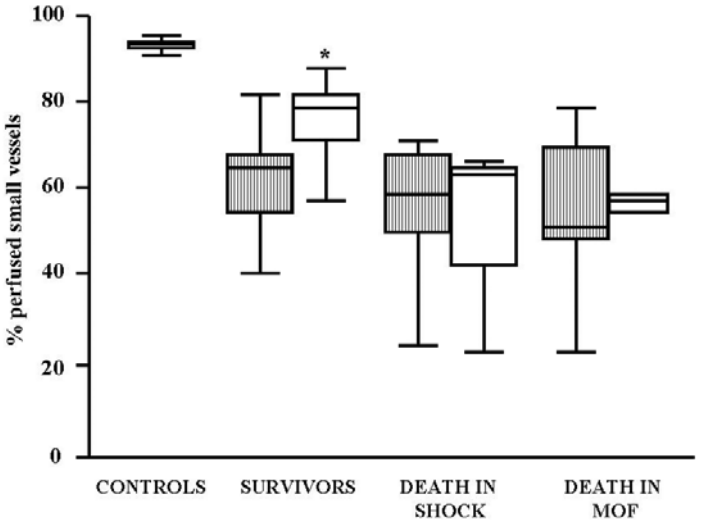


Fig. 2. Evolution of microcirculatory alterations in survivors and non-survivors. First day of shock *hatched rectangles*, last day *open rectangles*. *MOF* Multiple organ failure. From [27], with permission

Microcirculatory alterations can also be observed in other conditions than sepsis. The proportion of perfused capillaries was decreased in patients with severe heart failure and cardiogenic shock [26]. These alterations could also be fully reversed by the topical application of acetylcholine.

Microvascular blood flow is also altered after cardiac surgery. In 28 patients submitted to cardiac surgery, the proportion of perfused capillaries decreased after cardiopulmonary bypass, remained altered during the first hours of admission in the critical care unit, and almost normalised the day after surgery [30]. However, these alterations were far less pronounced than in patients with septic or cardiogenic shock.

Are microcirculatory alterations influenced by systemic factors?

One question is whether these microvascular blood flow alterations are influenced by systemic factors. If yes, then monitoring of the microcirculation may be useless, as these alterations can be inferred from more easily applicable monitoring techniques.

As microcirculatory and macrocirculatory alterations usually coexist, it is quite difficult to separate the influence of each factor. Experimental studies suggest that microcirculatory alterations can occur even when blood flow or perfusion pressure is maintained [8, 9, 31]. Using OPS on the sublingual microcirculation in 96 patients with severe sepsis and septic shock, we observed that the severity of microcirculatory alterations was not related to arterial pressure, the use of vasopressors or cardiac index [32].

Are these alterations cause or effect ?

Another question is whether these microvascular blood flow alterations are the initial mechanism, leading to alterations in tissue metabolism, or are they secondary to cellular events, with flow directly reflecting heterogeneous metabolic alterations? It is difficult to separate these two alternatives. Several arguments nevertheless suggest that microcirculatory alterations may be the triggering event. First, in a pivotal study, Ellis et al. [33] reported in a model of peritonitis induced by cecal ligation that heterogeneity of microvascular blood flow increased with an increased number of stopped-flow capillaries (from 10 to 38%) and in the proportion of fast-flow to normal-flow capillaries. In addition, in the well perfused capillaries, O_2 extraction was increased, not decreased, and VO_2 of this segment was also increased. These results strongly argues against a sepsis-induced mitochondrial dysfunction, at least in the early phase of sepsis. Indeed a primary mitochondrial dysfunction would have been accompanied by a decreased VO_2 and O_2 extraction in this segment. Similarly, Ince et al. [16] reported that microvascular PO_2 is decreased in sepsis, which is incompatible with primary metabolic alterations. This suggests that the decrease in extraction capabilities that is observed in sepsis is related to blood

flow heterogeneity but not to impaired capacities of the tissues to use oxygen. Second, we observed that the severity of alteration in sublingual microcirculation is inversely related to sublingual PCO_2 and that both alterations can be reversed [34]. If flow matched metabolism, PCO_2 would not have been increased in these patients. All together, these observations suggest that microcirculatory alterations are involved in the pathophysiology of sepsis-induced organ dysfunction and do not match metabolic alterations, at least in the early phases of sepsis.

Remaining questions

It also remains unclear whether microcirculatory alterations are similar and occur simultaneously and with the same degree of severity in the various microvascular beds. Animal models have clearly shown that similar alterations occur in striated muscles [3, 33], small bowel mucosa [6], liver [35], pancreas [36], and skinfold [4]. However, none of these models simultaneously investigated different organs; hence, the severity and time course of these lesions may vary between the different organs. This may be of particular importance for bedside monitoring of the human microcirculation, especially as accessible sites are limited. Preliminary data in humans nevertheless suggest that similar microvascular alterations can be observed in the sublingual area and on ileostomies and colostomies [37].

Conclusions

The microcirculation is a key element in tissue oxygenation, as it is where most of oxygen and nutrient exchanges take place. Studying the microcirculation in humans has long been difficult as laser-Doppler or plethysmography techniques do not take into account heterogeneity of blood flow. OPS imaging techniques allow direct visualisation of the human microcirculation. Using this approach, we demonstrated that the sublingual microcirculation of patients with acute circulatory failure is markedly altered. In addition, rapid improvement of the microcirculation, which occurred well before an improvement in systemic haemodynamics, was predictive of a good outcome. These alterations are not influenced by arterial pressure or vasopressor agents and cannot be detected by classical monitoring devices. Monitoring the microcirculation of patients with acute circulatory failure may help to identify those patients in whom further interventions may be required.

References

1. Zhao KS, Junker D, Delano FA et al (1985) Microvascular adjustments during irreversible hemorrhagic shock in rat skeletal muscle. Microvasc Res 30:143-153
2. Cryer HM, Garrison RN, Kaebnick HW et al (1987) Skeletal microcirculatory responses to hyperdynamic Escherichia coli sepsis in unanesthetized rats. Arch Surg 122:86-92
3. Lam CJ, Tyml K, Martin CM et al (1994) Microvascular perfusion is impaired in a rat model of normotensive sepsis. J Clin Invest 94:2077-2083
4. Dammers R, Wehrens XH, Oude EM et al (2001) Microcirculatory effects of experimental acute limb ischaemia-reperfusion. Br J Surg 88:816-824
5. Baker CH, Wilmoth FR (1984) Microvascular responses to E. coli endotoxin with altered adrenergic activity. Circ Shock 12:165-176
6. Farquhar I, Martin CM, Lam C et al (1996) Decreased capillary density in vivo in bowel mucosa of rats with normotensive sepsis. J Surg Res 61:190-196
7. McCuskey RS, Urbaschek R, Urbaschek B (1996) The microcirculation during endotoxemia. Cardiovasc Res 32:752-763
8. Boczkowski J, Vicaut E, Aubier M (1992) In vivo effects of Escherichia coli endotoxemia on diaphragmatic microcirculation in rats. J Appl Physiol 72:2219-2224
9. Nakajima Y, Baudry N, Duranteau J et al (2001) Microcirculation in intestinal villi. A comparison between hemorrhagic and endotoxin shock. Am J Respir Crit Care Med 164:1526-1530
10. Vicaut E, Hou X, Payen D et al (1991) Acute effects of tumor necrosis factor on the microcirculation in rat cremaster muscle. J Clin Invest 87:1537-1540
11. Groeneveld AB, Hartemink KJ, de Groot MC et al (1999) Circulating endothelin and nitrate-nitrite relate to hemodynamic and metabolic variables in human septic shock. Shock 11:160-166
12. Hollenberg SM, Broussard M, Osman J et al (2000) Increased microvascular reactivity and improved mortality in septic mice lacking inducible nitric oxide synthase. Circ Res 86:774-778
13. Walley KR (1996) Heterogeneity of oxygen delivery impairs oxygen extraction by peripheral tissues: theory. J Appl Physiol 81:885-894
14. Humer MF, Phang PT, Friesen BP et al (1996) Heterogeneity of gut capillary transit times and impaired gut oxygen extraction in endotoxemic pigs. J Appl Physiol 81:895-904
15. Drazenovic R, Samsel RW, Wylam ME et al (1992) Regulation of perfused capillary density in canine intestinal mucosa during endotoxemia. J Appl Physiol 72:259-265
16. Ince C, Sinaasappel M (1999) Microcirculatory oxygenation and shunting in sepsis and shock. Crit Care Med 27:1369-1377
17. Zuurbier CJ, van Iterson M, Ince C (1999) Functional heterogeneity of oxygen supply-consumption ratio in the heart. Cardiovasc Res 44:488-497
18. De Backer D, Dubois MJ (2001) Assessment of the microcirculatory flow in patients in the intensive care unit. Curr Opin Crit Care 7:200-203
19. Groner W, Winkelman JW, Harris AG et al (1999) Orthogonal polarization spectral imaging: a new method for study of the microcirculation. Nat Med 5:1209-1212
20. Slaaf DW, Tangelder GJ, Reneman RS et al (1987) A versatile incident illuminator for intravital microscopy. Int J Microcirc Clin Exp 6:391-397
21. Mathura KR, Vollebregt KC, Boer K et al (2001) Comparison of OPS imaging and conventional capillary microscopy to study the human microcirculation. J Appl Physiol 91:74-78

22. Langer S, von Dobschuetz E, Harris AG et al (2000) Validation of the orthogonal polarization spectral imaging technique on solid organs. In: Messmer K (ed) Orthogonal polarization spectral imaging. Karger, Basel, pp 32-46
23. Laemmel E, Tadayoni R, Sinitsina I et al (2000) Using orthogonal polarization spectral imaging for the experimental study of microcirculation: comparison with intravital microscopy. In: Messmer K (ed): Orthogonal polarization spectral imaging. Karger, Basel, pp 50-60
24. Harris AG, Sinitsina I, Messmer K (2000) The Cytoscan(TM) Model E-II, a new reflectance microscope for intravital microscopy: Comparison with the standard fluorescence method. J Vasc Res 37:469-476
25. De Backer D, Creteur J, Preiser JC et al (2002) Microvascular blood flow is altered in patients with sepsis. Am J Respir Crit Care Med. 166(1):98-104
26. De Backer D, Creteur J, Dubois MJ et al (2004) Microvascular alterations in patients with acute severe heart failure and cardiogenic shock. Am Heart J 147:91-99
27. Sakr Y, Dubois MJ, De Backer D et al (in press) Persistant microvasculatory alterations are associated with organ failure and death in patients with septic shock. Crit Care Med
28. Buwalda M, Ince C (2002) Opening the microcirculation: can vasodilators be useful in sepsis? Intensive Care Med 28:1208-1217
29. Spronk PE, Ince C, Gardien MJ et al (2002) Nitroglycerin in septic shock after intravascular volume resuscitation. Lancet 360:1395-1396
30. Dubois MJ, De Backer D, Schmartz D et al(2002) Microcirculatory alterations in cardiac surgery with and without cardiopulmonary bypass. Intensive Care Med 28:S76(Abstract)
31. Tugtekin I, Radermacher P, Theisen M et al (2001) Increased ileal-mucosal-arterial PCO_2 gap is associated with impaired villus microcirculation in endotoxic pigs. Intensive Care Med 27:757-766
32. De Backer D, Sakr Y, Creteur J et al(2003) Microvascular alterations are independent of systemic factors in patients with septic shock. Intensive Care Med 29:S10(Abstract)
33. Ellis CG, Bateman RM, Sharpe MD et al (2002) Effect of a maldistribution of microvascular blood flow on capillary O(2) extraction in sepsis. Am J Physiol 282:H156-H164
34. De Backer D, Creteur J, Dubois MJ. (2003) Microvascular alterations in patients with circulatory failure. In: Vincent J-L (ed), Yearbook of intensive care and emergency medicine. Springer, Berlin, Heidelberg, New York, pp 535-544
35. Corso CO, Gundersen Y, Dörger M et al (1998) Effects of nitric oxide synthase inhibitors N^G-nitro-L-arginine methyl eshter and aminoethyl-isothiourea on the liver microcirculation in rat endotoxemia. J Hepatol 28:61-69
36. Foitzik T, Eibl G, Hotz HG et al (2000) Endothelin receptor blockade in severe acute pancreatitis leads to systemic enhancement of microcirculation, stabilization of capillary permeability, and improved survival rates. Surgery 128:399-407
37. Spronk PE, Rommes JH, Hesselink EJ et al (2003) Comparison of sublingual and intestinal microvascular flow in critically ill patients. Intensive Care Med 29:S179(Abstract)

Chapter 49

Carbon dioxide monitoring to evaluate cell oxygenation

J. Creteur

Tissue hypoxia plays a crucial role in the pathogenesis of multiple organ failure [1], which remains one of the main causes of death in the intensive care units. Its prevention, which can be achieved by maintaining adequate tissue perfusion, is crucial in the therapeutic management of critically ill patients. Optimal performance of this management requires needs monitoring of global and/or regional tissue oxygenation parameters. Such monitoring which should allow to identify identification of patients at risk and help to guide early and aggressive therapy, which has proved to be effective in patients with severe sepsis or in septic shock [2]. Carbon dioxide monitoring is one of these tools used to assess tissue oxygenation. This review will describe carbon dioxide monitoring techniques thatwhich are already or nearly clinically available or expected to be so shortly, with an emphasis on their rationale and methodologyical.

Venoarterial PCO_2 gradient

The venoarterial PCO_2 gradient ($VAPCO_2$) normally does not exceed 6 mmHg. Nevertheless, elevated $VAPCO_2$ has been observed in all types of circulatory failure (cardiogenic, obstructive, hypovolaemic and distributive shock) [3]. According to the Fick equation applied to the cardiac output (CO), CO_2 excretion (equivalent to CO_2 production [VCO_2] in steady state) is equal to the product of CO times the difference in CO_2 content betweenin mixed venous blood ($CvCO_2$) and arterial blood ($CaCO_2$) blood: for a given CO_2 production (VCO_2), $VAPCO_2$ is inversely proportional to cardiac output (CO):

$$VCO_2 = CO \times (CvCO_2 - CaCO_2)$$

The normal relation between pressure and content of CO2 is almost linear over the usual physiological range of CO2 content. Therefore, by rearranging the Fick equation and substituting PCO2 for CCO2, a modified Fick equation can be obtained :

$$VAPCO_2 = k\ (VCO_2/CO)$$

where $VAPCO_2$ is the venoarterial PCO_2 gradient and k is a constant.

This makes $VAPCO_2$ directly proportional to oxygen consumption (VO_2) and inversely proportional to cardiac output. This hypothesis has been confirmed by two experimental studies performed in our animal laboratory in anaesthetised dogs [4, 5]. In these studies, the cardiac output was progressively decreased by the induction of progressive haemorrhage [4] or cardiac tamponade [5]. While the

dogs' oxygen consumption (VO_2) remained constant, the progressive decrease in cardiac output was accompanied by a progressive increase in $VAPCO_2$ from approximately 4 mmHg to 15 mmHg in both studies. In this situation of nondependence between VO_2 and oxygen delivery (DO_2) (i.e., in the absence of tissue hypoxia) and stable VCO_2, the progressive increase in $VAPCO_2$ is due to the decrease in tissue CO_2 clearance (stagnation phenomenon) following the decrease in cardiac output.

Always in the same studies [4, 5], when oxygen delivery (DO_2) was more decreased further to reach the VO_2/DO_2 dependence phase (i.e. in the presence of tissue hypoxia, anaerobic metabolism and increase in arterial lactate concentration), $VAPCO_2$ abruptly increased up to values approaching 30 mmHg. This abrupt increase in $VAPCO_2$ can not be explained by an increase in VCO_2 since Zhang et al. [5] had clearly demonstrated that VCO_2 decreased concomitantly to the decrease in VO_2 during the VO_2/DO_2 dependence phase. There are two possible reasons for the abrupt increase in $VAPCO_2$ in such conditions:

1. Because the relation between cardiac output and venoarterial CO_2 content gradient is not linear but curvilinear (Fick equation), a dramatic increase in venoarterial CO_2 content gradient must be observed for a decrease in cardiac output in the lowest range. Nevertheless, this phenomenon will presumably be attenuated in hypoxic conditions, since the decrease in VCO_2 shifts to the left the VCO_2 isopleth to the left.
2. The striking $VAPCO_2$ widening at very low cardiac outputs widening may be explained further by the curvilinearity of the relation between venous CO_2 content ($CvCO_2$) and venous partial pressure of CO_2 ($PvCO_2$). Indeed, this relation is no longer linear in the highest range of CCO_2, so that $VAPCO_2$ changes are greater than CCO_2 changes in such extreme conditions. Furthermore, the disparities between CCO_2 and PCO_2 at high levels of CCO_2 are exaggerated by high oxygen saturation and by the reduction in pH which constantly follows the increase in $PvCO_2$ and may be of further importance if metabolic acidosis coexists. Consequently, in the case of low-flow states, the increase in $PvCO_2$ resulting from CO_2 stagnation is greater in extent than the increase in $CvCO_2$.

All these studies, which were designed to study the detection of hypoxia by $VAPCO_2$ analysis, used experimental models of progressive decrease in CO. As mentioned above, this technique plays as a confounding role. In this context, Vallet et al. [6] studied the effects of the decrease in oxygen transport on $VAPCO_2$ in an isolated dog hindlimb model. These authors showed that $VAPCO_2$ increased significantly when limb hypoxia was created by ischaemia (low blood flow), while it remained unchanged when hypoxia was related to hypoxaemia (maintained blood flow). This study underlines that the absence of an increased $VAPCO_2$ does not preclude the presence of tissue hypoxia and that a decreased blood flow is a major determinant in the increased $VAPCO_2$. At least two clinical studies confirm these experimental data. Bakker et al. [3] separated a population of 64 patients with septic shock into a first group with $VAPCO_2$ above 6 mmHg and a second with $VAPCO_2$ below 6 mmHg. Cardiac output and oxygen transport were lower in the first group,

while oxygen consumption and arterial lactate concentrations were similar in both groups, suggesting a closer correlation between $VAPCO_2$ and CO than between $VAPCO_2$ and signs of tissue hypoxia. Wendon et al. [7] reported $VAPCO_2$ values below 3 mm Hg in patients with fulminant hepatitis despite evidence of tissue hypoxia demonstrated by an increase in oxygen consumption following prostacyclin infusion.

It seems, then, that the analysis of $VAPCO_2$ lacks sensitivity in detection of tissue hypoxia in critically ill patients. It has recently been proposed that this sensitivity could be increased by using the ratio between $VAPCO_2$ and the arteriovenous oxygen content gradient ($VAPCO_2/CaO_2\text{-}CvO_2$). This suggestion is based on the fact that during the development of hypoxia VCO_2 will be reduced by less than VO_2 (because of the anaerobic CO_2 production), leading to an increase in the respiratory quotient (VCO_2/VO_2) and the $VAPCO_2/CaO_2\text{-}CvO_2$. In a retrospective study in intensive care patients, Mekontso-Dessap et al. [8] demonstrated that the $VAPCO_2/CaO_2\text{-}CvO_2$ ratio was the more sensitive variable for detection of tissue hypoxia, defined here as an arterial lactate concentration above 2 meq/l.

Therefore, even if $VAPCO_2$ can increase in aerobic conditions (in the absence of hypoxia), this increase must be interpreted as a cardiac output too low for the oxygen demand, and in the short term there is a risk that hypoxia will develop. Conversely, a normal $VAPCO_2$ does not preclude the presence of global tissue hypoxia when cardiac output is maintained, or regional hypoxia in a single badly perfused organ.

Gastric tonometry

Because the stomach is a relatively easy organ to access, gastric tonometry is a minimally invasive means of determining perfusion to the stomach and may provide crucial information about perfusion in the rest of the splanchnic bed. Gastric tonometry attempts to determine the perfusion of the gastric mucosa using measurements of local PCO_2 [9]. CO_2 diffuses from the mucosa into the lumen of the stomach and subsequently into the silicone balloon of the tonometer. After an equilibration period, the PCO_2 within the balloon is thought to be equal to the gastric mucosal CO_2 ($PgCO_2$) and can be measured by one of two means: (1) saline tonometry, in which saline solution is anaerobically injected into the balloon, sampled after an equilibration period and measured using a blood gas analyser; or (2) air tonometry, in which air is pumped through the balloon and the PCO_2 is determined automatically by an infrared detector on a semi-continuous basis. If we assume that arterial bicarbonate is equal to mucosal bicarbonate, intramucosal pH (pHi) can be calculated from the Henderson-Hasselbalch equation. Unfortunately, this assumption is incorrect. Simulations of mesenteric ischaemia indicate that use of the arterial bicarbonate level will result in errors in the determination of gastric pHi [10]. In addition, acute respiratory acid/base disturbances will also introduce errors into the calculation of pHi [11]. Metabolic acidosis (and its subsequent decrease in arterial bicarbonate), as found in renal failure, can lead to the calculation

of a low pHi value in the absence of any gut hypoperfusion. Consequently, pHi has been replaced by the PCO_2 gap (the difference between gastric mucosal and arterial PCO_2) as a better way to determine the adequacy of the perfusion to the stomach [12, 13].

There are a number of factors that can cause errors in the determination of gastric PCO_2 ($PgCO_2$), and these must be taken into account. If saline tonometry is used some blood gas analysers will consistently and dramatically underestimate the PCO_2 in the saline solution [14]. Use of buffered saline solutions will improve the accuracy of the PCO_2 determination, but the time needed before a steady state is reached in the tonometer is increased [15]. Gastric acid secretion can also increase CO_2 production by titration of luminal acid with bicarbonate in the gastric mucus or refluxed duodenal contents, thereby introducing additional errors into determination of the PCO_2 gap. Use of H_2-blockers will reduce this error in healthy volunteers [16], but not in critically ill patients [17]. Sucralfate does not appear to interfere with the determination of gastric pHi [18]. Gastric, but not duodenal, feedings will cause a false reduction in gastric pHi (or increase in $PgCO_2$) [19, 20]. Controversy persists on the usefulness of H_2-blocker administration during gastric tonometry monitoring, but the main limitation for routine continuous use of such a technique is the impossibility of ensuring the reliability of $PgCO_2$ values when patients are fed through conventional nasogastric tubes.

Interpretation of the PCO_2 gap

According to the Fick equation, the determinants of the PCO_2 gap are mucosal blood flow and mucosal VCO_2, so that the PCO_2 gap is a good marker of the adequacy of the balance between local blood flow and metabolism. In healthy volunteers, a PCO_2 gap of 8 mmHg seems to reflect an adequate balance between mucosal CO_2 production and regional perfusion [21]. For a constant VCO_2, the decrease in gastric mucosal blood flow will lead to a decrease in mucosal CO_2 washout and a subsequent increase in $PgCO_2$. When DO_2 to the mucosa is reduced below metabolic demand, acidosis ensues. Under anaerobic conditions, H+ ions are generated by two mechanisms: (1) excessive production of lactic acid related to the accelerated anaerobic glycolysis, since pyruvate can no longer be cleared by the Krebs cycle; and (2) hydrolysis of adenosine triphosphate (ATP) and adenosine diphosphate (ADP). In the latter case the protons generated will be buffered by HCO_3^- ions passing into the cell so that CO_2 will be generated.

Low cardiac output states (ischaemic hypoxia)

In contrast to sepsis, systemic low flow states cause splanchnic hypoperfusion with no initial change in splanchnic oxygen consumption, regardless of whether the aetiology is a cardiac one or acute hypovolaemia. Following a diversion of blood supply mediated by sympathetic adrenergic stimulation [22], both the liver (which can redistribute an additional 1 l of blood to the systemic circulation under cardiovascular stress) and the gut are efficient means of ensuring that vital organs are perfused during acute hypovolaemia [23, 24].

Guzman et al. [25] studied the effects on $PgCO_2$ when a reduction in DO_2 was induced by progressive haemorrhage in dogs . They reported a marked increase in $PgCO_2$ well before the systemically critical DO_2 value was reached. In this situation, an increase in $PgCO_2$ could be used as an early index of haemodynamic instability.

Gastric tonometry during induced short-term hypovolaemia in healthy volunteers showed reduced gastric pHi, and this resolved with resuscitation [26]. Interestingly, this was the only significant clinical indicator of hypovolaemia, with heart rate, blood pressure and peripheral perfusion showing no change after a 20–25% blood volume venesection. Moreover, after simulated [27] and actual [23] hypovolaemia in healthy human volunteers, splanchnic vasoconstriction was observed beyond the period of restoration of normal systemic haemodynamics even after apparently adequate fluid resuscitation.

Using a canine model of cardiac tamponade, Schlichtig and Bowles [28] have demonstrated that the production of CO_2 from anaerobic pathways is difficult to detect in ischaemic hypoxic tissue without the use of direct or indirect measurements of tissue PCO_2 (such as gastric tonometry). $VAPCO_2$ as a global parameters could not detect localised ischaemic hypoxia, because the efferent venous blood flow can be high enough to wash out the CO_2 produced from the constantly perfused tissues and, because of the marked fall in CO_2 production from the anaerobic pathway that should occur in these circumstances, total CO_2 production can be markedly decreased [29]. Therefore, tissue-to-arterial PCO_2 gradients are thought to be more reliable markers of tissue hypoxia than $VAPCO_2$ [28].

One of the problems that has plagued gastric tonometry is that the value of pHi or PCO_2 at which hypoxia occurs is unknown. In a canine model of cardiac tamponade, Schlichtig and Bowles [28] measured intestinal DO_2 and tonometric CO_2 in the jejunum and ileum. They determined that hypoxia occurred a PCO_2 gap of around 25–35 mmHg. Therefore, any value between 8 and 25 mmHg for PCO_2 gap must be interpreted as the reflection of moderate hypoperfusion without hypoxia.

As already mentioned, during the development of low-flow states the PCO_2 gap increases early, before systemic haemodynamic alterations are observed. This property can be used to detect occult hypovolaemia in an apparently haemodynamically stabilised patient. The susceptibility of the gut mucosa to any decrease in systemic blood flow can be explained by at least two mechanisms. First, splanchnic blood flow is reduced early during even minor cardiovascular alterations in an attempt to preserve the blood supply to more vital organs, namely the heart and the brain. Second, the tip of the gut villus may be particularly susceptible to a reduction in blood flow, in view of the local countercurrent mechanism supplying oxygen, which is responsible for the presence of a PO_2 gradient between the basis and the top of the villi [30].

Hypoxic and anaemic hypoxia

Several investigators have questioned the ability of gastric mucosal PCO_2 to detect tissue hypoxia. Nevière et al. [31] reported that the increase in PCO_2 gap in pigs was less pronounced in hypoxic hypoxia (decrease in PaO_2) than in ischaemic hypoxia (decrease in blood flow). Similarly, the increase in PCO_2 gap was blunted in anaemic hypoxia in sheep [32]. This suggests that maintenance of flow limits the increase in PCO_2 gap. These experimental studies demonstrate clearly that the principal determinant for the PCO_2 gap is blood flow. When mucosal blood flow is maintained, even when there is evidence of mucosa hypoxia PCO_2 gap does not increase [31]. Therefore, in this condition a normal PCO_2 gap cannot exclude severe hypoxia. Nevertheless, such severe hypoxic or anaemic hypoxia is very uncommon in clinical practice.

Severe sepsis/septic shock

Interpretation of the PCO_2 gap is more complex in sepsis. Indeed, this syndrome may be associated with coexistence of a normal or high CO, inter- and intra-organ blood flow redistribution, altered microcirculation and oxygen extraction capabilities. These alterations are particularly marked in the splanchnic regions, and they can all interfere theoretically with the gut tissue's production and elimination of CO_2.

Some researchers in this field argue that in the presence of high flow, the increase in PCO_2 gap found in sepsis reflects a metabolic alteration (endotoxin-mediated cell mitochondrial toxicity, the so-called cytopathic hypoxia [33]) more than hypoperfusion. This hypothesis was initially strengthened by experimental studies. Experimental studies [34, 35] have reported that mucosal acidosis may occur in sepsis even when mucosal blood flow is preserved or increased [34, 35] and the mucosa is well oxygenated [34]. Van der Meer et al. [34] have demonstrated in pigs that endotoxin infusion results in a significant increase in intramucosal hydrogen ion concentration, while mucosal perfusion, assessed by laser-Doppler flowmetry, does not change significantly and mucosal PO_2, assessed by microelectrodes, increases significantly [34]. In a similar porcine model of endotoxic shock, Revelly et al. [35] have shown that pHi is inversely correlated with mucosal blood flow, suggesting that the decrease in pHi during endotoxic shock may be due to direct metabolic alterations induced by endotoxin rather than to mucosal hypoperfusion. Kellum et al. [36] found no correlation between PCO_2 gap and portal venous blood flow or gut lactate production during endotoxic shock in dogs.

Clinical data also cast doubt on the idea that gastric tonometry can be used as a reliable marker of hepatosplanchnic perfusion in septic patients. We [37] measured gastric PCO_2 gap, hepatosplanchnic blood flow (via indocyanine green infusion), ShO_2 and hepatic venoarterial PCO_2 gradient in 36 patients with severe sepsis and found there were no correlations between gastric PCO_2 and any of the other indices of hepatosplanchnic oxygenation. Similar findings have been recorded in cardiac surgery patients treated with dobutamine [38, 39].

Despite these conflicting results, strong evidence nonetheless argues for a predominant role of a decrease in mucosal blood flow in the increase in PCO_2 gap found in sepsis. Experimentally, sepsis and endotoxaemia have been associated with alterations in gut mucosal oxygenation measured by PO_2 electrodes or laser-Doppler in pigs [40, 41] or in dogs [42], even when global perfusion has been maintained [42]. In different models of normotensive sepsis, microcirculatory alterations at the level of the gut villi (decrease in the capillary density and/or in the number of well-perfused capillaries) have been reported in rats [43-45] and in dogs [46]. Tugtekin et al. [47] demonstrated in septic pigs that the increased PCO_2 gap was related to the heterogeneity of gut mucosal blood flow (assessed with the orthogonal polarization spectral imaging technique) even though CO and mesenteric blood flow were maintained.

In addition to many animal investigations, support for the notion that gastric pHi can be used to assess local mucosal perfusion comes from a study of 17 patients who underwent mechanical ventilation [48] A low gastric pHi in these patients was associated with a lower mucosal blood flow as determined by laser-Doppler flowmetry than in patients with a normal pHi. In septic patients Nevière et al. [49] demonstrated that the increase in gastric mucosal blood flow induced by a dobutamine infusion was followed by a decrease in $PgCO_2$. In haemodynamically septic patients, we [50] have reported that there was a decrease in PCO_2 gap during a dobutamine infusion only in patients with inadequate hepato-splanchnic blood flow (i.e. low fractional splanchnic blood flow, suprahepatic venous oxygen desaturation). Even though splanchnic blood flow increased in all patients, splanchnic oxygen consumption increased only in those who experienced a dobutamine induced-decrease in PCO_2 gap, which could be explained by a blood flow redistribution to the initially hypoperfused gut mucosa.

Microcirculatory alterations are ubiquitous in sepsis and can thus take place in all parts of the body. We have evaluated the relations between sublingual PCO_2 ($PslCO_2$) and sublingual microcirculatory alterations (assessed by the orthogonal polarisation spectral imaging technique [Cytoscan®, Cytometrics, Philadelphia, Pa., USA]) during resuscitation of patients with septic shock. Resuscitation manoeuvres (mainly increase in blood flow with fluid challenge and dobutamine infusion) decreased the $PslCO_2$ gap progressively from 40±18 to 15±9 mmHg (Fig. 1) and, at the same time, increased the percentage of well-perfused capillaries (%WPC) from 46±13% to 62±8% (p.05 for both changes). At baseline, there was a correlation between $PslCO_2$ and the %WPC (r^2=0.80). Even though cytopathic hypoxia can occur, the main determinant of tissue PCO_2 seems to be microcirculatory blood flow: first, at baseline we found a correlation between tissue PCO_2 and the %WPC, and secondly, the improvement in microcirculation was followed by a decrease in tissue PCO_2. Finally, it seems difficult to imagine that the increase in tissue PCO_2 found in sepsis is due exclusively to cytopathic hypoxia in the presence of maintained tissue perfusion. First, this maintained flow should be able to clear a great part of the CO_2 produced. Secondly, in view of the curvilinearity of the relationship between tissue PCO_2 and blood flow, changes in blood flow in normal or high-value ranges should have almost no effect on $PgCO_2$, which is not the case

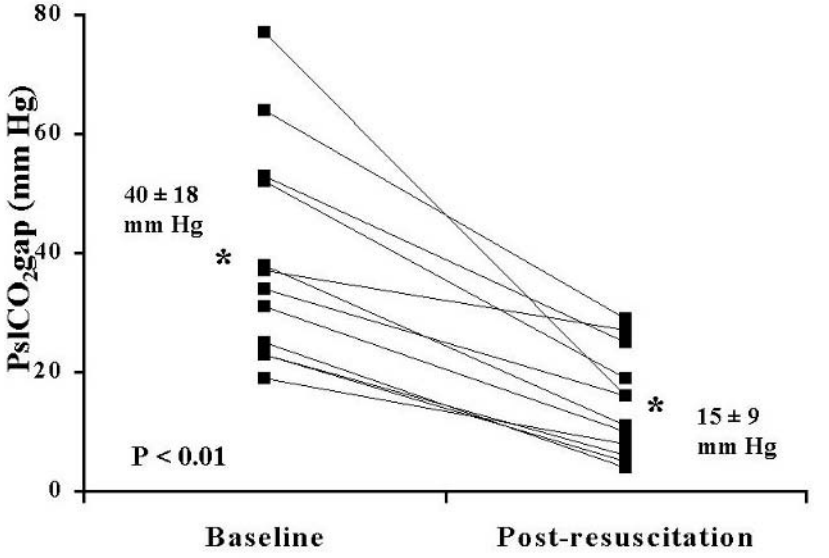


Fig. 1. Progressive decrease in $PslCO_2$ gap from 40±18 to 15±9 mmHg (p.05) following resuscitation manoeuvres (mainly increase in blood flow with fluid challenge and dobutamine infusion)

in the majority of experimental and clinical studies.

Several studies have demonstrated that an increase in gastric mucosal PCO_2 is associated with a poor outcome in critically ill patients, including patients with septic shock [51] and postoperative patients [52]. Increased PCO_2 gap, which is independent of systemic acidosis and hypercarbia, is also associated with a worse outcome in septic patients [53].

Although gastric tonometry does not reflect global hepato-splanchnic perfusion in sepsis, it remains a valuable monitoring tool. On the one hand, if mucosal gastric acidosis in sepsis is due primarily to mucosal hypoperfusion, and if gastric tonometry, by detecting mucosal hypoperfusion, can lead to therapeutic interventions that could decrease the development of multiple organ failure, then the lack of correlation between PCO_2 gap and the systemic and even the regional haemodynamic and/or oxygenation parameters argues for the use of gastric tonometry as the only method available for detection of gastric mucosal hypoperfusion. On the other hand, if gastric intramucosal acidosis in sepsis is primarily due to direct metabolic cellular alterations mediated by an endotoxin, gastric tonometry can provide a valuable assessment of metabolic alterations. Either scenario can account for the prognostic value of gastric tonometry that has been shown in a number of studies [51, 53-56).

Should measurements be confined to the stomach?

As it is now established that the measurement of gastrointestinal luminal PCO_2 could be of clinical significance, the stomach has become the natural choice for the performance of gastrointestinal tonometry because of its ease of access. It is not, however, devoid of potential sources of artefact, in particular the production of CO_2 from the reaction of gastric acid and refluxed duodenal contents. The midgut or sigmoid may provide useful information [57]. The former is difficult to access, and tonometry performed in the latter is technically more challenging than gastric tonometry and also not devoid of potential artefacts, e.g. bacterial production of CO_2. Knuesel et al. [58] specifically addressed the problem of the potential redistribution of blood flow within the splanchnic bed during an acute decrease in splanchnic blood flow and its impact on regional CO_2 measurements. The authors designed a complex surgical model in pigs, in which a shunt between the proximal and the distal abdominal aorta generated a specific decrease in splanchnic blood flow with minor changes in CO or arterial pressure. Tonometry catheters were inserted in the jejunum and in the stomach. The authors [58] were the first to observe that regional redistribution between the various splanchnic organs did not occur. Accordingly, jejunal and gastric tonometric values increased be similar amounts. This is of particular importance, as some authors have reported that gastric tonometry may be less sensitive than jejunal tonometry [59]. The physiological basis for this limitation would be the hepatic arterial buffer response, which would favour coeliac trunk vasodilatation and, hence, preservation of gastric perfusion. However, this compensatory response cannot be maintained and is lost in sepsis. Hence, differences between gastric and jejunal PCO_2 are probably more closely related to specific technical problems, such as gastro-oesophageal reflux, than to blood flow redistribution inside the splanchnic area.

Haldane effect

The effect of oxygen saturation on the relationship between carbon dioxide content and PCO_2 is known as the Haldane effect: at a given CO_2 content, venous or mucosal PCO_2 increases with increasing venous or mucosal oxygen saturation. Calculating CO_2 content, Jakob et al. [59] suggested that the Haldane effect may explain the paradoxical increase in PCO_2 gap together with an increase in splanchnic blood flow in patients after cardiac surgery. They effectively reported that patients whose PCO_2 gap increased had a greater increase in DSO_2, which is a condition in which the Haldane effect is more likely to occur. Nevertheless, a number of methodological problems were identified [60]: the use of saline tonometry and its potential methodological drawbacks, the changes in PCO_2 gap that were within the range of error, the failure to take account of temperature in the simplified formulas used to calculated CO_2 content, even though patients experienced major changes in temperature. All these remarks lead us to conclude [60] that the Haldane effect cannot have been involved in the increase in PCO_2 gap that was observed in some of these patients. Knuesel et al. [58] tried to evaluate the role of the Haldane effect in PCO_2

gradients in an animal model of acute hepato-splanchnic hypoperfusion. They observed that the Haldane effect had a minor role in their results as, in most cases, PCO_2 gradients and CO_2 content differences evolved in a similar manner.

Sublingual capnometry

Weil et al. [61, 62] observed that sublingual PCO_2 was increased in various shock states, reflecting the severity of the shock states, and was related to outcome. They also reported that sublingual capnometry and gastric tonometry revealed parallel alterations, suggesting that both areas can be similarly and simultaneously affected [64]. In addition, sublingual PCO_2 was inversely related to changes in tongue, splanchnic and renal blood flows [64]. Hence, the sublingual region may be affected in a similar way to other areas, including the splanchnic area. These observations led to the conclusion that sublingual PCO_2 monitoring may serve as a technically simple, noninvasive and rapid response monitor of the severity of circulatory shock states, avoiding some of the methodological drawbacks of gastric tonometry.

Conclusions

Enthusiasm for new technologies has pushed clinical researchers to conduct large studies evaluating the effects of monitoring-guided therapy on in critically ill patients outcome. Perhaps these studies were conducted too early, before sufficient knowledge of the physiological significance of the values provided by these new technologies had been gathered. $VAPCO_2$ monitoring has clearly shown its limitations in the detection of tissue hypoxia, especially in the presence of maintained or increased cardiac output such as is seen in septic shock. Monitoring hepato-splanchnic oxygenation by gastric tonometry might prove useful if one believes that gut ischaemia contributes to the development of multiple organ failure. Sublingual capnometry seems to be a valuable tool for use in assessing the severity of circulatory shock and the degree of sepsis-induced microcirculatory alterations. Further studies will be necessary to determine (1) the hypoxia threshold values provided by these different monitoring techniques and (2) the efficacy of different treatments intended to correct these variables.

References

1. Sibbald WJ, Bersten A, Rutledge FS (1989) The role of tissue hypoxia in multiple organ failure. In: Reinhart K, Eyrich K (eds) Clinical aspects of oxygen transport and tissue oxygenation. Springer, Berlin Heidelberg New York, pp 102-114
2. Rivers E, Nguyen B, Havstad S et al (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345:1368-1377
3. Bakker J, Vincent JL, Gris P et al (1992) Venoarterial carbon dioxide gradient in septic shock. Chest 101:509-515
4. Van der Linden P, Rausin I, Deltell A et al (1995) Detection of tissue hypoxia by arteriovenous gradient for PCO2 and pH in anesthetized dogs during progressive hemorrhage. Anesth Analg 80:269-275
5. Zhang H, Vincent JL (1993) Arteriovenous difference in PCO_2 and pH are good indicators of critical hypoperfusion. Am Rev Respir Dis 148:867-871
6. Vallet B, Teboul JL, Cain SM et al (2000) Veno-arterial CO_2 difference during regional ischemic or hypoxic hypoxia. J Appl Physiol 89:1317-1321
7. Wendon JA, Harrison PM, Keays R et al (1991) Arterial-venous pH differences and tissue hypoxia in patients with fulminant hepatic failure. Crit Care Med 19:1362-1364
8. Mekontso-Dessap A, Castelain V, Anguel N et al (2002) Combination of venoarterial PCO_2 difference with arteriovenous O_2 content difference to detect anaerobic metabolism in patients. Intensive Care Med 2002 28:272-277
9. Mythen MG, Woolf R, Noone RB (1998) Gastric mucosal tonometry: towards new methods and applications. Anasthesiol Intensivmed Notfallmed Schmerzther 33 (Suppl 2): S85-S90
10. Morgan TJ, Venkatesh B, Endre ZH (1999) Accuracy of intramucosal pH calculated from arterial bicarbonate and the Henderson-Hasselbalch equation: assessment using simulated ischemia. Crit Care Med 27:2495-2499
11. Pernat A, Weil MH, Tang W et al (1999) Effects of hyper- and hypoventilation on gastric and sublingual PCO_2. J Appl Physiol 87:933-937
12. Schlichtig R, Mehta N, Gayowski TJ (1996) Tissue-arterial PCO_2 difference is a better marker of ischemia than intramural pH (pHi) or arterial pH-pHi difference. J Crit Care 11:51-56
13. Vincent JL, Creteur J (1998) Gastric mucosal pH is definitely obsolete—Please tell us more about gastric mucosal PCO_2..Crit Care Med 26:1479-1480
14. Takala J, Parviainen I, Siloaho M et al (1994) Saline PCO_2 is an important source of error in the assessment of gastric intramucosal pH. Crit Care Med 22:1877-1879
15. Knichwitz G, Kuhmann M, Brodner G et al (1996) Gastric tonometry: precision and reliability are improved by a phosphate buffered solution. Crit Care Med 24:512-516
16. Heard SO, Helsmoortel CM, Kent JC et al (1991) Gastric tonometry in healthy volunteers: effect of ranitidine on calculated intramural pH. Crit Care Med 19:271-274
17. Calvet X, Baigorri F, Duarte M et al (1998) Effect of ranitidine on gastric intramucosal pH in critically ill patients. Intensive Care Med 24:12-17
18. Calvet X, Baigorri F, Duarte M et al (1997) Effect of sucralfate on gastric intramucosal pH in critically ill patients. Intensive Care Med 23:738-742
19. Marik PE, Lorenzana A (1996) Effect of tube feedings on the measurement of gastric intramucosal pH. Crit Care Med 24:1498-1500
20. Levy B, Perrigault PF, Gawalkiewicz P et al (1998) Gastric versus duodenal feeding and gastric tonometric measurements. Crit Care Med 26:1991-1994
21. Kolkman JJ, Steverink PJGM, Groeneveld ABJ et al (1998) Characteristics of time-dependent PCO_2 tonometry in the normal human stomach. Br J Anaesth 81:669–675

22. Chien S (1967) Role of the sympathetic nervous system in hemorrhage. Physiol Rev 47:214-288
23. Price HL, Deutsch S, Marshall BE et al (1966) Hemodynamic and metabolic effects of hemorrhage in man, with particular reference to the splanchnic circulation. Circ Res 18:469-474
24. Vatner SF (1974) Effects of hemorrhage on regional blood flow distribution in dogs and primates. J Clin Invest 54:225-235
25. Guzman JA, Lacoma JF, Kruse JA (1998) Relationship between systemic oxygen supply dependency and gastric intramucosal PCO_2 during progressive hemorrhage. J Trauma 44:696-700
26. Hamilton-Davies C, Mythen MG, Salmon JB et al (1997) Comparison of commonly used clinical indicators of hypovolaemia with gastrointestinal tonometry. Intensive Care Med 23:276-281
27. Edouard AR, Degremont AC, Duranteau J et al (1994) Heterogeneous regional vascular responses to simulated transient hypovolemia in man. Intensive Care Med 20:414-420
28. Schlichtig R, Bowles SA (1994) Distinguishing between aerobic and anaerobic appearance of dissolved CO_2 in intestine during low flow. J Appl Physiol 76:2443–2451
29. Zhang H, Rogiers P, De Backer D et al (1996) Regional arteriovenous differences in PCO_2 and pH can reflect critical organ oxygen delivery during endotoxemia. Shock 5:349–356
30. Bustamante SA, Jodal M, Nilsson NJ et al (1989) Evidence for a countercurrent exchanger in the intestinal villi of suckling swine. Acta Physiol Scand 137:207-213
31. Nevière R, Chagnon JL, Teboul JL et al (2002) Small intestine intramucosal PCO(2) and microvascular blood flow during hypoxic and ischemic hypoxia. Crit Care Med 30:379–384
32. Dubin A, Estenssoro E, Baran M et al (2003) Intramucosal-arterial PCO_2 gap fails to reflect intestinal dysoxia in anemic hypoxia (abstract). Intensive Care Med 28:S127
33. Fink MP (1998) Cythopathic hypoxia: mitochondrial dysfunction as a potential mechanism contributing to organ failure in sepsis. In: Sibbald WJ, Messmer K, Fink MP (eds) Update in intensive care and emergency medicine, vol 33: Tissue oxygenation in acute medicine. Springer–Verlag, Berlin Heidelberg New York, pp 128-137
34. VanderMeer TJ, Wang H, Fink MP (1995) Endotoxemia causes ileal mucosal acidosis in the absence of mucosal hypoxia in a normodynamic porcine model of septic shock. Crit Care Med 23:1217–1225
35. Revelly JP, Ayuse A, Brienza N et al (1996) Endotoxic shock alters distribution of blood flow within the intestinal wall. Crit Care Med 24:1345-1351
36. Kellum JA, Rico P, Garuba AK et al (2000) Accuracy of mucosal pH and mucosal-arterial carbon dioxide tension for detecting mesenteric hypoperfusion in acute canine endotoxemia. Crit Care Med 28:462-466
37. Creteur J, De Backer D, Vincent JL (1999) Does gastric tonometry monitor splanchnic perfusion? Crit Care Med 27:2480–2484
38. Parviainen I, Ruokonen E, Takala J (1995) Dobutamine-induced dissociation between changes in splanchnic blood flow and gastric intramucosal pH after cardiac surgery. Br J Anaesth 74:277-282
39. Thoren A, Jakob SM, Pradl R et al (2000) Jejunal and gastric mucosal perfusion versus splanchnic blood flow and metabolism: an observational study on postcardiac surgical patients. Crit Care Med 28:3649-3654
40. Bonatii J, Gruber E, Schwarz B et al (1996) Effects of short-term endotoxemia and dopamine on mucosal oxygenation in porcine jejunum. Am J Physiol 270:G667-G675
41. Nevière R, Chagnon JL, Vallet B et al (1997) Dobutamine improves gastrointestinal mucosal blood flow in a porcine model of endotoxic shock. Crit Care Med 25:1371-1377

42. Vallet B, Lund N, Curtis SE et al (1994) Gut and muscle PO_2 in endotoxemic dogs during shock and resuscitation. J Appl Physiol 76:796-800
43. Farquhar I, Martin CM, Lam C et al(1996) Decreased capillary density in vivo in bowel mucosa of rats with normotensive sepsis. J Surg Res 61:190-196
44. Lam C, Tyml K, Martin C et al (1994) Microvascular perfusion is impaired in a rat model of normotensive sepsis. J Clin Invest 94:2077-2083
45. Schmidt H, Secchi A, Wellmann R et al (1996) Effect of endotoxemia on intestinal villus microcirculation in rats. J Surg Res 61:521-526
46. Drazenovic R, Samsel RW, Wylam ME et al (1992) Regulation of perfused capillary density in canine intestinal mucosa during endotoxemia. J Appl Physiol 72:259-265
47. Tugtekin I, Radermacher P, Theisen M et al (2001) Increased ileal-mucosal-arterial PCO_2 gap is associated with impaired villus microcirculation in endotoxic pigs. Intensive Care Med 27:757–766
48. Elizalde JI, Hernandez C, Llach J et al (1998) Gastric intramucosal acidosis in mechanically ventilated patients: role of mucosal blood flow. Crit Care Med 26:827-832
49. Nevière R, Mathieu MD, Chagnon JL et al (1996) The contrasting effects of dobutamine and dopamine on gastric mucosal perfusion in septic patients. Am J Respir Crit Care Med 154:1684-1688
50. Creteur J, De Backer D, Vincent JL (1999) A dobutamine test can disclose hepatosplanchnic hypoperfusion in septic patients. Am J Respir Crit Care Med 160:839–845
51. Maynard N, Bihari D, Beale R, et al (1993) Assessment of splanchnic oxygenation by gastric tonometry in patients with acute circulatory failure. JAMA 270:1203–1210
52. Bennett-Guerrero E, Panah MH, Bodian CA et al (2000) Automated detection of gastric luminal partial pressure of carbon dioxide during cardiovascular surgery using the Tonocap. Anesthesiology 92:38–45
53. Levy B, Gawalkiewicz P, Vallet B et al (2003) Gastric capnometry with air-automated tonometry predicts outcome in critically ill patients. Crit Care Med 31:474–480
54. Doglio GR, Pusajo JF, Egurrola A et al (1992) Gastric mucosal pH as a prognostic index of mortality in critically ill patients. Crit Care Med 19:1037-1040
55. Friedman G, Berlot G, Kahn RJ et al (1995) Combined measurements of blood lactate levels and gastric intramucosal pH in patients with severe sepsis. Crit Care Med 23:1184-1193
56. Marik PE (1993) Gastric intramucosal pH: a better predictor of multiorgan dysfunction syndrome than oxygen-derived variables in patients with sepsis. Chest 104:225-229
57. Walley KR, Friesen BP, Humer MF et al (1998) Small bowel tonometry is more accurate than gastric tonometry in detecting gut ischemia. J Appl Physiol 85:1770–1777
58. Knuesel R, Jakob S, Brander L et al (2003) Changes in regional blood flow and PCO_2 gradients during isolated abdominal aortic blood flow reduction. Intensive Care Med 29:2255-2265
59. Jakob SM, Kosonen P, Ruokonen E et al (1999) The Haldane effect – an alternative explanation for increasing gastric mucosal PCO_2 gradients? Br J Anaesth 83:740–746
60. De Backer D, Creteur J, Vincent JL (2000) The Haldane effect – an explanation for increasing gastric mucosal PCO2 gradients? Br J Anaesth 85:169
61. Nakagawa Y, Weil M H, Tang W et al (1998) Sublingual capnometry for diagnosis and quantitation of circulatory shock. Am J Respir Crit Care Med 157:1838-1843
62. Weil M H, Nakagawa Y, Tang W et al (1999) Sublingual capnometry: a new noninvasive measurement for diagnosis and quantitation of severity of circulatory shock. Crit Care Med 27:1225-1229
63. Povoas H P, Weil M H, Tang W et al (2000) Comparisons between sublingual and gastric tonometry during hemorrhagic shock. Chest 118:1127-1132

64. Jin X, Weil M H, Sun S et al (1998) Decreases in organ blood flows associated with increases in sublingual PCO_2 during hemorrhagic shock. J Appl Physiol 85:2360-2364

Chapter 50

The microcirculation in distress; monitoring and recruitment

P. Goedhart, C. Ince

Orthogonal polarisation spectral imaging (OPS) has opened the road to detailed clinical monitoring of the function of the microcirculation during surgery and intensive care. Combining these images with laser-Doppler microcirculatory flow measurements and haemoglobin saturation measurements using spectrophotometry provides a comprehensive set of non-invasive tools for the clinical study of the microcirculation. The smallest vessels can be considered as collapsible tubes that need to be open to assure oxygenation on a micro-scale to the cells. Prolonged impairment of the microcirculation in the capillaries can damage cells due to hypoxia. It has been suggested that the microcirculation should be monitored using techniques described in this paper and treated to ensure optimal microcirculatory perfusion. Vasopressors, for example, can raise a low blood pressure, but the vasoconstriction can also cut off the blood supply to the capillaries. This article reviews the clinical and possible recruitment manoeuvres during surgery and intensive care.

The importance of the microcirculation

The microcirculation is the level at which most cells exchange oxygen, nutrients and carbon dioxide. It is a complex network of resistance and exchange, in which oxygen transport depends on a host of factors: oxygen saturation, oxygen consumption, viscosity, deformability of red blood cells, flow, shunting of vessels, vasodilatation, vasoconstriction or stasis in arterioles and capillaries, diffusion constants of gasses and nutrients, and distances from cells to the nearest blood vessel. Capillaries can be considered as collapsible tubes that receive blood through the resistance vessels, the arterioles. In recent years, progress has been made in making the microcirculation more visible using non-invasive techniques, such as orthogonal polarisation spectral (OPS) imaging [1] and laser-Doppler measurement [2]. OPS imaging under health shows that individual cells are usually well distributed between the capillaries with a preserved functional capillary density (e.g. perfused capillaries). One of the most striking findings of the microcirculation as seen by OPS imaging during shock and sepsis is the heterogeneity of the microcirculatory flow, with some capillaries having a preserved functional density (e.g. perfused capillaries) and others having either a sluggish blood flow or no flow

at all. Capillaries can be recruited and de-recruited depending on intrinsic and extrinsic factors. When the flow ceases in the capillaries, cells that are close to the capillaries are suddenly far away from their source of oxygen and nutrients as the diffusion distance of oxygen to the cell increases. Oxygen and carbon dioxide transport is not only governed by passive diffusion, but also by convective flow in the interstitial space caused by hydrostatic force [3].

Since most cells depend on the flow in the capillaries to obtain oxygen for respiration, maintaining microcirculatory flow can be considered as a main clinical target to be achieved during surgery and intensive care. A prolonged shutdown of the capillary flow could lead to hypoxia, cell dysfunction, ultimately leading to organ failure.

Clinical monitoring of the microcirculation

OPS imaging and dark-field imaging

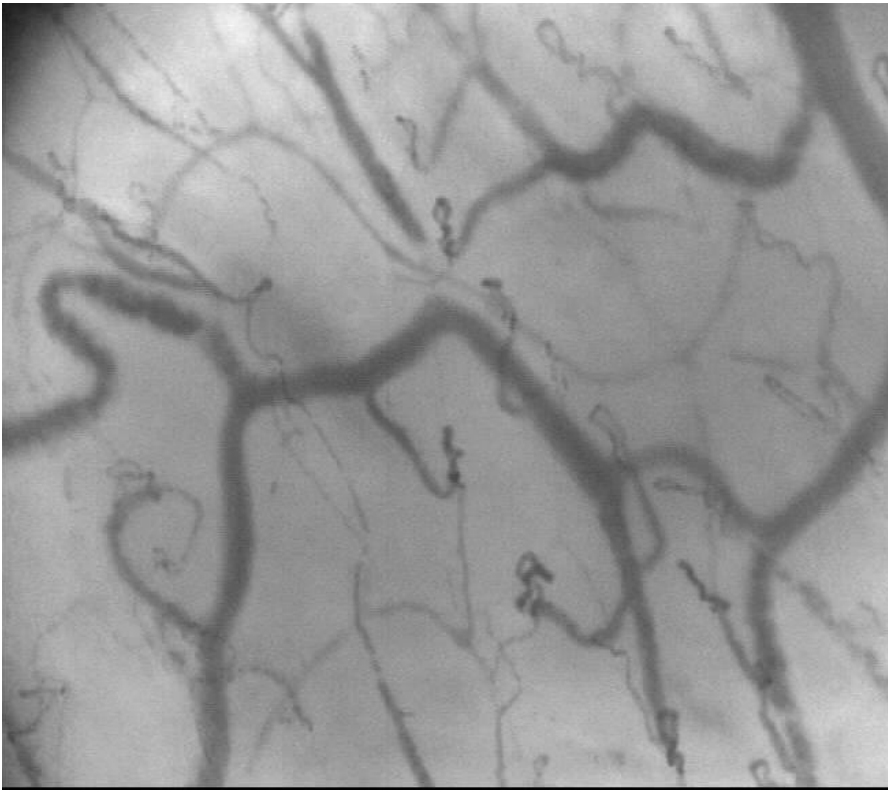


Fig. 1. Orthogonal polarisation spectral (OPS) image of the sublingual circulation in a healthy volunteer

Both orthogonal polarisation imaging as well as dark field illumination filter out surface reflection, making it possible to observe the microcirculation of the organ surface without having to use trans-illumination. OPS imaging works as follows: linearly polarized light is projected from the OPS probe into the tissue and illuminates the tissue. A camera connected to a microscope picks up the image of the tissue through an orthogonally placed polarizer, which blocks all the directly reflected light with the original polarization. Deeper in the tissue, the light is scattered and deflected and the polarization of this light changes. By eliminating the superficially backscattered light, the OPS imaging device obtains a picture of the deeper tissue (Fig. 1). The red blood cells in the microcirculation can be seen particularly well by using a green filter. Similar images can be made by dark-field illumination. The recorded results can be analysed afterwards using a semi-quantitative method. Each visible vessel is scored for diameter: large (50-100 μm), medium (25-50 μm) and small (10-25 μm) The flow in each vessel can be scored for flow: no flow, sludging, moderate flow and normal flow. The numbers and types of vessels in the visible area are also scored to determine vessel density [4]. A disadvantage of this technique is that, although the changes in the microcirculation can be obvious during the online measurement, scoring the circulation afterwards is time-consuming and cumbersome.

Micro-laser-Doppler measurements by use of fibres placed on tissue surfaces can measure flow in the underlying microcirculation. This method measures the velocity of red blood cells in the circulation. Laser light backscattered by moving erythrocytes changes frequency. The velocity of the red blood cells is measured by the change in the frequency of the backscattered laser light; the flow is calculated from this velocity. From these changed frequencies, a non-quantitative velocity profile of all moving cells can be measured in the volume being assessed. Applications are available that combine measurement of different determinants of microcirculatory oxygenation. The O2C (LEA Medizintechnik Giessen, Germany) combines the velocity measurement with measurement of haemoglobin saturation in the microcirculation. The O2C consists basically of a probe with aligned optical fibers. Four fibres are connected, respectively, to a laser light source, a laser light detector, a white light source and a white light detector. The relative haemoglobin content is measured by the amount of backscattered light from the white light source. The oxygen saturation is calculated from the spectrum of the backscattered white light. A different version of the same idea is offered by the Oxylite (Oxford Optronix, Oxford, UK) which combines a tissue oxygen electrode and a laser-Doppler probe [5]. The advantage of such a dual measurement is that information about microcirculatory oxygen availability and oxygen delivery is provided.

Determinants of microcirculatory perfusion

Capillary perfusion in the smallest vessels is determined by capillary resistance, blood viscosity, deformability of the erythrocytes, aggregation of the erythrocytes and the pressure drop over the capillaries. In order for blood to pass through the

capillaries, there must be a critical pressure difference between the entrance and exit of the capillary that is large enough to allow the 8-μm erythrocytes and even bigger leucocytes to enter the less than 5-μm capillaries. Cells can be transported through the capillaries driven by a pressure gradient. To start capillary flow, a threshold pressure gradient is needed to breakdown erythrocyte aggregates, deform the red blood cells, widen the capillary and ultimately push the cells through the capillary. When the pressure drops below this threshold value, the flow will stop. Above the threshold value, the arterioles, the viscosity and the pressure drop determine the flow velocity. Capillary resistance can also vary since capillaries are lined with a variable thickness of glycocalyx. A damaged glycocalyx can result in adhesion of leucocytes [6] to the vessel walls, which will enhance capillary resistance. A damaged glycocalyx can also result in oedema, which can compress the capillaries, resulting in a higher capillary resistance.

Blood viscosity is a further determinant of the flow in the capillaries: the lower the viscosity, the faster the flow at the same pressure drop over the capillary. Whole-blood viscosity is determined by: the haematocrit, temperature, plasma viscosity, the aggregation of the erythrocytes and their deformability. Viscosity causes a pressure drop over the circulation – the higher the viscosity, the greater the pressure drop. Extreme haemodilution can cause the viscosity to drop to the extent that a critically low pressure follows. When this occurs, an insufficient driving pressure prevents the erythrocytes from entering the capillaries, resulting in ischemia. This effect could contribute to the shunting observed during extreme haemodilution [7]. Thus, there is an optimal haematocrit for oxygen transport.

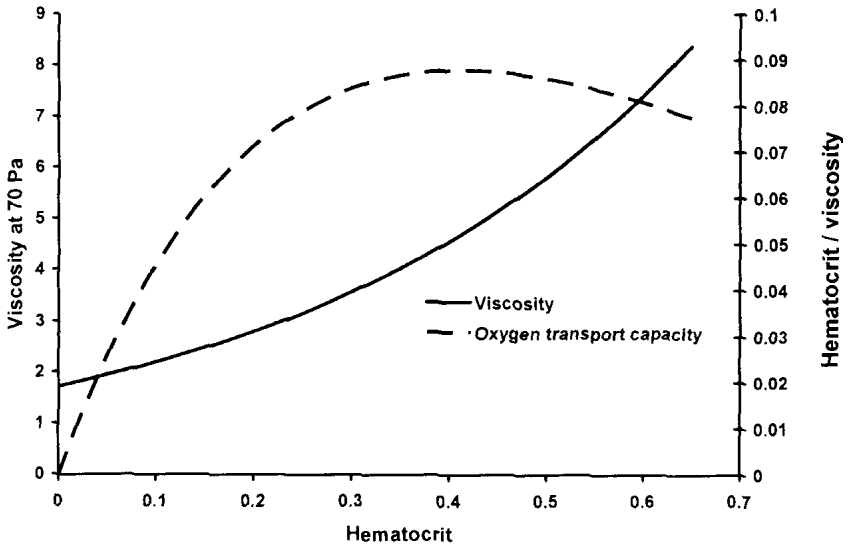


Fig. 2. Viscosity vs. haematocrit and oxygen transport capacity

The transport capacity of blood is proportional to the haematocrit and inversely proportional to the viscosity. When plotted against haematocrit, the optimum transport capacity at high shear rates is at about a haematocrit of 38%. Diluting the blood below a haematocrit of 20% can lead to capillary fall-out in surgical patients (unpublished data). Blood with this low haematocrit also has a very low viscosity; the pressure drop over the capillaries could therefore become too low for the cells to enter the capillaries. Although controversial, according to Bertuglia [8], improvement of microcirculatory perfusion can be attained by increasing the plasma viscosity such that a higher pressure drop would force the cells through the capillaries. As can be seen in Fig. 2, a high haematocrit is not optimal for oxygen delivery. Only when a trained heart can pump against a high-viscosity resistance can a benefit from the high oxygen content per litre of blood at high haematocrit be obtained. At lower temperatures, the effect of viscosity becomes more apparent. Blood viscosity increases by 2% for every decrease in degree Celsius below 37°C. The microcirculation in the extremities will therefore suffer more from viscosity-related circulation problems.

Pushing 8-μm erythrocytes into and through the less than 5-μm capillaries is much easier when the erythrocytes are flexible and deformable. That is why red blood cell deformability is one of the determinants of blood flow through capillaries. The LORCA [9] measures erythrocyte deformability using laser diffraction of an erythrocyte suspension under shear conditions. The outcome is deformability (length erythrocytes – width erythrocytes)/(length erythrocytes + width erythrocytes) vs. shear stress plot (Fig. 3).

In severe malaria, reduced erythrocyte deformability is a predictor of a fatal outcome of the disease [10, 11] and altered haemorheological properties are also an important characteristic of the blood in septic patients.

Red blood cell aggregation can also be measured by the LORCA [12] but a high erythrocyte sedimentation rate is also an indicator of enhanced red blood cell aggregation. Erythrocyte aggregates can be bound so strongly that entrance to the capillaries requires extra pressure just to break down the aggregates. Large acute-phase proteins, but also high-molecular-weight dextrans (>300,000 kDa) can cause the formation of these strongly bound aggregates [13] which can raise the flow threshold.

Recruiting the microcirculation

Several therapeutic manoeuvres are able to recruit the capillary and thereby the microcirculatory perfusion: the pump function of the heart can be improved [14], the blood viscosity can be lowered by haemodilution [15] and the microvascular resistance of the circulation can be lowered by vasodilatation therapy [16]. Since OPS imaging allows the therapy to be monitored, improvements in an impaired microcirculation can be observed.

An impaired microcirculation can have several causes, as discussed above. In his analytic review, Ward [17] described the need for continuous monitoring of the

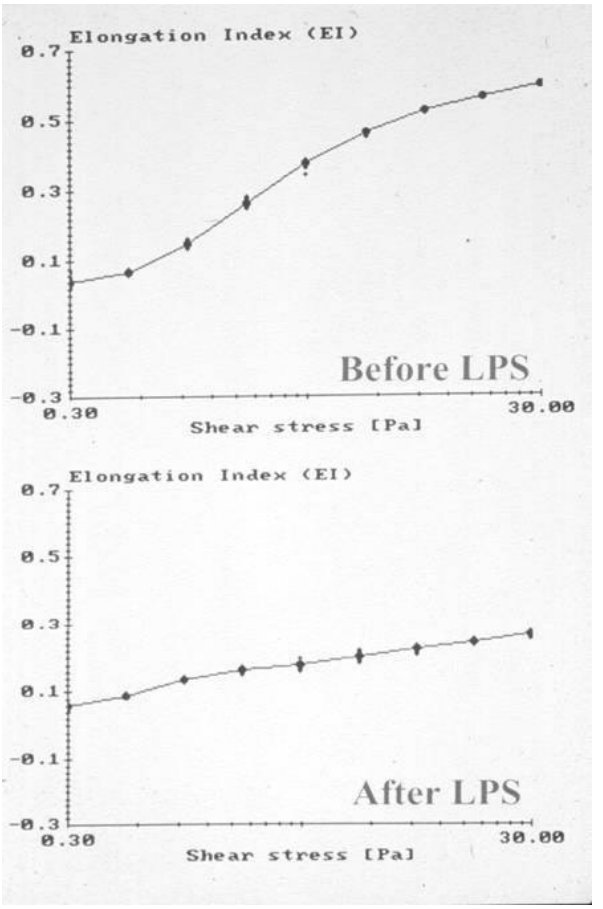


Fig. 3. A plot of red blood cell deformability vs. shear stress in a pig experiment with lipopolysaccharide (LPS)-induced sepsis

microcirculation to ensure the ongoing adequacy of resuscitation. Vincent, also in a review, stated that, "It is thus fundamental to maintain sufficient oxygen availability to the cell; the hypoxic cell is doomed to become dysfunctional and to die" [18]. An OPS imaging device could be one of the online tools to assess the impact of treatment on the microcirculation[19]. Dorffler-Melly found that raising the blood pressure using vasopressors [20] slows down the distribution of low-molecular-weight heparin and postulated that vasopressors cause impaired peripheral circulation . Our OPS imaging results show that the capillary flow slows down or stops following the administration of vasopressors. Using vasopressors for a longer period could damage the tissue because they can locally deprive the cells of their oxygen supply through the capillaries [21]. If hypovolaemia is the cause of an impaired microcirculation, vasopressors would raise the blood pressure, but the microcirculation would still be impaired. A better option for the microcirculation

in this case would be to supply more volume. Spronk [4] assessed an impaired microcirculation during sepsis using OPS imaging and he corrected this condition using nitroglycerin.

In conclusion, comprehensive monitoring of the microcirculation is now feasible in the clinical arena. Consequently, rescue of the microcirculation will become an important clinical target [22].

References

1. Lindert J, Werner J, Redlin M et al (2002) OPS imaging of human microcirculation: a short technical report. J Vasc Res 39:368-372
2. Walter B, Bauer R, Krug A et al (2002) Simultaneous measurement of local cortical blood flow and tissue oxygen saturation by near infra-red laser Doppler flowmetry and remission spectroscopy in the pig brain. Acta Neurochir Suppl 81:197-199
3. Taylor AE, Moore TM (1999) Capillary fluid exchange. Am J Physiol 277:S203-S210
4. Spronk PE, Ince C, Gardien MJ et al (2002) Nitroglycerin in septic shock after intravascular volume resuscitation. Lancet 360:1395-1396
5. Griffiths JR, Robinson SP (1999) The OxyLite: a fibre-optic oxygen sensor. Br J Radiol 72:627-630
6. Constantinescu AA, Vink H, Spaan JA (2003) Endothelial cell glycocalyx modulates immobilization of leukocytes at the endothelial surface. Arterioscler Thromb Vasc Biol 23:1541-1547
7. van Bommel J, Siegemund M, Henny CP et al (2001) Critical hematocrit in intestinal tissue oxygenation during severe normovolemic hemodilution. Anesthesiology 94:152-160
8. Bertuglia S (2001) Increased viscosity is protective for arteriolar endothelium and microvascular perfusion during severe hemodilution in hamster cheek pouch. Microvasc Res 61:56-63
9. Hardeman MR, Goedhart P, Breederveld D (1987) Laser diffraction ellipsometry of erythrocytes under controlled shear stress using a rotational viscosimeter. Clin Chim Acta 165:227-234
10. Dondorp AM, Angus BJ, Hardeman MR et al (1997) Prognostic significance of reduced red blood cell deformability in severe falciparum malaria. Am J Trop Med Hyg 57:507-511
11. Dondorp AM, Angus BJ, Chotivanich K, Silamut K et al (1999) Red blood cell deformability as a predictor of anemia in severe falciparum malaria. Am J Trop Med Hyg 60:733-737
12. Hardeman MR, Dobbe JG, Ince C (2001) The laser-assisted optical rotational cell analyzer (LORCA) as red blood cell aggregometer. Clin Hemorheol Microcirc 25:1-11
13. Baskurt OK, Bor-Kucukatay M, Yalcin O et al (2000) Standard aggregating media to test the "aggregability" of rat red blood cells. Clin Hemorheol Microcirc 22:161-166
14. De Backer D, Creteur J, Dubois MJ et al (2004) Microvascular alterations in patients with acute severe heart failure and cardiogenic shock. Am Heart J 147:91-99
15. Long DS, Smith ML, Pries AR et al (2004) Microviscometry reveals reduced blood viscosity and altered shear rate and shear stress profiles in microvessels after hemodilution. Proc Natl Acad Sci USA 101:10060-10065
16. Buwalda M, Ince C (2002) Opening the microcirculation: can vasodilators be useful in sepsis? Intensive Care Med 28:1208-1217

17. Ward KR, Ivatury RR, Barbee RW (2001) Endpoints of resuscitation for the victim of trauma. Journal of Intensive Care Medicine 16:55-75
18. Vincent JL, De Backer D (2004) Oxygen transport – the oxygen delivery controversy. Intensive Care Med. (Epub ahead of print)
19. De Backer D (2003) OPS techniques. Minerva Anestesiol 69:388-391
20. Dorffler-Melly J, de Jonge E, Pont AC et al (2002) Bioavailability of subcutaneous low-molecular-weight heparin to patients on vasopressors. Lancet 359:849-850
21. Vincent JL, Sundin DP, Trzaskoma BL et al (2004) Change in first day vasopressor use is predictive of outcome in severe sepsis, regardless of steroid use. Crit Care Med A116. 2-20-2004 (Abstract)
22. Ince C (2004) Microcirculation in distress: A new resuscitation end point? Crit Care Med 32:1963-1964

Chapter 51

Tissue metabolism in different types of shock

S. Klaus, J. Pöling, L. Bahlmann

Shock has been defined as "inadequate perfusion of body tissue that begins at the cellular level and, if left untreated, results in death of tissue, organs and ultimately in the entire organism" [1, 2]. Another definition underlines that shock is the "state, in which profound and widespread reduction in the effective delivery of oxygen and other nutritients leads to first reversible and later irreversible cellular injury"; it is not just low blood pressure [2]! Although many clinical causes of shock exist, the basic cellular derangement in all types involves an imbalance of microcirculation and oxygen dynamics. Whenever cellular oxygen demand outweighs supply, both the cell and the organism are in a state of shock. On the cellular and tissue level, shock begins when DO2 to the cells is inadequate to meet the metabolic demand [3, 4].

Therefore, the major therapeutic goals in shock are sufficient tissue perfusion and oxygenation, but early diagnosis still remains a major problem [1, 5].

On a multicellular level, the definition of shock becomes more difficult because not all tissues and organs will experience the same amount of oxygen imbalance for a given clinical disturbance. It is an important aim to adequately define and monitor oxygen utilisation on the cellular level, and to correlate this physiology to useful clinical parameters and diagnostic tests.

Microdialysis has been introduced into the clinical routine in the field of neurosurgical critical care more than ten years ago, and has proved to be a reliable way of monitoring tissue metabolism [6-8]. The aim of the presented animal experimental studies was to objectify potential differences in "cellular stress" and tissue vulnerability during acute haemorrhage shock and induction of endotoxaemia/sepsis. There are further illucidated subsequent tissue effects of different treatment and pretreatment strategies with correlation of these parameters with the results of conventional haemodynamic monitoring [9-12].

Any derangement of either the pump (heart), the fluid (blood) or the container (blood vessel) can affect perfusion! Depending on the aetiology of the disturbance, we separate different categories of shock, which are clinically characterised by specific constellations of haemodynamic values. The question arises, whether particular haemodynamic values are strictly associated with metabolic changes, and whether the currently available monitoring is able to sufficiently reflect the ongoing pathophysiology in the tissue. It is well known that during states of low perfusion, e.g. in haemorrhage shock or endotoxaemia, blood on the microcirculatory level partly bypasses the tissue. Hence, it seems to be of high priority to know what is the current metabolic status of the tissue [13, 14].

Most clinicians define "therapeutic endpoints" regarding haemorrhage shock by restoration of MAP, filling pressures, cardiac index, and blood lactate levels. However, as yet in these conditions only limited information has been revealed about the cellular nutrition. We introduced in vivo microdialysis for the measurement of
a.) tissue vulnerability of different compartments, and
b.) the effect of different therapeutic interventions
during porcine experimental haemorrhage and endotoxaemia shock models.

Material and methods

Female German mixed-breed pigs (body weight 29 ± 9 kg) were involved in this study after approval by the local institutional review board. Pigs were randomly assigned to group HS (haemorrhage shock, n = 7) and group ES (endotoxin shock, n = 7).

The animals were fasted overnight before the experiments, while fluid intake was unrestricted. After premedication with an intramuscular injection of ketamine (20 mg/kg) and midazolam (5 mg/kg), the animals were anaesthetised with etomidate (1mg/kg). A fixed minute volume of 12.5 ml/kg at a rate of 12 per minute (inspiratory/expiratory time ratio 1:2) and an inspiratory oxygen concentration of 30 % (EVA, Fa. Dräger, Lübeck, Germany) was adjusted for ventilation after tracheostomy.

All animals received Ringer's solution at a rate of 3 ml/kg/h, adapted from previous studies. Additionally, a continuous infusion of fentanyl (0.025 mg/kg/h), midazolam (1.8 mg/kg/h) and muscle relaxation with pancuronium bromide (0.1 mg/kg/h) was administered for maintenance of analgo-sedation.

For haemodynamic monitoring, an arterial catheter (18G, Vyggon Co., Ecouen, France) was inserted into the right femoral artery. A pulmonary artery catheter (Vigilance CCO, Baxter Co., USA) was inserted via the right internal jugular vein to monitor continuous cardiac output (CCO), mixed venous oxygen saturation (SvO_2), and the core body temperature. Arterial blood pressure, central venous pressure, pulmonary artery pressure and heart rate were recorded online and digitised by a monitor (Sirecust 1281, Siemens/Germany). The values were recorded every thirty minutes after start of the observation period.

Arterial blood samples were drawn every hour for analysis of paO_2, $paCO_2$, pH, arterial base excess and lactate concentrations (ABL700, Radiometer Copenhagen), while SvO_2 was measured continuously with the CCO (Baxter vigilance) catheter.

Haemorrhage shock

Haemorrhage shock was induced by acute hypovolaemic haemodilution with blood loss of 30 ± 8 ml/kg via the 8 F central venous shed. It was aimed to reduce the mean arterial pressure to 30 mmHg, and in the untreated group to maintain it at this level for 240 minutes. Measurements were performed every 30 minutes.

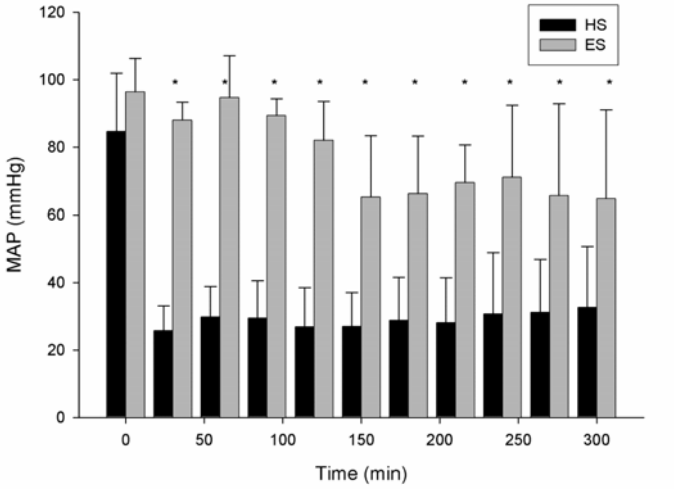
Endotoxin infusion

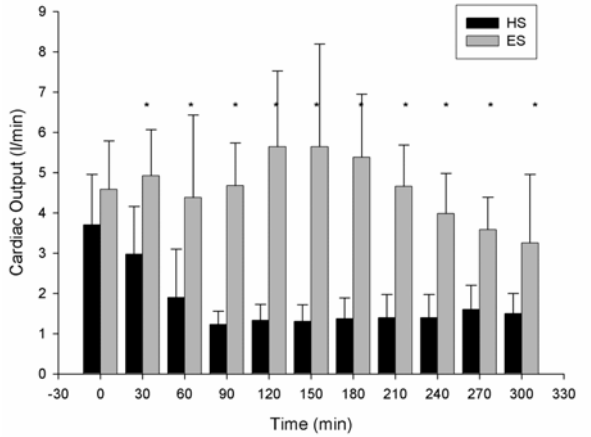
Endotoxin shock was induced by administration of endotoxin from Salmonella friedenau (H 909), at a constant dose of 1 µg/kg/h until the death of the animal. Measurements were performed every 30 minutes.

Microdialysis

After paramedian laparatomy, microdialysis catheters (CMA 60, CMA/ Microdialysis, Solna, Sweden) were inserted into the right hepatic lobe, the right femoral muscle and subcutaneously in the right gluteal area. Each microdialysis catheter was perfused at a flow rate set to 0.5 µl/min (CMA 107; CMA-Microdialysis, Solna, Sweden). The catheters were perfused with lactate-free Ringer's solution, and the dialysate collected in microvials for subsequent analysis.

Due to low perfusion rate and the length of the membrane part of the microdialysis catheters (30 mm), the recovery rate was previously described with 80-85% of the concentration within the interstitial tissues. Thus, the actual interstitial concentrations were closely represented by the obtained samples. The dialysate was analysed for metabolites of the carbohydrate and lipid metabolism (lactate and glycerol) using a photometric assay (CMA 600, Solna/Sweden).

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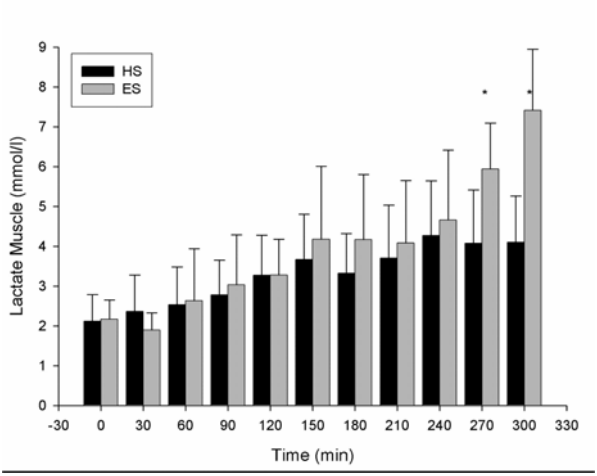
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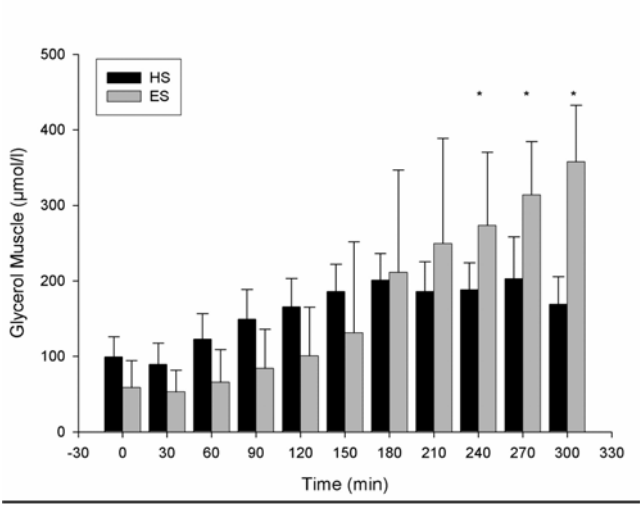
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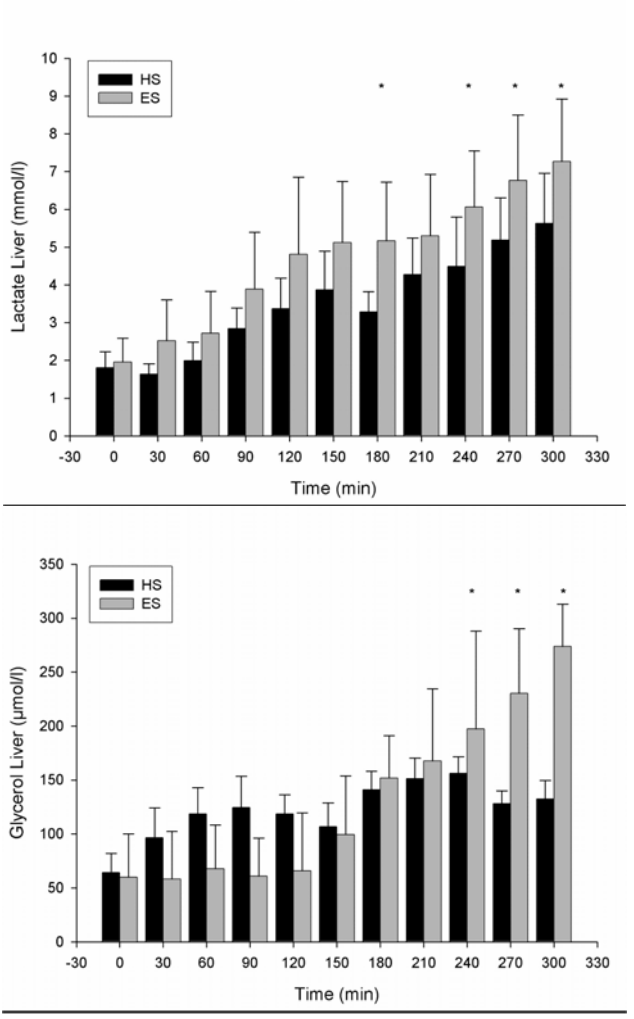


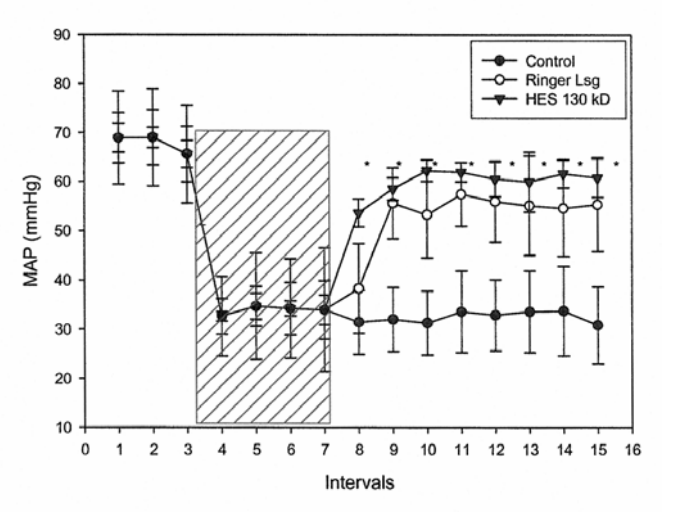
Fig. 1. Haemodynamic and metabolic parameters after induction of endotoxin shock (ES) and haemorrhage shock (HS). Despite "better" haemodynamic values, metabolic monitoring presented more-pronounced deterioration of the tissue during endotoxaemia

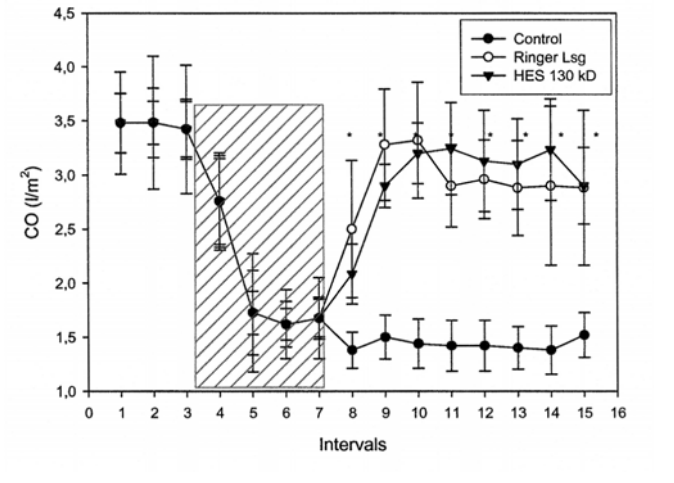
Results

Even though a significant reduction in MAP and CO with significant higher values for the endotoxin shock group (ES) was observed, interstitial accumulation of lactate in the muscle and liver of the ES-animals was more pronounced than during haemorrhage shock (Fig. 1, $p<0.05$). Even interstitial glycerol levels as a parameter of cell membrane damage reached significantly higher values than the animals after induction of haemorrhage shock.

Haemorrhage shock and metabolic effects of volume therapy to the intestine

Preparation of all animals was performed according to the protocol previously described. After induction of haemorrhage shock, the period of low perfusion states was maintained for 60 minutes. One group of animals (n = 7) was administered 130 kD HES (Voluven, Fresenius Kabi, Germany), while another group (n = 7) received continuous infusion lactate free Ringer's solution (Fa. B-Braun, Melsungen, Germany) to achieve MAP of 60 mmHg. Before, during and after 60 min of shock, all animals were observed subsequently for 180 min, and microdialysis analysis was performed in the jejunum.





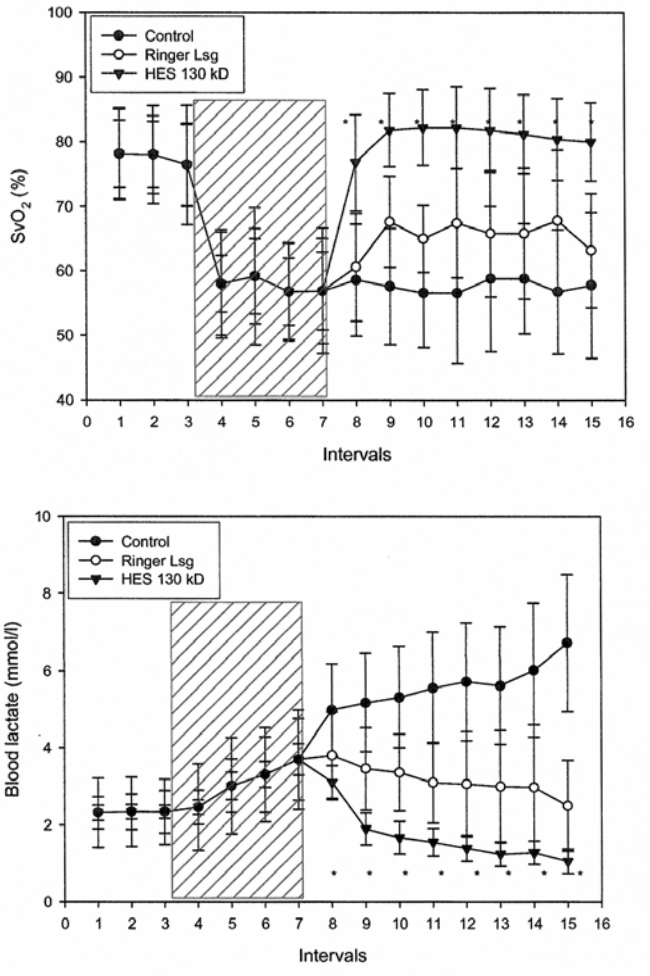


Fig. 2. Values for MAP and CO, SvO2 and blood lactate after induction of haemorrhage shock (shaded area) and different therapeutic interventions of volume replacement

Haemodynamics

Induction of haemorrhage shock significantly reduced mean arterial pressure (MAP) in all animals. Administration of Ringer's solution as well as 130kD HES completely restored MAP to baseline values, while the control group remained at significantly lower values. Cardiac output (CO) during the shock period decreased to significantly lower levels and remained at low levels in the control group. CO returned to baseline values after infusion of 130 kD HES and Ringer's solution (Fig. 2). Infusion of HES 130 kD was associated with higher SVO_2 and lower blood lactate levels compared to crystalline fluid therapy.

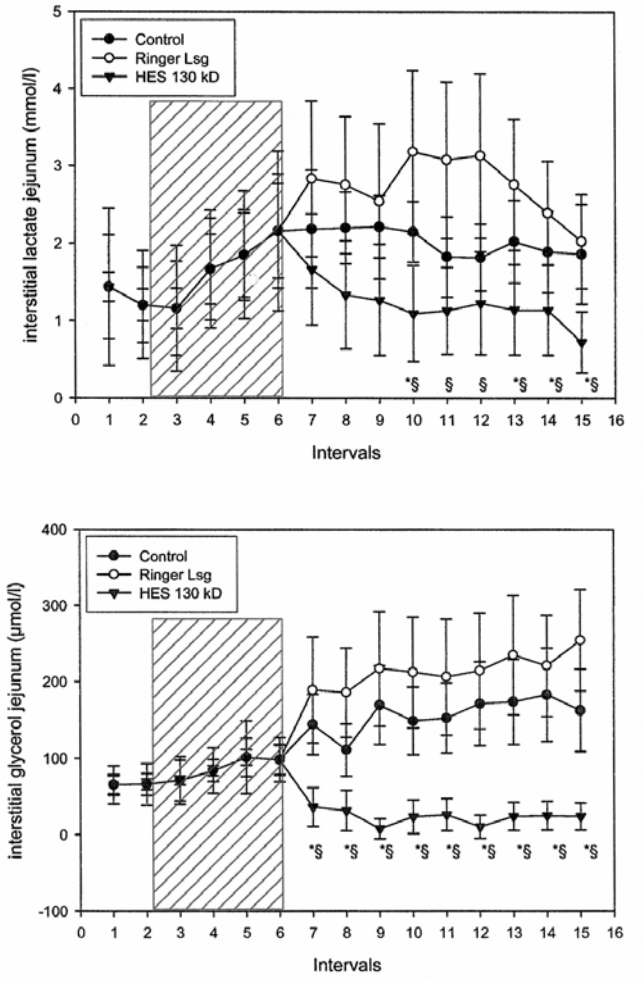


Fig. 3. Values for interstitial concentrations of lactate and glycerol in the jejunum after induction of haemorrhage shock (shaded area) and different therapeutic interventions

Microdialysis

Interstitial lactate concentrations in the jejunum were significantly lower in the 130 kD HES group compared to the Ringer and the untreated groups (Fig. 3, $p<0.05$). Interstitial lactate in the jejunum during crystalloid volume "therapy" was even higher compared to the control group (n.s.).

Interstitial glycerol as one parameter of cell membrane damage increased to significant higher values in the control and Ringer group compared to the animals who were treated with 130 kD HES, again with slightly higher values of the crystalline volume group compared to untreated animals (Fig. 3, $p<0.05$).

Discussion

Shock is currently interpreted as a clinical syndrome resulting from an imbalance between tissue oxygen demand and supply [2]. Impaired oxygen delivery is the primary problem in hypovolaemic and septic forms of shock. Declines in cellular oxygen delivery lead to more oxygen extraction from the capillary blood. With severe decreases in oxygen transport, compensatory increase in the oxygen extraction ratio is insufficient to maintain aerobic metabolism [15, 16]. When tissue hypoxia is present, lactate production increases, and ATP formation continues via glycolysis [17]. The amount of lactate produced is believed to correlate with the total oxygen debt, the magnitude of hypoperfusion, and the severity of shock. Serial lactate determinations have been suggested to be helpful in patients resuscitated from shock to assess the adequacy of therapeutic interventions. However, determination of blood lactate levels is a global parameter without any information about regional metabolic disorders [18]. This information can be revealed by the use of microdialysis [19-21].

Haemorrhagic shock is caused by the loss of both circulating blood volume and oxygen-carrying capacity, while the pathophysiology of endotoxaemia and sepsis and, subsequently, lactic acidosis has not fully been understood yet. Increased lactate production during anaerobic and aerobic metabolism and decreased lactate clearance are likely contributors to hyperlactaemia. The additional possible mechanisms for hyperlactaemia include activation of glycolysis and inhibition of pyruvate dehydrogenase [22]. Some investigators have observed that patients with sepsis have decreased lactate clearance rather than increased lactate production [22]. Skeletal muscle and lung tissue have been shown to produce lactate during sepsis [10, 12].

Therefore, hyperlactaemia may be secondary to increased lactate production in the gut, liver, lungs, and skeletal muscles; decreased lactate clearance in the liver; or a combination of both. Still, other investigators have suggested that hyperlactaemia may occur secondarily to inflammatory mediator down-regulating pyruvate-dehydrogenase in skeletal muscles, rather than tissue hypoxia. However, these findings suggest the importance of a direct functional monitoring of the tissues. Despite the conflicting results from these studies, hyperlactaemia in patients with sepsis is a marker of the severity of stress response.

Clinically, the use of lactate as an index of tissue perfusion has several limitations. The presence of liver diseases causes a decreased ability to clear lactate during periods of increased production. Various causes of type-B lactate acidosis may produce hyperlactaemia and lactate acidosis in the absence of tissue perfusion. For significant increase in blood lactate to occur, lactate must be released into the systemic circulation and the rate of production must exceed hepatic, renal and skeletal muscle uptake [15, 16, 23, 24]. Therefore, regional hypoperfusion of tissues may be present despite normal blood lactate concentrations. This is the major advantage of the microdialysis technique: detection of metabolic derangements while global parameters are still not affected.

The predominant haemodynamic feature of septic shock is arterial vasodilation. Diminished peripheral arterial vascular tone may result in dependency of

blood pressure on cardiac output, causing vasodilation to result in hypotension and shock if insufficiently compensated by a rise in cardiac output.

In patients experiencing septic shock, the delivery of oxygen is relatively high, but the global oxygen extraction ratio is relatively low. The oxygen uptake increases with a rise in body temperature despite a fall in oxygen extraction. The basic pathophysiologic problem seems to be a disparity between the uptake and oxygen demand in the tissues, which may be more pronounced in some areas than in others.[25] This is termed maldistribution of blood flow, either between or within organs, with a resultant defect in capacity to extract oxygen locally [24]. During a fall in oxygen supply, cardiac output becomes distributed so that most vital organs, such as the heart and brain, remain relatively better perfused than nonvital organs. However, sepsis leads to regional changes in oxygen demand and regional alteration in blood flow of various organs, again, a phenomenon microdialysis can reveal important information of [26].

The microcirculation is the key target organ for injury in patients with sepsis syndrome and haemorrhage shock. Microdialysis monitoring might give an additional insight into the pathophysiology of tissue response to clinical stress factors like anaemic shock, endotoxaemia or sepsis, respectively [4, 21, 27, 28]. This monitoring device seems to be able to reveal information about organ dysfunction at an early stage, at a time, when global haemodynamic monitoring is not able to detect.

References

1. Crinnion JN, Homer-Vanniasinkam S, Gough MJ (1993) Skeletal muscle reperfusion injury: pathophysiology and clinical considerations. Cardiovasc Surg 1:317-324
2. Sibbald WJ, Messmer K, Fink MP (2000) Roundtable conference on tissue oxygenation in acute medicine, Brussels, Belgium, 14-16 March 1998. Intensive Care Med 26:780-791
3. Luchette FA, Jenkins WA, Friend LA et al (2002) Hypoxia is not the sole cause of lactate production during shock. J Trauma 52:415-419
4. Levy B, Gawalkiewicz P, Vallet B et al (2003) Gastric capnometry with air-automated tonometry predicts outcome in critically ill patients. Crit Care Med 31:474-480
5. Oldner A, Goiny M, Ungerstedt U (1996) Splanchnic homeostasis during endotoxin challenge in the pig as assessed by microdialysis and tonometry. Shock 6:188-193
6. Lonnroth P, Smith U (1990) Microdialysis – a novel technique for clinical investigations. J Intern Med 227:295-300
7. Ungerstedt U, Pycock C (1974) Functional correlates of dopamine neurotransmission. Bull Schweiz Akad Med Wiss 30:44-55
8. Ungerstedt U (1991) Microdialysis – principles and applications for studies in animals and man. J Intern Med 230:365-373
9. Klaus S, Staubach KH, Eichler W et al (2003) Clinical biochemical tissue monitoring during ischaemia and reperfusion in major vascular surgery. Ann Clin Biochem 40:289-291
10. Klaus S, Staubach KH, Heringlake et al (2003) Tissue metabolism during endotoxin shock after pretreatment with monophosphoryl lipid A. Cardiovasc Res 59:105-112
11. Klaus S, Heringlake M, Bahlmann L (2003) Biochemical tissue monitoring during hypoxia and reoxygenation. Resuscitation 56:299-305

12. Klaus S, Heringlake M, Bahlmann L (2003) Metabolic changes detected by microdialysis during endotoxin shock and after endotoxin preconditioning. Intensive Care Med 29:634-641
13. Ungerstedt U (1997) Microdialysis – a new technique for monitoring local tissue events in the clinic. Acta Anaesthesiol Scand Suppl 110:123
14. Muller M (2002) Science, medicine, and the future: Microdialysis. BMJ 324:588-591
15. Tenhunen JJ, Kosunen H, Takala JA et al (1999) Intestinal luminal microdialysis: a new approach to assess gut mucosal ischemia. Anesthesiology 91:1807-1815
16. Tenhunen JJ, Jakob SM, Takala JA (2001) Gut luminal lactate release during gradual intestinal ischemia. Intensive Care Med 27:1916-1922
17. Alston TA (1999) Elevated hypoxanthine in endotoxic shock. Crit Care Med 27:690-691
18. Rixen D, Raum M, Tenhunen J et al (2002) Local lactate and histamine changes in small bowel circulation measured by microdialysis in pig hemorrhagic shock. Shock 18:355-359
19. Arner P (1995) Techniques for the measurement of white adipose tissue metabolism: a practical guide. Int J Obes Relat Metab Disord 19:435-442
20. Ungerstedt J, Nowak G, Ungerstedt U (2003) Intraperitoneal microdialysis (IPM): a new technique for monitoring intestinal ischemia studied in a porcine model. Shock 20:91-96
21. Bahlmann L, Wagner K, Klaus S (2002) Subcutaneous microdialysis for metabolic monitoring in abdominal aortic surgery. J Clin Monit Comput 17:309-312
22. Fink MP (2002) Bench-to-bedside review: Cytopathic hypoxia. Crit Care 6:491-499
23. Tenhunen JJ, Kosunen H, Juvonen P et al (1996) Intestinal mucosal microdialysis: histamine release in splanchnic ischemia/reperfusion injury in piglets. Inflamm Res 45(1):S52-S53
24. Tenhunen JJ, Uusaro A, Karja V et al (2003) Apparent heterogeneity of regional blood flow and metabolic changes within splanchnic tissues during experimental endotoxin shock. Anesth Analg 97:555-563
25. Martikainen TJ, Tenhunen JJ, Uusaro A, Ruokonen E (2003) The effects of vasopressin on systemic and splanchnic hemodynamics and metabolism in endotoxin shock. Anesth Analg 97:1756-1763
26. Martinez A, Chiolero R, Bollman M et al (2003) Assessment of adipose tissue metabolism by means of subcutaneous microdialysis in patients with sepsis or circulatory failure. Clin Physiol Funct Imaging 23:286-292
27. Bahlmann L, Klaus S, Heringlake M et al (2002) Microdialysis in abdominal surgery. Langenbecks Arch Surg 386:499-501
28. Bahlmann LM, Misfeld M, Klaus S et al (2004). Myocardial redox state during coronary artery bypass grafting assessed with microdialysis. Intensive Care Med 30:889-894

Chapter 52

Organ dysfunction in circulatory shock – altered perfusion, metabolism or tight junctions? Do we need a shift of paradigm?

J.J. Tenhunen

Several recent articles have described the present understanding of proinflammatory mediator cascades [1], oxidative injury/reactive oxygen species [2], coagulation pathways [3], microcirculatory (endothelial) alterations [4–6], programmed cell death [7–10] and mitochondrial dysfunction with ATP depletion [11–13], as potential cornerstones of multiple organ dysfunction following circulatory shock, be it septic, cardiogenic or haemorrhagic in origin. While readers are encouraged to update their knowledge of the different prominent theories of the development of multiple organ dysfunction with the aforementioned material, this review will focus on pondering the relevance and potential of a new hypothesis for a common subcellular mechanism in MODS, epithelial dysfunction, following the variety of injurious pathways. In addition, the possible methods by which early epithelial dysfunction could be recognised will be briefly discussed.

Circulatory shock

Perfusion heterogeneity – ischaemia–reperfusion

In circulatory shock, by definition, tissue perfusion is inadequate to maintain a normal oxygen and nutrient supply to the tissues, on the one hand, and draining of metabolic products from the tissues on the other. Depending on the classically defined subtype of circulatory shock, the alterations to perfusion can be assumed or are largely accepted to be heterogeneous between and within organs [14–17]. The perfusion defect may also be related to shunting [6]. The temporal dependence of the perfusion heterogeneity between various tissues is apparent [16]. In other words, at different time points in haemorrhagic, cardiogenic or septic shock, the systemic and regional blood flows may be redistributed. Furthermore, different vasoactive drug interventions can profoundly alter the distribution of blood flow at different points in the critical illness [18–20]. Inadequate tissue perfusion may cause ischaemia (and thereby decrease ATP) and, if prolonged, cell death. If necrotic cell death occurs, there is a link with augmentation of the inflammatory response in the form of HMGB1 release from

necrotic (but not apoptotic cells) [21]. Subsequent reperfusion can induce reperfusion injury through oxidative stress (reactive oxygen species), causing further cellular injury.

Inflammation and coagulation

Myriad proinflammatory mediators have been implicated in developing multiple organ dysfunction syndrome (MODS), but none of the mediator-targeted interventions in patient populations have led to dramatic changes in outcome. While the complexity of the inflammatory cascades and cross talk with the coagulation pathways must be accepted, it is tempting to speculate that downstream effects of various proinflammatory signals might be drawn together and pinpointed and new therapeutic strategies developed. Therefore, the putative link between inflammatory mediators and epithelial cell function will be evaluated. We may find that one of the new cytokines, HMGB1, is involved in the pathogenesis of MODS. Tracey's group has revealed the mitochondrial DNA-binding protein as a late-acting cytokine in a variety of inflammatory states [22]. If HMGB1 proves to be one of the more important mediators in sepsis and MODS, could it be linked to epithelial dysfunction?

ATP depletion—mitochondrial dysfunction

In addition to obvious ATP depletion by ischaemia [23], sepsis may induce ATP depletion as a consequence of metabolic down-regulation by an endocrinological response to inflammatory response [11–13]. In a patient group with severe sepsis or septic shock, Singer et al. demonstrated that the ATP content in muscle biopsies was decreased [11]. These authors set up the hypothesis that metabolic shutdown of mitochondria may lead to this ATP depletion [13]. ATP depletion, if profound, is one of the triggers for programmed cell death or, if prolonged, for necrosis [23]. Apoptosis is one potential candidate factor in epithelial hyperpermeability. Alternatively, could ATP depletion lead to altered epithelial cellular function via disintegration of tight junction complexes?

Apoptosis

In patients dying with sepsis or after traumatic haemorrhagic shock, necrosis of cells in parenchymal organs is rare [7–10]. Apoptosis, on the other hand, occurs both in the epithelial cells and in particular in the lymphocytes [7]. While apoptosis is also common in epithelial cells in normal conditions, the number of cells turning to apoptosis is convincingly increased in the development of MODS. Apoptotic cell death of intestinal epithelial cells may be one reason for 'leaky' epithelium. In some conditions, however, apoptosis of intestinal epithelial cells is controlled in such a manner that the epithelial barrier is maintained throughout the processes of apoptosis and disposal of the dead cell material [24]. This makes the idea that apoptosis is not necessarily the causative factor in epithelial hyperpermeability, or

at least, not as a generalised phenomenon between all parenchymal organs, plausible.

Common pathway downstream?

All the above-mentioned mechanisms of injury are obviously part of the myriad cascades and interconnected pathways leading to deranged organ function. None of them, however, provides an adequate explanation of the high mortality in MODS. Obviously all of them contribute to the outcome, but, to put it provocatively, none of them (with the exception of coagulation pathways and activated protein C) has proved to be a cause of death in MODS.

The paradigm of MODS in critical illness commonly accepted at present states that after primary successful resuscitation from an insult, gut- [25] and/or lung-derived [26] cytokine release leads to systemic inflammation, altered regional perfusion and/or metabolism and thereby, ultimately, to remote organ dysfunction. The final step from the local perfusion defect or from local metabolic derangement to actual cell/tissue/organ dysfunction is far from clear, however. We might assume that in the case of ischaemia, ischaemia/reperfusion, local inflammation and/or cellular metabolic turmoil (be it mitochondrial dysfunction or of some other type), the eventual signal for dysfunction would be cellular necrosis or apoptosis, with the ultimate demise of the patient. Even though apoptosis and necrosis may be present in tissues of septic shock or trauma patients, Hotchkiss et al. reported no marked necrosis in any of the organs investigated in their trauma, haemorrhage or septic shock patients with MODS. They did observe an increased rate of apoptosis, implying that apoptosis may indeed be one part of the death signalling in MODS. Nonetheless, they could not consider apoptosis as a cause of organ dysfunction in general [7–10]. Is it possible to draw all lines of evidence together and build up a connection with epithelial cell dysfunction as a eventual causative subcellular event in a failing organ?

Parenchymal organs and epithelium

In a grossly simplified way, we can consider all the parenchymal organs that are afflicted in MODS to have an epithelial cellular barrier between two compartments: the *lung*–alveolar to the interstitial (or vascular) space, *liver*–biliary duct to hepatic (or vascular) parenchyma, *kidney*–glomerular to the vascular and *gut*–intestinal luminal to the interstitial (or vascular). Characteristically, one of the compartments contains material or substances that are not normally allowed in the other. In the vasculature, on the other hand, intravascular and interstitial spaces are separated by the endothelial cell monolayer. Tight junctions between adjacent epithelial cells, as opposed to endothelial cells, form markedly smaller pores between the cells [27, 28], and therefore it is reasonable to assume that epithelial cells are more crucial for barrier function than endothelial cells are in parenchymal organs. Hypotheti-

cally, rather than the endothelial layer, the epithelial sheet would be the final frontier in the protection of the function of parenchymal organs. In fact, the concept of endothelial dysfunction and epithelial dysfunction can be combined and we can hypothesise about each tight junction component as a target for injurious events and thereby a parallel and/or sequential functional (not cell-structural) endothelial and epithelial disintegration as the specific reason for organ failure.

Tight junctions

Adjacent epithelial cells are attached to each other by the lateral cell membrane. The selective paracellular (between the adjacent cells) permeability of solutes and molecules is determined by a zipper-like porous contact line(s) between the cells. This contact area circling around the cells' apical–lateral wall is called the tight junction (TJ) complex or as a larger unit, apical junctional complex. The latter is made up of the TJ and the adherence junction. The TJ complex allows the epithelial cells to maintain polarity. It also allows the concentration gradients between the two compartments (for a recent review see [29]).

Furuse et al. [30] were the first to unravel the structural components of the TJ complex. They named the novel 65-kD protein occludin as an integral protein involved in the tight junction complex between the adjacent cells. The same investigators later identified two more new proteins as important structural parts of the TJ complex, claudins 1 and 2 [31]. Both occludin and claudins form the intercellular part of the TJ complex with their characteristic membrane four domain structure. Meanwhile, up to 24 members of the claudin family have been identified, while only one additional occludin has been characterised [31]. Integral parts of the TJ complex are the intracellular scaffolding proteins ZO-1, -2 and -3 (zonula occludens). They link the transmembrane proteins to intracellular cytoskeleton.

Evidence for the concept of epithelial dysfunction in circulatory shock and MODS?

Various series of experiments have been conducted by investigators in the Fink-Delude Laboratory at the University of Pittsburgh Medical Center and these indicate that indeed, epithelial dysfunction may well be one crucial part of the puzzle in MODS. On the basis of their findings and those of others, this laboratory has proposed epithelial dysfunction as a hallmark of MODS.

Yang et al. report that epithelial mucosal permeability is markedly increased following haemorrhagic shock and reperfusion in mice [33]. This permeability is associated with decreased expression and deranged localisation of ZO-1 TJ protein. The dysregulation of ZO-1 is at least partly caused by IL-6 up-regulation during ischaemia–reperfusion; IL-6 knockout mice do not develop marked gut hyperpermeability or bacterial translocation. Accordingly, ZO-1 immunolocalisation is not

altered. In a series of experiments, Han et al. investigated the effect of inflammatory cytokines and endotoxin shock on the TJ structure and function in three of the important parenchymal organs, intestine, liver and lung [34–37]. Through both NO-dependent and NO-non-dependent pathways, TJ protein expression and immunolocalisation was found to be altered in intestinal epithelial, hepatic and pulmonary epithelial cells in a experimental murine endotoxin shock model but also in in vitro cell cultures. Sappington et al. [38] then tested ethyl pyruvate as a new treatment strategy in human epithelial cells and endotoxaemic mice. While the intestinal epithelial hyperpermeability was obvious in nontreated animals and cells with the association to altered tight junction integrity, ethyl pyruvate prevented hyperpermeability and TJ dysregulation [38].

Linking with inflammation and apoptosis. The previous studies imply that inflammatory mediators may indeed alter TJ integrity with association to changes in functional integrity of epithelial cell layer. Others have investigated cytokines in relation to both TJ proteins and apoptosis: tumour necrosis factor alpha (TNF alpha) can induce both apoptosis [39] of epithelial cells and dysregulation of expression of TJ proteins [40] in in vitro studies. Apoptosis per se may be part of the pathophysiologic picture of increasing intestinal epithelial permeability [41]. On the other hand, when apoptosis and TJ derangement were compared in a study by Bruewer et al. [42], apoptosis was shown not to be the crucial part of barrier failure. Inhibiting apoptosis did not ameliorate the perturbation of barrier function measured by transepithelial resistance and permeability for large tracers. Meanwhile, TJ dysregulation proved to be important for hyperpermeability. Interestingly, in their investigation, occludin and claudin-1 were internalised from their normal intercellular location, whereas immunolocalisation of ZO-1, the important scaffolding protein, was not altered [42].

Linking with ATP depletion. Ischemia related ATP depletion may induce TJ disruption [43]. In an in vitro model of alveolar epithelial cells Cavanaugh et al. [44] showed recently that ATP depletion induced either chemically or, interestingly enough, by stretching of the epithelial cells altered the morphology of the TJs. On the basis of these findings, it seems reasonable to assume that ATP depletion, whether caused by inadequate oxygen supply or by sepsis-related metabolic changes, may lead to epithelial dysfunction.

Linking with oxidative stress. Oxidative stress (H_2O_2) to epithelial cells leads to TJ disruption, as suggested by Cuzzocrea et al. [45] in kidney epithelial cell cultures and in an in vivo animal model. Sheth et al. [46] studied the mechanisms of the injury and found that oxidative stress-induced TJ damage is related to IP-3 kinase activity.

Altogether, there is cumulative evidence in the literature that epithelial dysfunction is certainly part of the pathophysiological events in MODS. Whether it is indeed the ultimately responsible for the syndrome remains to be evaluated. Meanwhile, methods of monitoring epithelial dysfunction in a clinical setting are

needed. First of all, the heterogeneity of the degree of dysfunction between the various organs affected must be acknowledged and appreciated. Ideally, a method providing an opportunity for specific online monitoring of the epithelial function organ will be devised.

Organ-specific monitoring

While it would be highly desirable to create a specific assay for the integrity of tight junction complex in epithelia of the intact organs, for now, one has to rely on functional tests to reflect the status of epithelial barrier of parenchymal organs.

Liver. Epithelial layer between the intrahepatic bile canaliculi and the parenchyma restricts bile to biliary ducts. If the epithelial integrity breaks down, hyperbilirubinaemia ensues [33, 35–37]. One might speculate that serum bilirubin measurement would adequately reflect the integrity of hepatic epithelial cells.

Lung. There is no direct or indirect measure reflecting the status of alveolar epithelial integrity at present. Hypothetically, extravascular lung water would reflect the barrier function of both the endothelial and the epithelial layer, at least when the oxygenation parameters, such as PaO_2/FiO_2, and thorax X-ray and or CT scans imply alveolar oedema formation. Also, one might want to consider taking brush samples from the bronchial tree with fibreoptics to determine the TJ proteins in the shed bronchial epithelial cells.

Kidney. It is reasonable to assume that serum urea detection reflects the ability of glomerular epithelia to keep components of urine from entering capillary circulation. Thereby, serum urea may be an adequate measure of epithelial integrity in kidney. This, however, may be an over-simplified view, since serum urea does not increase until late in the developing kidney failure in critical illness. Therefore, hypothetically, researchers should attempt to determine a marker for early epithelial failure to be detected in the urine. Possibly, cytology of urine samples is one approach, with immunostaining for different TJ proteins of the shed epithelial cells.

Gut. Typically, and ironically, intestinal dysfunction was not included in multiple organ dysfunction scores [47]. Apparently, there was never a method that actually made it possible to quantify the dysfunction. With regard to intestinal mucosal epithelial integrity, it can be assumed that permeability is a functional parallel to the structure of TJs. Thereby, intestinal permeability measurements could be regarded as functional measures of the adequate assembly of TJ. Unfortunately, the permeability measurements used at present are not widely applied in the clinical setting, nor are they free of drawbacks, such as the dependence of kidney function [48]. An alternative approach could be to collect samples of intestinal fluid. Intestinal luminal lactate sampling by segmental occlusion [49], intestinal luminal microdialysis [50] or equilibration dialysis [51]. Each of these methods

allows direct collection of samples from the vicinity of intestinal epithelial cells. It is possible to argue about the extent to which intestinal luminal lactate per se reflects the permeability, of course. It must be seen as a nonspecific signal for epithelial cellular energy/metabolic alteration. However, it seems that luminal lactate release is associated with increasing intestinal mucosal permeability, as suggested by Solligard et al. [52] and Jorgensen [53]. Thus, while we need to find specific markers (others than immunostaining of the epithelial cells) for epithelial TJ disruption, intestinal luminal lactate may serve as a surrogate.

References

1. Pinsky MR (2004) Pathophysiology of sepsis and multiple organ failure: pro-versus anti-inflammatory aspects. Contrib Nephrol 144:31-43
2. Martins PS, Kallas EG, Neto MC et al (2003) Upregulation of reactive oxygen species generation and phagocytosis, and increased apoptosis in human neutrophils during severe sepsis and septic shock. Shock 20:208-212
3. Nimah M, Brilli RJ (2003) Coagulation dysfunction in sepsis and multiple organ system failure. Crit Care Clin 19:441-458
4. Buwalda M, Ince C (2002) Opening the microcirculation: can vasodilators be useful in sepsis? Intensive Care Med 28:1208-1217
5. Aird WC (2003) The role of the endothelium in severe sepsis and multiple organ dysfunction syndrome. Blood 101:3765-3777
6. Spronk PE, Ince C, Gardien MJ et al (2002) Nitroglycerin in septic shock after intravascular volume resuscitation. Lancet 360:1395-1396
7. Hotchkiss RS, Schmieg RE Jr, Swanson PE et al (2000) Rapid onset of intestinal epithelial and lymphocyte apoptotic cell death in patients with trauma and shock. Crit Care Med 28:3207-3217
8. Schmieg RE Jr, Tinsley KW, Swanson PE et al (2000) Rapid onset of hepatocyte apoptosis in a patient with trauma. J Trauma 49:542-546
9. Hotchkiss RS, Chang KC, Grayson MH et al (2003) Adoptive transfer of apoptotic splenocytes worsens survival, whereas adoptive transfer of necrotic splenocytes improves survival in sepsis. Proc Natl Acad Sci USA 100:6724-6729
10. Hotchkiss RS, Swanson PE, Freeman BD et al (1999) Apoptotic cell death in patients with sepsis, shock, and multiple organ dysfunction. Crit Care Med 27:1230-1251
11. Brealey D, Brand M, Hargreaves I et al (2002) Association between mitochondrial dysfunction and severity and outcome of septic shock. Lancet 360:219-223
12. Brealey D, Karyampudi S, Jacques TS et al (2004) Mitochondrial dysfunction in a long-term rodent model of sepsis and organ failure. Am J Physiol Regul Integr Comp Physiol 286:R491-R497
13. Singer M, De Santis V, Vitale D et al (2004) Multiorgan failure is an adaptive, endocrine-mediated, metabolic response to overwhelming systemic inflammation. Lancet 364:545-548
14. Hiltebrand LB, Krejci V, Banic A et al (2000) Dynamic study of the distribution of microcirculatory blood flow in multiple splanchnic organs in septic shock. Crit Care Med 28:3233-3241
15. Jakob SM, Tenhunen JJ, Laitinen S et al (2001) Effects of systemic arterial hypoperfusion on splanchnic hemodynamics and hepatic arterial buffer response in pigs. Am J Physiol Gastrointest Liver Physiol 280:G819-G827

16. Tenhunen JJ, Uusaro A, Karja V et al (2003) Apparent heterogeneity of regional blood flow and metabolic changes within splanchnic tissues during experimental endotoxin shock. Anesth Analg 97:555-563
17. Krejci V, Hiltebrand L, Banic A et al (2000) Continuous measurements of microcirculatory blood flow in gastrointestinal organs during acute haemorrhage. Br J Anaesth 84:468-475
18. Hiltebrand LB, Krejci V, Sigurdsson GH (2004) Effects of dopamine, dobutamine, and dopexamine on microcirculatory blood flow in the gastrointestinal tract during sepsis and anesthesia. Anesthesiology 100:1188-1197
19. Tenhunen JJ, Martikainen TJ, Uusaro A et al (2003) Dopexamine reverses colonic but not gastric mucosal perfusion defects in lethal endotoxin shock. Br J Anaesth 91:878-885
20. Martikainen TJ, Tenhunen JJ, Uusaro A et al (2003) The effects of vasopressin on systemic and splanchnic hemodynamics and metabolism in endotoxin shock. Anesth Analg 97:1756-1763
21. Scaffidi P, Misteli T, Bianchi ME (2002) Release of chromatin protein HMGB1 by necrotic cells triggers inflammation. Nature 418:191-195
22. Wang H, Bloom O, Zhang M et al (1999) HMG-1 as a late mediator of endotoxin lethality in mice. Science 285:248-251
23. Paxian M, Bauer I, Rensing H et al (2003) Recovery of hepatocellular ATP and "pericentral apoptosis" after hemorrhage and resuscitation. FASEB J 17:993-1002
24. Abreu MT, Palladino AA, Arnold ET et al (2000) Modulation of barrier function during Fas-mediated apoptosis in human intestinal epithelial cells. Gastroenterology 119:1524-1536
25. Deitch EA, Forsythe R, Anjaria D et al (2004) The role of lymph factors in lung injury, bone marrow suppression and endothelial cell dysfunction in a primate model of trauma-hemorrhagic shock. Shock 22:221-228
26. Ranieri VM, Suter PM, Tortorella C et al (1999) Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. JAMA 282:54-61
27. Kern DF, Malik AB (1985) Microvascular albumin permeability in isolated perfused lung: effects of EDTA. J Appl Physiol 58:372-375
28. Matsukawa Y, Lee VH, Crandall ED et al (1997) Size-dependent dextran transport across rat alveolar epithelial cell monolayers. J Pharm Sci 86:305-309
29. Schneeberger EE, Lynch RD (2004) The tight junction: a multifunctional complex. Am J Physiol Cell Physiol 286:C1213-C1228
30. Furuse M, Hirase T, Itoh M et al (1993) Occludin: a novel integral membrane protein localizing at tight junctions. J Cell Biol 123:1777-1788
31. Furuse M, Fujita K, Hiiragi T et al (1998) Claudin-1 and -2: novel integral membrane proteins localizing at tight junctions with no sequence similarity to occludin. J Cell Biol 141:1539-1550
32. Muresan Z, Paul DL, Goodenough DA (2000) Occludin 1B, a variant of the tight junction protein occludin. Mol Biol Cell 11:627-634
33. Yang R, Han X, Uchiyama T et al (2003) IL-6 is essential for development of gut barrier dysfunction after hemorrhagic shock and resuscitation in mice. Am J Physiol Gastrointest Liver Physiol 285:G621-G629
34. Han X, Fink MP, Yang R et al (2004) Increased iNOS activity is essential for intestinal epithelial tight junction dysfunction in endotoxemic mice. Shock 21:261-270
35. Han X, Fink MP, Uchiyama T et al (2004) Increased iNOS activity is essential for hepatic epithelial tight junction dysfunction in endotoxemic mice. Am J Physiol Gastrointest Liver Physiol 286:G126-G136

36. Han X, Fink MP, Uchiyama T et al (2004) Increased iNOS activity is essential for pulmonary epithelial tight junction dysfunction in endotoxemic mice. Am J Physiol Lung Cell Mol Physiol 286:L259-L267
37. Han X, Fink MP, Delude RL (2003) Proinflammatory cytokines cause NO*-dependent and -independent changes in expression and localization of tight junction proteins in intestinal epithelial cells. Shock 19:229-237
38. Sappington PL, Han X, Yang R et al (2003) Ethyl pyruvate ameliorates intestinal epithelial barrier dysfunction in endotoxemic mice and immunostimulated caco-2 enterocytic monolayers. J Pharmacol Exp Ther 304:464-476
39. Gitter AH, Bendfeldt K, Schulzke JD (2000) Leaks in the epithelial barrier caused by spontaneous and TNF-alpha-induced single-cell apoptosis. FASEB J 14:1749-1753
40. Poritz LS, Garver KI, Tilberg AF et al (2004) Tumor necrosis factor alpha disrupts tight junction assembly. J Surg Res 116:14-18
41. Bojarski C, Gitter AH, Bendfeldt K et al (2001) Permeability of human HT-29/B6 colonic epithelium as a function of apoptosis. J Physiol 535:541-552
42. Bruewer M, Luegering A, Kucharzik T et al (2003) Proinflammatory cytokines disrupt epithelial barrier function by apoptosis-independent mechanisms. J Immunol 171:6164-6172
43. Ye J, Tsukamoto T, Sun A et al (1999) A role for intracellular calcium in tight junction reassembly after ATP depletion-repletion. Am J Physiol 277:F524-F532
44. Cavanaugh KJ Jr, Oswari J, Margulies SS (2001) Role of stretch on tight junction structure in alveolar epithelial cells. Am J Respir Cell Mol Biol 25:584-591
45. Cuzzocrea S, Mazzon E, De Sarro A et al (2000) Role of free radicals and poly(ADP-ribose) synthetase in intestinal tight junction permeability. Mol Med 6:766-778
46. Sheth P, Basuroy S, Li C et al (2003) Role of phosphatidylinositol 3-kinase in oxidative stress-induced disruption of tight junctions. J Biol Chem 278:49239-49244
47. Marshall JC, Cook DJ, Christou NV et al (1995) Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. Crit Care Med 23:1638-1652
48. Oudemans-van Straaten HM, van der Voort PJ, Hoek FJ et al (2002) Pitfalls in gastrointestinal permeability measurement in ICU patients with multiple organ failure using differential sugar absorption. Intensive Care Med 28:130-138
49. Ljungdahl M, Rasmussen I, Raab Y et al (1997) Small intestinal mucosal pH and lactate production during experimental ischemia-reperfusion and fecal peritonitis in pigs. Shock 7:131-138
50. Tenhunen JJ, Kosunen H, Alhava E et al (1999) Intestinal luminal microdialysis: a new approach to assess gut mucosal ischemia. Anesthesiology 91:1807-1815
51. Due V, Bonde J, Espersen K et al (2002) Lactic acidosis in the rectal lumen of patients with septic shock measured by luminal equilibrium dialysis. Br J Anaesth 89:919-922
52. Solligard E, Juel IS, Bakkelund K et al (2004) Gut barrier dysfunction as detected by intestinal luminal microdialysis. Intensive Care Med 30:1188-1194
53. Jørgensen V L, Nielsen S L, Espersen K et al (2004) Increased permeability and lactate concentrations in the rectal mucosa in patients with septic shock (abstract). Intensive Care Med 31 (Suppl)

Chapter 53

Haemodynamic support of paediatric patients in septic shock

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Paediatric septic shock is a life-threatening illness that requires immediate recognition and early aggressive treatment [1]. Septic shock can be characterised as inadequate cellular oxygen delivery and utilisation, resulting in conversion from aerobic to anaerobic metabolism, lactic acid production and cellular damage. The cardiovascular consequences of shock include myocardial dysfunction, vascular tone and permeability abnormalities, and abnormal oxygen delivery and metabolism [2, 3]. The end-result might be multiple organ system failure and death.

The haemodynamic profile of septic shock is influenced by multiple sepsis-induced physiological changes and characterised by components of hypovolaemia and cardiogenic, distributive and cytotoxic shock [2]. This haemodynamic profile is modified by fluid resuscitation. After adequate fluid resuscitation the presence and severity of hypotension are directly dependent on impairment of contractility and the degree to which systemic vascular resistance is lowered. Even when cardiac output in septic shock has been normalised or is above normal, hypoperfusion abnormalities such as lactic acidosis, decreased urine output or altered mental status may persist.

Cardiocirculatory abnormalities in septic shock

Myocardial dysfunction

Myocardial dysfunction develops in nearly all patients with septic shock [4, 5]. Although hypotension, acidosis and electrolyte abnormalities can have a role in sepsis-related myocardial dysfunction, depressed myocardial dysfunction persists after correction of these factors. In 1985 Parillo et al. demonstrated the reversible presence of a myocardial-depressant factor in the serum of patients with acute septic shock [6]. Exposure of rat myocardial cells in vitro to serum from patients with acute septic shock reversibly decreased left ventricular ejection fraction (LVEF) to below that in controls. Further experiments have demonstrated that tumour necrosis factor (TNF)-α and interleukin (IL)-1β, in addition to other cytokines, depress myocardial function individually and synergistically [7, 8]. As a possible mechanism of action, some studies indicate that cytokine-stimulated NO production may result in decreased myocardial contractility.

In children in meningococcal septic shock, there is a negative correlation between serum levels of cardiac troponin I and LVEF, suggesting a role of myocyte cytotoxicity related to cardiac dysfunction [9]. Myocardial cellular ischaemia secondary to microcirculatory abnormalities may also be present. Decreased responsiveness of myocardium to β1-agonists during endotoxic shock has been known for many years [10]. Both right and left ventricular systolic and diastolic dysfunction occur with sepsis. Frank-Starling ventricular function curves during volume administration are lower in patients with septic shock than in controls [11].

In general, after fluid resuscitation adults in the early phases of septic shock have elevated end-diastolic volumes, normal to elevated cardiac index, elevated heart rate, and decreased LVEF. Left ventricular preload is elevated and afterload is reduced. Children more frequently demonstrate decreased cardiac output, occasionally with increased left ventricular afterload [12]. Right ventricular dysfunction is also decreased in septic shock; right ventricular afterload or pulmonary vascular resistance is usually elevated because of associated acute lung injury.

Positive pressure ventilation, inotropic agents, and vasoactive agents can have a significant impact on end-diastolic pressures and volumes. In survivors, cardiac dysfunction and dilatation are reversible, returning to normal in 7–10 days [5].

Abnormal vascular tone and permeability

Most children with septic shock present with hypovolaemia that is attributable in part to inadequate fluid intake, excessive fluid losses, and increased capillary permeability. Exposure to endotoxin, in the absence of fluid resuscitation, results in increased systemic vascular resistance (SVR) and decreased cardiac output [13].

Abnormal oxygen delivery and metabolism

Multiple inflammatory mediators cause local microvascular dilatation and constriction. Cytokines stimulate endothelial NO production, resulting in local vasodilatation. Microvascular dysregulation of blood flow may contribute to cellular hypoxia and organ failure, resulting in higher serum lactate levels and metabolic acidosis combined with decreased oxygen extraction.

Monitoring cardiac function and oxygen delivery

Echocardiogram

Echocardiography is an easily accessible bedside method of determining left ventricular systolic function and left ventricular afterload in children in septic shock [14]. A shortening fraction reflects contractility, but does not account for differences in preload and afterload. Wall stress analysis provides an assessment of contractility, preload and afterload [15]. Diastolic function is more difficult to assess.

Central venous catheter

In recent years there has been considerable interest in targeting filling pressures for fluid resuscitation therapy in patients with central venous catheters (CVCs) or pulmonary artery catheters (PACs).

Central venous pressure (CVP) can be measured in the right atrium or proximal superior or inferior vena cava. In the absence of tricuspid valve pathology, CVP reflects the right ventricular diastolic or filling pressure. The CVP reflects a combination of right ventricular diastolic function, intravascular volume, and systemic venous capacitance. The superior vena cava co-oximetry measurement is an accurate representation of mixed venous oxygen saturation. A target CVP of 8–12 mmHg is recommended in spontaneously breathing patients, whilst in patients being mechanically ventilated a higher target CVP of 12–14 mmHg is recommended to take account of the increased intrathoracic pressure [16]. Central or mixed venous oxygen saturation of 70% should be aimed for >70% [16, 17].

Pulmonary artery catheter

No clear reduction in mortality has been demonstrated with pulmonary artery catheter (PAC) use in adults. Experts appointed by the American College of Critical Care Medicine recommend the use of the PAC in selected paediatric patients [18]. Published studies suggest that PAC-associated complications are rather rare. A relatively large study showed that in children with fluid-refractory and dopamine-resistant shock, placement of a PAC made it possible to recognise incorrect cardiovascular support strategies that had been based on incorrect assessment of the haemodynamic state [12]. This new information guided a change to appropriate therapies that reversed shock, underlining the potential usefulness of PAC-derived data in such patients.

Arterio–venous oxygenation

Increased systemic oxygen extraction or decreased oxygen delivery will increase the arterio–venous oxygenation (AVO_2) difference. In general, patients in septic shock have a decreased AVO_2 difference, whereas in patients with nonhyperdynamic septic shock the AVO_2 difference is increased. The abnormal oxygen extraction associated with sepsis may make the AVO_2 difference a less accurate assessment of cardiac output and oxygen delivery than in other forms of shock.

Serum lactate

Serum lactate measurements reflect the degree of tissue hypoxia and anaerobic cellular metabolism and can usually be used as a marker of oxygen delivery and extraction. Although lactate measurements may be useful, this parameter lacks precision as a measure of tissue metabolic status [16].

Therapeutic strategies

Recently published protocols stress the need for recognition of early signs and symptoms of paediatric shock, the importance of aggressive fluid resuscitation and early intubation, and the necessity for continued monitoring and resuscitation during transport [1]. Advances in paediatric ICU management include improved monitoring capabilities, advances in support of paediatric respiratory failure and renal insufficiency and an increased emphasis on nutrition.

Volume resuscitation

Septic shock in children is often associated with capillary leak syndrome and with vasodilatation requiring aggressive initial fluid resuscitation to avoid severe hypovolaemia. Carcillo et al. reported that rapid fluid resuscitation in excess of 40 ml/kg in the first hour after emergency department presentation was associated with improved survival and decreased occurrence of persistent hypovolaemia, with no increase in the risk of cardiogenic pulmonary oedema or acute respiratory distress syndrome in this group of paediatric patients [19]. Despite universal agreement on aggressive fluid resuscitation as the initial intervention in septic shock patients, the identity of the optimum fluid for this purpose has been less clear. There is only one randomised controlled trial comparing the use of colloid and cristalloid resuscitation (dextran, gelatin, lactated Ringer's, or saline) in children with dengue shock [20]. All these children survived regardless of the fluid used, but the longest time to recovery from shock was observed in children who received lactated Ringer's solution. Among patients with the narrowest pulse pressure, there was a suggestion that colloids were more effective than cristalloids in restoring normal pulse pressure. In a recent practice position paper, a group chosen for outstanding results in resuscitation of meningococcal septic shock (5% mortality) reported using 5% albumin exclusively (20 ml/kg boluses over 5–10 min) and intubating all patients who required >40 ml/kg [1].

Fluid infusion is best initiated with boluses of 20 ml/kg titrated to clinical monitors of cardiac output, including heart rate, urine output, capillary refill and level of consciousness. Large fluid deficits typically exist, and initial volume resuscitation usually requires volumes of 40–60 ml/kg but can require as much as 200 ml/kg [18]. For patients who do not respond rapidly to initial fluid boluses, or those with insufficient physiological reserves, invasive haemodynamic monitoring should be considered. Filling pressures should be increased to optimise preload so as to attain maximal cardiac output. Fresh-frozen plasma can be infused to correct abnormal prothrombin time and partial thromboplastin time, but should not be pushed, because it has hypotensive effects probably caused by vasoactive kinins. In the absence of data, it is reasonable to maintain the haemoglobin concentration within the normal range for age in children who are in shock [18].

Vasopressor agents

Dopamine, epinephrine, norepinephrine, phenylephrine and vasopressin have been demonstrated to be effective in raising blood pressure in patients with septic shock. Dopamine remains the first-line vasopressor for high-cardiac-output, low-vascular-resistance shock [18]. However, there is an age-specific insensitivity to dopamine. Dopamine causes vasoconstriction by releasing norepinephrine from sympathetic vesicles. Immature animals and infants may not have developed their full component of sympathetic vesicles. Dopamine-resistant shock commonly responds to norepinephrine or high-dose epinephrine infusions [21, 22]. Phenylephrine is limited to use as a pure vasopresssor agonist because it has no β-adrenergic activity [2]. However, some infants and children remain in a state of severe hyperdynamic shock despite adequate fluid loading and titration of catecholamines. In this situation low-dose vasopressin can be successfully applied to improve the perfusion pressure [23, 24].

Vasopressin, an endogenous hormone produced in the hypothalamus, is released from the posterior pituitary gland in response to increased plasma osmolarity, hypovolaemia and hypotension [25]. Concentrations of vasopressin in plasma consistently rise in cardiogenic and hypovolaemic shock states, but for unknown reasons they are inappropriately low in sepsis [26].

V1-receptor stimulation in vascular smooth muscle produces more potent vasoconstriction than either angiotensin II or norepinephrine. The lack of pressor response in nonseptic patients might be related to an intact baroreflex response, resulting in heart rate reductions.

Although high endogenous levels of vasopressin in nonshock states do not produce hypertension, in shock states vasopressin stimulation of vascular V1 receptors appears to be an important mechanism of blood pressure rise. Infusion of low-dose vasopressin might be useful in norepinephrine-resistant shock. However, rebound hypotension often occurs when the drug is stopped, and vasopressin generally has to be given for several days. Terlipressin, a long-acting synthetic analogue of vasopressin, has a half-life of 6 h and, like vasopressin, is used for the treatment of variceal haemorrhage and diabetes insipidus. Terlipressin has recently been used as a rescue therapy for intractable hypotension during neonatal septic shock and in four children with catecholamine-resistant septic shock [27–29]. Low-dose terlipressin therapy did not result in rebound hypotension, and no other signs of excessive vasoconstriction were observed. The optimal timing of its use, dosage, interval between doses and duration of treatment have yet to be demonstrated, and further studies should be done to allow better definition of its therapeutic role.

Inotropic support

During the course of septic shock, adults may progress from hyperdynamic to nonhyperdynamic septic shock. After fluid resuscitation, children may immediately develop nonhyperdynamic septic shock characterised by decreased myocar-

dial function, decreased cardiac output, and elevated SVR. Traditionally, dobutamine has been the therapy of choice for infants and children with nonhyperdynamic septic shock [18]. There is extensive experience of dobutamine use in both neonatal and paediatric populations [30–32]. Dobutamine has been shown to increase cardiac index and left-ventricular stroke work index (LVSWI), with a small dose-dependent decrease in SVR in paediatric patients with septic shock. However, infants <12 months of age can be less responsive to dobutamine infusion. Dobutamine- or dopamine-refractory shock can be reversed with epinephrine infusion. Epinephrine is more commonly used in children than in adults. When children remain in a normotensive low-cardiac-output and high-vascular-resistance state despite epinephrine and nitrovasodilator infusions, then the use of a phosphodiesterase inhibitor III should be seriously considered.

The enzyme phosphodiesterase III is responsible for the degradation of cyclic adenosine monophosphate (cAMP). In the heart, the increase in cAMP improves myocardial contractility and relaxation by effects on calcium influx and efflux and myofilament calcium binding. In the vasculature, the accumulation of cAMP enhances calcium extrusion across the sarcolemma, thus relaxing arterial and venous smooth muscle. Phosphodiesterase III inhibitors such as milrinone, amrinone and enoximone have been shown to enhance cardiac performance in acute heart failure [33, 34]. In addition, milrinone, amrinone and enoximone improve cardiovascular function if added to volume expansion and catecholamine treatment in patients with septic shock [35–37]. Kumer et al. have shown that the contractility of rat cardiac myocytes stimulated with epinephrine is significantly reduced in the presence of TNF-α and that this is linked with proportionally reduced cAMP generation [38]. This effect of TNF-α is diminished by the administration of increasing concentrations of PDE-III inhibitors and produces a greater peak augmentation of contractility than in control cells without TNF-α [39]. These findings support the theory that ß-adrenergic receptor impairment in septic shock leads to decreased cAMP and calcium levels and to myocardial depression and, finally, uncoupling and nonresponsiveness of β-receptors to catecholamines.

However, further studies are needed to demonstrate the impact of phosphodiesterase III inhibitors on clinical morbidity and mortality.

Vasodilators

A combination of low-dose epinephrine and nitroprusside can provide increased contractility and effective vasodilatation [40]. These therapies benefit from very rapid onset and elimination. However, nitroprusside causes venous vasodilatation, which may result in an unwanted drop in right ventricular preload. In addition, nitroprusside can also cause a ventilation/perfusion mismatch that may be reflected in systemic hypoxaemia.

Glucose, calcium and hydrocortisone replacement

It is important to maintain metabolic and hormonal homeostasis in infants and children. Glucose should be checked, because hypoglycaemia can have negative neurological consequences and might be a reversible contributor to cardiac dysfunction. Glucose should be administered rapidly in this situation. Calcium replacement should be directed at normalisation of ionised calcium levels [41]. Consideration should also be given to the diagnosis and treatment of relative adrenal insufficiency [42–44]. Adrenal insufficiency, and particularly a low aldosterone state, may be more common in children with septic shock than previously thought. Children at risk for adrenal insufficiency (Waterhouse-Friderichsen syndrome, purpura fulminans, prior steroid exposure or central nervous system disease) should be treated with hydrocortisone. There are no strict definitions, but adrenal insufficiency in the case of catecholamine-resistant septic shock is assumed at a random total cortisol concentration <496 nmol/l [16]. The appropriate dosage of hydrocortisone in children with septic shock has been poorly investigated. The stress dose is 2 mg/kg as a bolus, followed by a 2-mg/kg infusion over 24 h. The reported shock dose of hydrocortisone is 25 times the stress dose.

Mechanical support

Extracorporeal membrane oxygenation (ECMO) can be considered for refractory septic shock. Goldman et al. reported on ECMO in 12 infants and children with intractable cardiorespiratory failure caused by meningococcal disease [45]. It was found in this retrospective analysis that 7 patients had undergone ECMO support because of intractable shock within 36 h of admission to intensive care, while in the other 5 patients ECMO was indicated for intractable acute respiratory failure later in the disease. The survival rate in these patients was 66%. Brain death supervened in 2 patients, and in 2 others ECMO was discontinued at the request of the families after 72 h of support, because each of the 2 had severe limb ischaemia requiring four-limb amputation. Data released by the Extracorporeal Life Support Organization (ELSO) registry in 1997 showed that in 76 (11.6%) of 655 children with acute respiratory failure undergoing ECMO sepsis was the primary disease [46]. The survival rate was lower in children with sepsis than in children without sepsis (36.8% vs 51.6%; $p<0.02$). However, the authors conclude that systemic sepsis does not have an independent influence on survival in paediatric ECMO and that this therapy should not be withheld solely because of sepsis, although neurological complications may occur more frequently in its presence.

Conclusions

Paediatric septic shock results in myocardial dysfunction, abnormalities of vascular tone and permeability and inadequate oxygen delivery. After fluid resuscitation has been completed for the initial hyperdynamic/low systemic vascular resistance

phase, in many children the haemodynamic profile may change to one of low cardiac output with high systemic vascular resistance. This progression is of considerable importance to paediatric intensivists, because it necessitates a change in treatment strategy from vigorous fluid resuscitation and administration of α-agonist vasopressor medications to relative fluid restriction, and perhaps the administration of inotropic medications to increase myocardial contractility and vasodilators with the aim of reducing afterload.

References

1. Pollard AJ, Britto J, Nadel S et al (1999) Emergency management of meningococcal disease. Arch Dis Child 80:290-296
2. Dellinger RP (2003) Cardiovascular management of septic shock. Crit Care Med 31:946-955
3. Tabbut S (2001) Heart failure in pediatric septic shock: utilizing inotropic support. Crit Care Med 29:S231-S236
4. Jardin F, Brunney D, Auvert B et al (1990) Sepsis-related cardiogenic shock. Crit Care Med 18:1055-1060
5. Parker MM, Shelhamer JH, Bacharach SL et al (1984) Profound but reversible myocardial depression in patients with septic shock. Ann Intern Med 100:483-490
6. Parrillo JE, Burch C, Shelhamer JH et al (1985) A circulating myocardial depressant substance in humans with septic shock: septic shock patients with a reduced ejection fraction have a circulating factor that depresses in vitro myocardial cell performance. J Clin Invest 76:1539-1553
7. Cain BS, Meldrum DR, Dinarello CA et al (1999) Tumor necrosis factor-α and interleukin-1β synergistically depress human myocardial function. Crit Care Med 27:1309-1318
8. Finkel MS, Oddis CV, Jacob TD et al (1992) Negative inotropic effects of cytokines on the heart mediated by nitric oxide. Science 257:387-389
9. Thiru Y, Pathan N, Bignall S et al (2000) A myocardial cytotoxic process is involved in the cardiac dysfunction of meningococcal septic shock. Crit Care Med 28: 2979-2983
10. Silverman H, Penaranda R, Orens JB et al (1993) Impaired beta-adrenergic receptor stimulation of cyclic adenosine monophosphate in human septic shock: association with myocardial hyporesponsiveness to catecholamines. Crit Care Med 21:31-39
11. Ognibene FP, Parker MM, Natanson C et al (1988) Depressed left ventricular performance: response to volume infusion in patients with sepsis and septic shock. Chest 93:903-910
12. Ceneviva G, Paschall A, Maffei F et al (1998) Hemodynamic support in fluid-refractory pediatric septic shock. Pediatrics 102:e19
13. Cholley BP, Lang RM, Berger DS et al (1995) Alterations in systemic arterial mechanical properties during septic shock: role of fluid resuscitation. Am J Physiol 269:H375-H384
14. Feltes TF, Pignatelli R, Kleinert S et al (1994) Quantitated left ventricular systolic mechanics in children with septic shock utilizing noninvasive wall-stress analysis. Crit Care Med 22:1647-1658
15. Colan SD, Borow KM, Newmann A (1984) Left ventricular end-systolic wall stress-velocity of fiber shortening relation: a load independent index of myocardial contractility. J Am Coll Cardiol 4:715-724

16. Dellinger RP, Carlet JM, Masur H et al (2004) Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med 32:858-873
17. Rivers E, Nguyen B, Havstad S et al (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 346:1368-1377
18. Carcillo JA, Felds AI, and the Task Force Committee members (2002) Clinical practice parameters for hemodynamic support of pediatric and neonatal patients in septic shock. Crit Care Med 30: 1365-1378
19. Carcillo JA, Davis AL, Zaritsky A (1991) Role of early fluid resuscitation in pediatric septic shock. JAMA 266:1242-1245
20. Bhan NT, Phuong CXT, Kneen R et al (2001) Acute management of dengue shock syndrome: a randomized double-blind comparison of 4 intravenous fluid regimens in the first hour. Clin Infect Dis 32:204-213
21. Meadows D, Edwards JD, Wilkins RG et al (1988) Reversal of intractable septic shock with norepinephrine therapy. Crit Care Med 16:663-666
22. Bollaert PE, Bauer P, Audibert G et al (1990) Effects of epinephrine on hemodynamics and oxygen metabolism in dopamine-resistant septic shock. Chest 98:949-953
23. O´Brian A, Clapp L, Singer M (2002) Terlipressin for norepinephrine-resistant septic shock. Lancet 359:1209-1210
24. Yunge M, Petros A (2000) Angiotensin for septic shock unresponsive to noradrenaline. Arch Dis Child 82:388-389
25. Holmes CL, Patel BM, Russell JA et al (2001) Physiology of vasopressin relevant to management of septic shock. Chest 120:989-1002
26. Sharshar T, Carlier R, Blanchard A et al (2002) Depletion of neurohypophyseal content of vasopressin in septic shock. Crit Care Med 30:497-500
27. Matok I, Leibovitch L, Vardi A et al (2004) Terlipressin as rescue therapy for intractable hypotension during neonatal septic shock. Pediatr Crit Care Med 5:116-118
28. Rodriguez-Nunez A, Fernandez-Sanmartin M, Martinon-Torres F et al (2004) Terlipressin for catecholamine-resistant septic shock in children. Intensive Care Med 30:477-480
29. Peters MJ, Booth RA, Petros AJ (2004) Terlipressin bolus induces systemic vasoconstriction in septic shock. Pediatr Crit Care Med 5:112-115
30. Perkin RM, Levin DL, Webb R et al (1982) Dobutamine: a hemodynamic evaluation in children with shock. Pediatrics 100:977-983
31. Habib DM, Padbury JF, Anas NG et al (1992) Dobutamine pharmacokinetics and pharmacodynamics in pediatric intensive care patients. Crit Care Med 20:601-608
32. Martinez AM, Padbury JF, Thio S (1992) Dobutamine pharmacokinetics and pharmacodynamics and cardiovascular responses in critically ill neonates. Pediatrics 89:47-51
33. Sorenson G, Ramamoorthy C, Lynn A et al (1993) Hemodynamic effects of amrinone and colloid administration in children following cardiac surgery. J Cardiothorac Anesth 7:560-565
34. Bailey J, Miller B, Kanter K et al (1997) A comparison of the hemodynamic effects of amrinone and sodium nitroprusside in infants after cardiac surgery. Anesth Analg 84: 294-298
35. Barton P, Garcia J, Kouatli A et al (1996) Hemodynamic effects of i.v. milrinone lactate in pediatric patients with septic shock. A prospective, double-blinded, randomized, placebo-controlled, intervention study. Chest 109:1302-1312
36. Irazuzta JE, Pretzlaff RK, Rowin ME (2001) Amrinone in pediatric refractory shock: an open label pharmacodynamic study. Pediatr Crit Care Med 2: 24-28
37. Ringe HI, Varnholt V, Gaedicke G (2003) Cardiac rescue with enoximone in volume and catecholamine refractory septic shock. Pediatr Crit Care Med 4:471-475

38. Kumar A, Thota V, Dee L et al (1996) Tumor necrosis factor alpha and interleukin 1 beta are responsible for in vitro myocardial cell depression induced by human septic shock serum. J Exp Med 183: 949-958
39. Kumar A, Kosuri R, Kandula P et al (1999) Effects of epinephrine and amrinone on contractility and cyclic adenosine monophosphate generation of tumor necrosis factor alpha-exposed cardiac myocytes. Crit Care Med 27: 286-292
40. Keely SR, Bohn DJ (1988) The use of inotropic and afterload-reducing agents in neonates. Clin Perinatol 15: 467-489
41. Cardenas-Rivero N, Chernow B, Stoiko MA et al (1989) Hypocalcemia in critically ill children. J Pediatr 114: 946-951
42. Hatherill M, Tibby SM, Hilliard T et al (1999) Adrenal insufficiency in septic shock. Arch Dis Child 80:51-55
43. Joosten KFM, DE Kleijn ED, Westerterp M et al (2000) Endocrine and metabolic responses in children with meningococcal sepsis: striking differences between survivors and nonsurvivors. J Clin Endocrinol Metab 85:3746-3753
44. Kleijn DE, Joosten KFM, Van Rijn B et al (2002) Low serum cortisol in combination with high adrenocorticotrophic hormone concentrations are associated with poor outcome in children with severe meningococcal disease. Pediatr Infect Dis J 21:330-333
45. Goldman AP, Kerr SJ, Butt W et al (1997) Extracorporeal support for intractable cardiorespiratory failure due to meningococcal disease. Lancet 349:466-469
46. Meyer DM, Jesson ME, Extracorporeal Life Support Organization (1997) Results of extracorporeal membrane oxygenation in children with sepsis. Ann Thorac Surg 63: 756-761

PAEDIATRIC CRITICAL CARE

Chapter 54

Recent advances in artificial ventilation in paediatric age

G.A. Marraro

The treatment of severe lung pathology remains an arduous task for intensivists, and this is confirmed by the difficulty of treating ARDS, which is still a lung disease with a high mortality risk, even though a number of highly invasive and innovative ventilatory strategies have been applied in recent years. Since the early days of its widespread use, artificial ventilation has proved to be of undoubted value in supporting lung ventilation and improving the survival of many patients, but side effects deriving from its use have emerged progressively, particularly when inappropriate ventilatory modes are chosen or when barotrauma and infections have not been sufficiently controlled in advance.

In 2000, a large, controlled clinical trial (861 patients from 10 academic centres with 75 ICUs) demonstrated that a ventilatory strategy favouring low rather than high tidal volume was more effective in improving survival in acute lung injury and ARDS in adults [1]. This trial not only confirmed the validity of artificial ventilation in improving survival rates, but also showed that a precise ventilatory model enables practitioners to achieve better results than would be possible with a different model. The ventilatory mode applied derived from the 'open the lung and keep it open' method [2], and uses lower (6–8 ml/kg) rather than high tidal volumes (>12ml/kg) and a high respiratory rate rather than a low one in order to maintain the predetermined minute volume required to obtain adequate gas exchange [1].

A similar study in paediatric patients has not yet been undertaken and would probably not be easy to carry out owing to an inadequate number of patients affected by ARDS, difficulty in collecting data from various centres, heterogeneity in the child population, multiple co-morbidities, widely differing underlying diseases, difficulty in controlling co-interventions and, finally, the complexity of protocol standardisation. The long time that would be required to complete such a study and the extremely high costs mean it would be a daunting task.

On the other hand, if we had waited for the data deriving from a large randomised clinical trial before applying new therapies in clinical practice, the efficacy of nitric oxide and surfactant and the beneficial effects deriving from HFOV and prone positioning would not have been seen.

Even though large randomised clinical trials are not yet available (are they really necessary to ensure correct, safe treatment?) we have sufficient scientific data on and knowledge of some specific issues connected with artificial ventilation in the treatment of severe lung pathology for safe, idoneous and correct ventilatory treatment to be easily performed.

The complications induced by high transpulmonary pressures (interstitial emphysema and gross air leaks), which cause barotrauma, have been known for many years [3]. Pressure-controlled ventilation has been proposed and widely used to control peak inspiratory pressure in neonates and infants, but this method has not reduced the incidence of bronchopulmonary dysplasia (BPD), which remains a disabling complication in ventilator-treated newborns. On the one hand, the control of peak inspiratory pressure reduces the risk of lung overdistension, but on the other it does not lead to the control of tidal volume, so that the lung, with the variation of airway resistance (e.g. increase in tracheal secretions), is alternatively hypo- and hyperventilated. Such unstable ventilation can probably lead to inhomogeneous lung pathology and open the door to the development of BPD.

It has long been common knowledge that tidal volume needs to be controlled to obtain adequate ventilation, reduce hypoventilation and atelectasis formation, and increase gas exchange. The use of a ventilatory volume-controlled mode with a large tidal volume was preferred earlier during anaesthesia, for example, and also in intensive care units managed by anaesthesiologists. This ventilatory mode has since been shown to induce volutrauma, a lung injury , manifest as increased alveolar-capillary permeability caused by overdistension of the lung [4, 5]. Reduction of tidal volume and increase in respiratory rate, maintaining a stable and prefixed minute volume, is fundamental in reducing volutrauma. Advantages deriving from this method have been clearly confirmed by the ARDS-Net trial [1].

Volume-controlled ventilation

Given that appropriate tidal volumes are critical in determining adequate alveolar ventilation and also in avoiding lung injury, volume-control ventilation has been demonstrated to be the safer and preferable ventilatory mode in neonates, infants and children.

Volume-controlled ventilation with low tidal volumes (6-8 ml/kg) and high respiratory rates have been demonstrated to be more efficacious and less barotraumatic than methods with large tidal volumes (12 ml/kg). Respiratory rate has to be adapted to maintain a predetermined minute volume and normocarbia. Generally, the respiratory rate for a specific patient is increased by 20–30% of the normal range.

A protective lung strategy using volume-controlled ventilation and low tidal volume may lead to CO_2 retention. Tidal volume can be limited so that the physiological dead space fraction for each breath rises to the point at which respiratory frequency cannot be increased to normalise effective alveolar minute volume. Investigation into the effects of hypercapnia on tissue oxygenation indicates increased cardiac output, reduced arterial–venous content difference and reduced lactate production. Hypercapnic acidosis must be avoided, as it is associated with decreased myocardial contractility, cerebral vasodilatation, decreased seizure threshold and hyperkalaemia. Moderate CO_2 retention (permissive hypercapnia), if compensated and allowed to develop gradually, can be well tolerated.

Permissive CO_2 retention is contraindicated in increased intracranial pressure and in pulmonary hypertension [6–8].

A large discrepancy between set and delivered tidal volumes occurs when uncuffed endotracheal tubes using are used during volume-controlled ventilation. In order to avoid hypoventilation, this discrepancy and the poor compliance of the infantile lung relative to the ventilatory circuit compliance must be taken into account.

During ventilation the pressure–volume curve must be adjusted so as to avoid overdistension of the lung and collapse of the lung unit and alveolar collapse. PEEP has to be maintained so as to keep the pressure–volume curve above the lower inflection point, to avoid repeated alveolar collapse and reopening due to low end-expiratory volume and to maintain alveolar recruitment throughout the respiratory cycle. Peak inspiratory pressure must be maintained under the superior inflection point in order to reduce overinflation. Haemodynamic implications can be reduced by maintaining normal volaemia and avoiding unnecessary high PEEP levels.

The idea that volutrauma and barotrauma can be reduced by means of pressure-regulated, volume-controlled (PRVC) ventilation has been proposed. This method involves ventilating a constant and predetermined tidal volume, adapting the pressure continuously in order to use the minimum needed to introduce the predetermined quantity of gas according to compliance and resistance [9].

PRVC ventilation

PRVC ventilation is a mode of ventilation that delivers controlled tidal and minute volume in a pressure-limited manner using the lowest possible insufflation pressure. The gas flow is decelerated and pressure, and flow constantly vary, breath by breath, in order to achieve the preset tidal volume at the minimum peak inspiratory pressure. It is particularly useful in ventilated patients when there are rapid changes in lung compliance and airway resistance, for instance when surfactant and bronchodilators are used [9–12].

This ventilation mode can be useful:

- If compliance and resistance within the lung vary rapidly (e.g. with surfactant, theophylline or nitric oxide administration, etc.);
- To reduce high ventilatory peak pressure (e.g. in premature infants, interstitial emphysema, etc.);
- In the presence of spasm of the bronchi and bronchioles (e.g. in asthma, bronchiolitis);
- In all patients in whom PEEP levels must be reduced to avoid haemodynamic complications.

Large controlled clinical trials are required to evaluate the benefits of PRVC ventilation in acute lung pathology (difficulty in reopening consolidated areas which need high peak pressure), in ventilation of healthy lungs in comatose or deeply sedated patients (i.e., neurosurgical children) and during weaning from ventilation.

Mechanical ventilation can worsen lung injury, creating atelectasis as lung units collapse and reopen, which is known as atelectrauma [13]. The opening and closing of small airways is considered to be partly responsible for barotrauma, because it is necessary to apply high pressure to open closed lung units. The application of continuous distending positive pressure (PEEP) is thought to reduce the tendency of lung units to collapse and to recruit atelectasic or consolidated lung areas. Apart from reducing atelectasis, PEEP allows continuous distension of the lung during the entire respiratory cycle, as well as improving functional residual capacity and consequently gas exchange. The PEEP level recommended is the upper inferior inflection point of the pressure-volume curve. This point indicates the moment in which the resistance of the airways to opening has been overcome and the alveoli begin to fill.

Mechanical ventilation can lead to subtle lung injury (biotrauma) manifest in the release of inflammatory mediators which can lead to distal organ dysfunction and multiorgan failure [14, 15]. Reduction of lung stress, control of inflammation, reduction of FiO2 to the minimum compatible level and the use of protective lung strategies are fundamental to the reduction of biotrauma [16–22].

Protective lung strategy

In the mid-1980s the idea of protecting the lung and re-expanding only the nonventilating areas favoured the development of independent lung ventilation [23–25].

Although the method was never validated by large-scale controlled clinical studies, the theory behind its application attracted attention, on the one hand because of the damage that can be caused to the less pathologic lung when it is overexpanded to achieve adequate gas exchange, and on the other because of the necessity of re-opening the more pathologic lung as quickly as possible to improve gas exchange, reduce the ventilation/perfusion ratio and limit trauma to the less damaged lung [26–29].

The next step was to focus attention not only on reopening the lung, but also on keeping it open throughout the entire breathing cycle, with the aim of preventing trauma deriving from the pressure required to reopen the terminal bronchioles and overcome the shear forces that favour the onset of lung damage. The 'open up the lung and keep it open' concept [2, 30, 31] is what we can call the state-of-the-art ventilation at present. It involves the application of methods to open and recruit the lung immediately artificial ventilation is started and whenever atelectasis occurs. Once the lung has been reopened various techniques can be applied to ensure that it remains open.

Open up the lung

The recruitment of the lung involves special manoeuvres that can lead to reopening of nonventilating lung areas and improvement in oxygenation and gas exchange [32–34]. In order to obtain opening of the lung, several manoeuvres can be proposed.

1. Manual ventilation is a very simple and efficacious manoeuvre that does not require either special equipment or extra nursing. This procedure can be applied either at the start of mechanical ventilation or during the treatment. In the presence of inhomogeneous lung pathology or when the inflation pressure is not strictly controlled, overdistension of better ventilated lung units creating barotrauma (interstitial emphysema and in some cases even lung rupture) can develop. Progressive and well-controlled insufflation pressures can reduce this risk and can keep side effects to a minimum.
2. The use of a high PEEP level for a short time at the beginning of mechanical support has been proposed as an efficacious recruitment manoeuvre [35]. Reducing such a high PEEP to a useful level appears to be more effective than the direct application of the lower level considered necessary.
   It is possible to increase alveolar recruitment by lengthening the inspiratory pause during volume-controlled ventilation using a square wave. At the end of inspiration, when the flow is interrupted, delaying the beginning of the expiratory phase favours the redistribution of the gases in the alveoli, leading to progressive reopening of the collapsed alveoli. The disadvantage of this method is connected with the fact that alveolar recruitment occurs at peak inspiratory pressure, thus increasing the risk of barotrauma.
3. The possibility of applying the 'sigh' during ventilation is a current research topic, and this is indeed an option in some newer ventilators. This type of ventilation model was used in anaesthesiology until 1970 to compensate atelectasis during ventilation in surgery. An advantage deriving from this ventilatory mode is the possibility of doubling tidal volume automatically for one or more breaths. Preliminary data are promising but need clinical confirmation before the technique can be prescribed as part of normal routine [36].
4. Another good method of recruiting the lung during artificial ventilation is to place patients in the prone position. This method makes it possible to recruit the dorsal part of the lung to ventilation, to reduce ventilation/perfusion inhomogeneity and to increase secretion drainage from the dependent lung area towards the trachea and principal bronchi, where they can be more easily suctioned. An improvement of ventilation and compliance follows, which can promote better gas exchange and a reduction of FiO_2 in ventilated gases (lowering the risk of oxygen toxicity) [37–41].
5. The possibility of using bronchoalveolar lavage (BAL) in the presence of material obstructing the bronchi (e.g. cystic fibrosis, proteinosis) to remove the material and favour the reopening of collapsed lung units is well known. Encouraging results have been reported with the early treatment of chest trauma and aspiration with BAL and surfactant supplementation. Natural surfactant instillation can replace the surfactant removed during BAL and make up for the deficiency. This method seems to reduce the frequency of complications such as chemical pneumonia, which can lead to the development of ARDS [42, 43]. Controlled clinical trials are in progress to evaluate the effects of this treatment.
6. Very recently the possibility of removing pulmonary secretions during artificial ventilation or spontaneous breathing using special equipment has been demon-

strated. The removal of secretions appears to be a good way of recruiting the lung and improving gas exchange. Experience in neuromuscular patients who do not have an effective cough reflex and whose cases are frequently complicated by pneumonia or respiratory failure as a result of the inability to expel secretions, has enabled scientists to understand the importance of the removal of secretions in favouring better breathing. Several machines that mobilise secretions and simulate cough artificially are under study. At present, HFPV, high-frequency chest wall oscillation, in-exsufflation, and RTX in secretion clearance mode have been subjected to more investigation in clinical practice, and the preliminary results are really encouraging [44–50].

Keep the lung open

When the lung is open, it is necessary to keep it open during the total respiratory cycle. Ventilation-induced lung injury (VILI) is due to the shear and stretch forces necessary to reopen small airways and alveoli. The treatment recommended to obtain this result is the application of high PEEP levels when the lung is recruited, along with improvement of oxygen transport and haemodynamic implications [2, 30, 32, 35]. HFOV seems to be a good method of keeping the lung open [51–53].

High Frequency Oscillatory Ventilation

The ventilator is usually a reciprocating pump of the piston variety or a loudspeaker system driven by an electronic oscillator. Both systems generate a sinusoidal respiratory flow pattern. It follows from this that the I:E ratio is usually fixed at 1:1, although variable-ratio pumps have recently been described. The pump is used to produce a reciprocating flow in the airways, whilst an auxiliary gas flow – bias flow – is used to clear the extracted carbon dioxide and to provide fresh gases to the system. These systems behave as a T-piece circuit, and the efficiency of carbon dioxide removal is a function of the magnitude of the bias flow.

A number of mechanisms have been proposed to explain the gas exchange in HFOV. Direct alveolar ventilation, asymmetrical velocity profiles, Taylor dispersion, pendeluft, cardiogenic mixing, accelerated diffusion and acoustic resonance appear to participate in gas exchanges both individually and/or together [54, 55].

The advantages of HFOV are the maintenance of open airways; smaller phase volume and pressure change; gas exchange at significantly lower airway pressures; less involvement of the cardiovascular system; and less depression of endogenous surfactant production. HFOV is recommended in order to reduce lung barotrauma and consequent lung injury in nonhomogeneous lung pathology, in air leaks, in persistent pulmonary hypertension of the newborn (PPHN) and in the ventilation of premature babies [56-58].

The contraindications to HFOV are pulmonary obstruction from fresh meconium aspiration, inhalation of foreign matter, BPD, RSV bronchiolitis and intracranial haemorrhage.

The complications of HFOV are due to lung overinflation in the case of obstructive lung disease, intracranial haemorrhage, reduction in heart rate (from increased vagal activity), development of BPD, necrotising tracheobronchitis, increased permeability of lung epithelium and insufficient humidification of tracheobronchial secretions, which can lead to bronchiolar obstruction [59–61].

A limited number of large clinical trials on the use of HFOV in infants and children have been published, but they have demonstrated the benefits deriving from reopening the closed alveoli and keeping them open, and reducing air leak. There are no data from randomised controlled trials supporting the use of rescue HFOV in term or near-term infants with severe pulmonary dysfunction. The Cochrane Review [62] showed no evidence of a reduction in mortality at 28 days, in the number of children requiring extracorporeal membrane oxygenation, in days spent on a ventilator, days receiving oxygen or days in hospital.

Conclusions

Many things have changed in recent years and are still changing in the ways of ventilating and assisting paediatric patients affected by severe respiratory failure [63].

Starting from 2000, protective ventilation has played a fundamental part in reducing *barotrauma*, *volutrauma*, *atelectrauma* and *biotrauma*, which are implicated in unsuccessful treatment. This mode of ventilation became indispensable after the ARDS-Net trial was published [1] and has led to a great improvement in the prognoses of mechanically ventilated patients, and specifically of those affected by severe ARDS.

The improvement obtained with protective ventilation could cause suspicion that certain collateral therapies (e.g. iNO, surfactant) may have benefited indirectly from this new way of ventilating. The improvement in survival is probably due to better overall treatment of patients and greater attention being paid to the ventilation method used [64, 65]. Continuous mobilisation of patients (e.g. prone positioning) in order to recruit dependent lung areas and avoid retention of secretions, the use of methods to improve cough, naturally or artificially, to eliminate endopulmonary secretions more easily, earlier application of mechanical ventilation, and the reduction of deep sedation and muscle paralysis, which cancel cough reflexes and allow secretion accumulation in dependent lung areas, from which they are difficult to remove, are taking on a fundamental role in the treatment of children who are affected by respiratory failure and artificially ventilated, which had been somewhat overlooked until recently.

References

1. Acute Respiratory Distress Syndrome Network (2000) Ventilation with lower tidal volume as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 342:1301-1308
2. Lachmann B (1992) Open up the lung and keep the lung open. Intensive Care Med 18:319-321
3. Dreyfuss D, Saumon G (1998)Ventilator-induced lung injury:lessons from experimental studies (state of art). Am J Respir Crit Care Med 157:294-330
4. Dreyfuss D, Soler P, Basset G et al (1988) High inflation pressure pulmonary edema: respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. Am Rev Respir Dis 137:1159-1164
5. Auten RL, Vozzelli M, Clark RH (2001) Volutrauma. What is it, and how do we avoid it? Clin Perinatol 28:505-515
6. Hickling K, Joyce C (1995) Permissive hypercapnia in ARDS and its effect on tissue oxygenation. Acta Anaesthesiol Scand 39:201-208
7. Woodgate PG, Davies MV (2001) Permissive hypercapnia for the prevention of morbidity and mortality in mechanically ventilated newborn infants. Cochrane Review. Cochrane Database Syst Rev 2:CD002061
8. Feihl F, Perret C (1994) Permissive hypercapnia: how permissive should we be? Am J Respir Crit Care Med 150:1722-1737
9. Marraro G, Mannucci F, Galbiati AM (1994) The advantages of a new mode of artificial ventilation: pressure-regulated volume controlled (PRVC) ventilation. Pediatr Res 35, 4 Suppl 344A:2047
10. Marraro G, Casiraghi G, Galbiati AM (1995) A study of pressure regulated volume control ventilation in natural surfactant treated infants with RDS. Pediatr Res 4 Suppl 223A:1321
11. Esteban A, Frutos F, Tobin MJ et al (1995) A comparison of four methods of weaning from mechanical ventilation. N Engl J Med 332:345-350
12. Hazelzet JA, Petru R, Ouden CD et al (1993) New modes of mechanical ventilation for severe respiratory failure. Crit Care Med 21(9 Suppl):S366-S367
13. Slutsky AS (1999) Lung injury caused by mechanical ventilation. Chest 116 (Suppl 1):S9-S15
14. Tremblay L, Valenza R, Ribeiro SP et al (1997) Injurious ventilatory strategies increase cytokines and c-fos mRNA expression in an isolated rat lung model. J Clin Invest 99:944-952
15. Ranieri VM, Suter PM, Tortorella C et al (1999) Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. JAMA 282:5-61
16. Ranieri VM, Giunta F, Suter PM et al (2000) Mechanical ventilation as a mediator of multisystem organ failure in acute respiratory distress syndrome. JAMA 284:43-44
17. Coalson JJ, Kuehl TJ, Prihoda TJ et al (1988) Diffuse alveolar damage in the evolution of bronchopulmonary dysplasia in the baboon. Pediatr Res 24:357-366
18. de Lemos RA, Coalson JJ, Gerstmann DR et al (1987) Oxygen toxicity in the premature baboon with hyaline membrane disease. Am Rev Respir Dis 136:677-682
19. Tin W (2004) Optimal oxygen saturation for preterm babies:do we really know? Biol Neonate 85:319-325
20. Van Kaam AH, Dik WA, Haitsma JJ et al (2003) Application of the open-lung concept during positive-pressure ventilation reduces pulmonary inflammation in newborn piglets. Biol Neonate 83:273-280

21. Van Kaam AH, Haitsma JJ, De Jaegere A et al (2004) open lung ventilation improves gas exchange and attenuates secondary lung injury in a piglet model of meconium aspiration. Crit Care Med 32:443-449
22. Von der Hardt K, Kandler MA, Fink L et al (2004) High frequency oscillatory ventilation suppress inflammatory response in lung tissue and microdissected alveolar macrophages in surfactant depleted piglets. Pediatr Res 339-346
23. Marraro G (1987) Synchronized independent lung ventilation in pediatric age. ACP Applied Cardiopulm Pathophys 2:283-288
24. Marraro G (1992) Simultaneous independent lung ventilation in pediatric patients. Crit Care Clin 8:131-145
25. Marraro G (1994) Selective endobronchial intubation in paediatrics: the Marraro Paediatric Bilumen Tube. Paediatr Anaesth 4:255-258
26. Luchetti M, Marraro G, Galassini E (2003) Independent lung ventilation as a protective strategy in unilateral lung disease in children. Biocybernet Biomed Eng 23: 77-87
27. Turner MWH, Buchanan CCR, Brown SW (1997) Paediatric one lung ventilation in the prone position. Paediatr Anaesth 7:427-429
28. Pawar DK, Marraro GA (2004) One lung ventilation in infants and children. Paediatr Anaesth (in press)
29. Hammer GB, Engel TP (2004) Single lung ventilation in children. Available online at: http://gasnet.med.yale.edu/slvc/index.php
30. Haitsma JJ, Lachman RA,.Lachmann B (2003) Open lung in ARDS. Acta Pharmacol Sin 24:1304-1307
31. Rimensberger PC, Pache JC, McKerlie C et al (2000) Lung recruitment and lung volume maintenance: a strategy for improving oxygenation and preventing lung injury during both conventional mechanical ventilation and high-frequency oscillation. Intensive Care Med 26:745-755
32. Rimensberger PC, Cox PN, Frndova H et al (1999) The open lung during small tidal volume ventilation: concepts of recruitment and "optimal" positive end-expiratory pressure. Crit Care Med 27:1946-1952
33. Hess DR, Bigatello LM (2002) Lung recruitment: the role of recruitment maneuvers. Respir Care 47:308
34. Tusman G, Bohm SH, Tempra A et al (2003) Effects of recruitment maneuver on atelectasis in anesthetized children. Anesthesiology 96:14-32
35. Foti G, Cereda M, Sparacino ME et al (2000) Effects of periodic lung recruitment maneuvers on gas echange and respiratory mechanics in mechanically ventilated adute respiratory distress syndrome (ARDS) patients. Intensive Care Med 26:501-507
36. Pelosi P, Bottino N, Chiumello D et al (2003) Sigh in supine and prone position during acute respiratory distress syndrome. Am J Respir Crit Care Med 167:521-527
37. Pelosi P, Brazzi L, Gattinoni L (2002) Prone position in acute respiratory distress syndrome. Eur Respir J 20:1017-1028
38. Kornecki A, Frndova H, Coates AL et al (2001) A randomized trial of prolonged prone positioning in children with acute respiratory failure. Chest 119:211-218
39. Curley MA, Thompson JE, Arnold JH (2000) The effects of early and repeated prone positioning in pediatric patients with acute lung injury. Chest 118:156-163
40. Numa AH, Hammer J, Newth CJ (1997) Effect of prone and supine positions on functional residual capacity, oxygenation, and respiratory mechanics in ventilated infants and children. Am J Respir Crit Care Med 156:1185-1189
41. Matthews BD, Noviski N (2001) Management of oxygenation in pediatric acute hypoxemic respiratory failure. Pediatr Pulmonol 32:459-470

42. Marraro G, Pesci A, Croce AM et al (2004) Broncholaveolar lavage (BAL) with porcine derived surfactant in ARDS: hemodynamic and gas excgange assessment. Appl Cardiopulm Pathophys 13:60-61
43. Marraro G, Pesci A, Croce AM et al (2004) Inflammation marker evaluation during and after bronchlaveolar lavage (BAL) with porcine drived surfactant in ARDS triggered by aspiration and chest trauma. Appl Cardiopulm Pathophysiol 13:61-62
44. Ben-Abraham R, Gur I, Bar-Yshay E et al (2004) Application of a cuirass and institution of biphasic extra-thoracic ventilation by gear-protected physicians. J Crit Care 19:36-41
45. Hill NS (2002) Ventilatory management for neuromuscular disease. Semin Respir Crit Care Med 23:293-305
46. Gomez-Merino E, Sancho J, Marin J et al (2002) Mechanical insufflator-exsufflator. Am J Phys Med Rehabil 81:579-583
47. Toussaint M, De Win H, Steens M et al (2003) Effect of intrapulmonary percussive ventilation on mucus clearance in duchenne muscular dystrophy patients: a preliminary report. Respir Care 48:940-947
48. Varekojis SM, Douce FH, Flucke RL et al (2003) A comparison of the therapeutic effectiveness of and preference for postural drainage and percussion, intrapulmonary percussive ventilation, and high-frequency chest wall compression in hospitalized cystic fibrosis patients. Respir Care 48:24-28
49. Deakins K, Chatburn RL (2002) A comparison of intrapulmonary percussive ventilation and conventional chest physiotherapy for the treatment of atelectasis in the pediatric patient. Respir Care 47:1162-1167
50. Langenderfer B (1998) Alternatives to percussion and postural drainage. A review of mucus clearance therapies: percussion and postural drainage, autogenic drainage, positive expiratory pressure, flutter valve, intrapulmonary percussive ventilation, and high-frequency chest compression with the ThAIRapy Vest. J Cardiopulm Rehabil 18:283-289
51. Imai Y, Nakagawa S, Ito Y et al (2001) Comparison of lung protection strategies using conventional and high-frequency oscillatory ventilation. J Appl Physiol 91:1836-1844
52. Dembinski R, Max M, Bensberg R et al (2002) High-frequency oscillatory ventilation in experimental lung injury:effects on gas exchange. Intensive Care Med 28:768-774
53. Pillow JJ, Sly PD, Hantos Z (2004) Monitoring of lung volume recruitment and derecruitment using oscillatory mechanics during high-frequency ventilation in the preterm lamb. Pediatr Crit Care Med 5:172-180
54. Arnold JH (1996) High frequency oscillatory ventilation: theory and practice in paediatric patients. Paediatr Anaesth 6:437-441
55. Hess D, Mason S, Branson R (2001) High-frequency ventilation design and equipment issues. Respir Care Clin N Am 7:577-598
56. Habib RH, Pyon KH, Courtney SE (2002) Optimal high-frequency oscillatory ventilation settings by nonlinear lung mechanics analysis. Am J Respir Crit Care Med 166:950-953
57. Arnold JH, Anas NG, Luckett P et al (2000) High-frequency oscillatory ventilation in pediatric respiratory failure: a multicenter experience. Crit Care Med 28:3913-3919
58. Calvert S (2002) Prophylactic high-frequency oscillatory ventilation in preterm infants. Acta Paediatr Suppl 91:16-18
59. Clark RH, Wiswell TE, Null DM et al (1987) Tracheal and bronchial injury in high-frequency oscillatory ventilation compared with conventional positive pressure ventilation. J Pediatr 111:114-118
60. Mammel MC, Ophoven JP, Lewallen PK et al (1991) Acute airway injury during high-frequency jet ventilation and high-frequency oscillatory ventilation. Crit Care Med 19:394-398

61. Man GCW, Ahmed IH, Logus JW et al (1987) High-frequency oscillatory ventilation increases canine pulmonary epithelial permeability. J Appl Physiol 63:1871-1876
62. Henderson-Smart DJ, Butha T, Cools F et al (2003) Elective HFOV vs conventional ventilation for acute pulmonary dysfunction in preterm infants. Cochrane Database Syst Rev 2003(4):CD000104
63. Marraro G (2004) Do we really need more confirmation on the usefulness of inhaled nitric oxide in children's acute respiratory distress syndrome? Pediatr Crit Care Med 5: (in press)
64. Slutsky AS, Ranieri VM (2000) Mechanical ventilation: lessons from the ARDSNet trial. Respir Res 1:73-77
65. Marraro GA (2003) Innovative practices of ventilatory support with pediatric patients. Pediatr Crit Care Med 4:8-20

Chapter 55

Complications in paediatric regional anaesthesia

G. Ivani, V. Mossetti

Paediatric regional anaesthesia has become accepted throughout the world during the last two decades: axial blocks, especially caudal ones, are now routinely practised all over the world; several factors have contributed to the wide acceptance, but the main reason is the documentation of the safety and efficacy of this mode of anaesthesia in books, papers published in peer-reviewed journals and presented at meeting and reports from daily clinical practice. We can now say that paediatric regional anaesthesia is one of the most effective methods for perioperative analgesia and pain control. Many factors contribute to the wide use of regional anaesthesia in children: the perception of pain and the subsequent necessity for adequate pain relief, the demonstration of the efficacy of regional anaesthesia in stress control and the large amount of information emerging from congresses, books and papers on this topic; indeed, industry has helped paediatric anaesthesiologists by producing what we needed and asked for: new, dedicated tools and safer drugs. In parallel with this increasing use of regional techniques, an increasing number of papers reporting complications have appeared in the medical literature. In conclusion, we can say that safety depends on experience and on adequate guidelines, but also on the drugs used, whose main characteristic must be reduced toxicity, and on the multimodal approach that allows the use of multiple drugs in low doses or concentrations for a synergistic action.

Data from the literature

Although many complications have been occasionally reported after all peripheral or axial blocks, few precise data are available on the epidemiology and morbidity of regional anaesthesia in children. The study of Morray et al., examining the ASA database from 1985 to 1992, found a total of 2,400 claims, including 238 (10%) paediatric cases. The mortality rate of 50% among the paediatric cases was higher than that in the adult cases (35%), but only 7 children had received a regional block.

Fox et al. [1] examined the 160 incidents associated with regional anaesthesia amongst the first 2,000 incidents reported to the Australian Incident Monitoring Study. The report concerned 83 epidural anaesthesias, 42 spinal, 14 brachial plexus blocks, 4 intravenous local anaesthesias, 3 ocular blocks and 14 local infiltrations. There were 24 drug errors, 10 of which involved the wrong drug and 4 inappropriate use, and all the rest involved problems specific to regional anaesthesia.

In 1993–1994 The French-Language Society of Paediatric Anaesthetists (ADARPEF) designed a blinded 1-year prospective study to evaluate precisely which regional techniques were used in children and what complications were encountered [2]. Data from 85,412 paediatric anaesthesia cases were collected, including 24,409 regional anaesthesias 15,013 of which were central blocks and 9,396, peripheral nerve blocks. A total of 23 incidents were reported, all during central block procedures (none following peripheral nerve blocks), most of these being dural puncture (8 cases), inadvertent intravascular injection (6), technical problems (3), overdosage (2), arrhythmias (2), transient paraesthesia (1), apnoea after morphine overdose (1), and a transient skin lesion (1). This study, involving 38 institutions from three different countries, is interesting in that it established the overall safety of regional anaesthesia in paediatrics (23 incidents with no sequelae, no deaths and no legal implications among 24,409 procedures). It also showed that central blocks, especially caudal central blocks, were not as simple and safe as commonly believed, whereas, in contrast, peripheral nerve blocks, which were practised even in the youngest patients (premature infants), were safer than commonly stated. Two additional findings were important: (1) half of all complications were directly related to inappropriate performance of the block; and (2) in most cases adverse effects arose with very common techniques in healthy patients, whereas the most hazardous techniques (thoracic epidural, spinal anaesthesia in ex-premature infants) did not lead to complications. This means that with great care, complications can be virtually completely avoided.

After a French prospective survey involving 40,240 anaesthetics in 440 institutions chosen at random, 27 major complications causally related to anaesthesia and occurring within the first 24 h were reported. The overall risk of complications was found to be significantly higher in infants than in children. Moreover, the life-threatening complications in infants occurred during maintenance of anaesthesia and were due to respiratory failure, while in children accidents were observed equally during induction, maintenance of and recovery from anaesthesia, and circulatory failure was as frequent as respiratory failure as a cause of life-threatening complications.

In Italy the SIAARTI group [3] reported a survey of paediatric anaesthesia and surgery outcome in 9,289 patients. In all 3.4% of patients experienced complications, 21 of which were severe and 7 resulted in death.

In a recent survey [4], the incidence of minor sequelae following general anaesthesia in children was found to be higher than previously reported. The most common adverse effects recorded were nausea (48%), vomiting (35%), sore throat (31%), visual disturbances (26%), inadequate analgesia (20%) and headache (20%).

The comparison of mortality and morbidity rates of different types of anaesthetic regimen is not an easy task, and it would be imprudent to conclude that regional anaesthetic techniques, used either alone or in association with light general anaesthesia, were far safer than deep general anaesthesia: patient selection might differ considerably, in addition to which some surgical procedures cannot be performed under regional anaesthesia alone. When appropriate, regional anaesthetic techniques used either alone, which is a clearly established practice in the case of spinal anaesthesia in infants born prematurely, or in combination with

light general anaesthesia could reduce the incidence of respiratory failure, which is the main cause of severe complications in infants [5].

In addition, it should be kept in mind that the incidence of haemodynamic disturbances caused by central blocks is virtually nil in infants and children up to 8 years of age and that circulatory failure is a major cause of anaesthetic-related complications in children.

Complications of a regional block

Several categories of complications have been reported following regional block procedures. Some are related to the performance of the block technique itself: these are the true complications of regional anaesthesia. Other complications can result from poor selection, inappropriate environmental conditions concerning safety precautions and inadequate monitoring of patients (especially during the postoperative period). These complications are entirely avoidable.

When regional anaesthesia is to be induced in children, we must consider two kind of problems: problems unique to the paediatric population, and problem that are common to both children and adults.

Problems unique to children

Small dimensions. The first and obvious anatomical difference between adults and children is the size of the patient, which means that practitioners must move slowly in locating peripheral nerves or central structures and use microadjustments for precision. In newborns and infants, for instance, there is often less than 1 cm between sacral hiatus and dural sac and between skin and epidural space. The small size of the children leads to two kind of complications: increasing failure rate and greater risk of close structure injury. These two points require a good knowledge of paediatric anatomy and the use of adequate instruments [6, 7]. Consideration of the failure/complication rate in the large ADARPEF survey of shows that 50% of complications are ascribed to wrong equipment [2]. Therefore, the needles should be the shortest that can easily reach the nerve to be blocked; short and short bevelled caudal needles, short Tuohy needles, small catheters, use of a nerve stimulator and short insulated needles for peripheral blocks are all mandatory for a safe performance. Despite the potential difficulties that can arise from the anatomical differences in children, the anatomy of the developing child also has advantages. One such advantage is the ease with which nerves are blocked by local anaesthetics, which is due to their thin myelin sheaths, small fibre diameter, and short internodal distances. This allows production of an adequate surgical block with lower concentrations of local anaesthetics in infant and younger children. Other anatomical advantages in paediatric patients are the loose connective tissue around neuroaxial structures centrally, and nerve sheaths that are only loosely attached to the nerve trunks peripherally. These factors should lead to an improved spread of local anaesthetic without the dense anatomical barriers that may be present in adults.

Reduced emunctory functions in newborns and infants. The physiology of newborn and infants differs from that of older children and adults: metabolism and clearance of drugs, including local anaesthetics, are reduced. In small children there is a lower level of alpha-1-glycoprotein, which means a higher fraction of free local anaesthetic; in addition, there is considerable individual variation and little information is available on diffusion, protein binding and local metabolism; and local spread is easier in children and fat is less dense. Therefore, we have a narrow therapeutic window and increased toxicity. Strict adherence to drugs guidelines is essential to avoid overdosage, both with single-shot and with continuous infusion [8].

Owing to their pharmacological effects, local anaesthetics have potential cerebral and cardiac toxicity, which becomes clinically evident in the case of inadvertent intravascular injection, massive overdose or accumulation (continuous infusion of a normal dose of local anaesthetic). These risks are real and can be minimized only with adequate monitoring throughout performance of the block. Moreover, the availability of new local anaesthetics, e.g. levoenantiomers such as ropivacaine and levobupivacaine, can make regional anaesthesia safer, and the addition of such adjuvants as clonidine and ketamine contribute to the reduction of risks connected with toxicity, since when these drugs are used it is possible to reduce the concentration of local anaesthetics [9–13].

In order to reduce these kind of complications it is mandatory to follow guidelines using safer drugs and adjuvants.

Needs of unconscious children. The persisting story in the last decade of the twentieth century about safety of a block in an anaesthetised child is probably really over, and now, early in the new century, we can say that performance of a block is safer in a lightly anaesthetised child than in an awake child (risk of dural puncture, spinal cord damages, pain, fear). The concern that combined regional and general anaesthesia could aggravate the risks is based on adult data. In children there is evidence that combination of the two techniques decreases the risks associated with either when used in isolation. Obviously deep anaesthesia or heavy sedation should be avoided, because any warning signals that something is going wrong could then easily be missed. Light general anaesthesia without muscle relaxation or narcotics guarantees immobility and avoids the dangerous effects related to respiratory and circulatory failure.

Problems that are the same as in adults

These are complications that can occur during the performance of regional anaesthesia that are not related to the patient's age. There are four categories of complications that can be connected with regional techniques: (1) local complications, which are related to the devices used, the absence of techniques to prevent bacterial contamination or local toxicity of the solution administered; (2) focal neurological complications, which result from an unusual spread of the solution injected or from distant neurological consequences of local lesions (vascular or traumatic); (3) regional complications, which are directly related to the pharma-

codynamic effects of the local anaesthetic used (nerve blockade, changes in local vascularity), whether or not it has been injected into the desired anatomical space; (4) general or systemic complications due either to inadvertent intravascular injection or to massive overdosage.

Local complications

a) Damage to blood vessels and compressive haematomas. These lesions involve blood vessels, potentially resulting in a compressive haematoma, and are probably the most feared complication of epidural and spinal anaesthesia, because they can lead to definitive paraplegia. Diagnosis requires urgent investigations such as MRI or CT scan before emergency surgery is performed. The type of the needle directly influences the rate of vascular puncture at epidural levels. Damage to arteries can occur during peripheral and plexus nerve blocks, and presenting symptoms may be delayed by several hours.
b) Local complications attributable to the technique of nerve and space localisation. The technique used to localise the nerve trunk or the epidural space involves its own risks: electrical damage to the nerve if an inappropriate nerve stimulator is used, dilution and increased volume of local anaesthetic when using the fluid detection of epidural space, gas embolism when using the gas detection of the epidural space.
c) Use of wrong solutions. This complication can easily be avoided by careful attention to the vials and syringes used. A simple and very effective way to prevent such errors is to use a specific cart for regional block procedures.
d) Bacterial contamination. During the performance of any type of block, the child concerned is exposed to bacterial contamination. The most serious problems are those encountered with central block procedures, and complications such as epidural abscess, meningitis, radiculopathies have all been reported. The use of a bacterial filter is extremely effective in preventing bacterial contamination of epidural or peripheral catheters.
e) Catheter-related complications. Placing a catheter both in the epidural space and in a peripheral nerve has been associated with several complications, the most common being misplacement, kinking, withdrawal and section of the catheter.
f) Failure of the block. Failure of the technique also has to be regarded as a complication, because it increases the overall morbidity by the need for additional anaesthetic techniques. The failure rate of any technique decreases with practice, but even the most experienced anaesthetist is occasionally forced to abandon a technique for various reasons.

Focal complications

a) Focal complications related to loss of resistance technique. The loss of resistance technique used to localise the epidural space has been implicated in several focal complications when air was the medium injected. Some were minor, such as patchy anaesthesia due to epidural bubbles, whilst others were serious and

even life-threatening, such as lumbar compression, subcutaneous cervical emphysema and venous air embolism. This severe complication has been reported in paediatric cases [14–16] even with use of the hanging drop method [17]. Because of these complications, and also because it causes dilution of local anaesthetics and increased spread of solution and makes it difficult to diagnose inadvertent dural penetration, some authors have suggested abandoning the fluid technique [18]. In children the loss of resistance technique should be applied with a small volume of air (1 ml) [19].

b) Postdural puncture headache. This complication seems to be rare in paediatric patients.

Regional complications

a) Hypotension. Sympathetic blockade caused by the local anaesthetic is the most frequent immediate cause of hypotension, which is uncommon in children under 8 years of age and is moderate in degree even in adolescents [20]. The reasons for this are still unknown: the immaturity of the autonomic nervous system has always been and still is considered the main reason, but the small proportion of blood sequestered in the lower limbs is also important, as is a smaller reaction to sympathetic blockade [21].
b) Respiratory failure. Intercostal muscle paralysis can seriously impair breathing if the upper limit of the block is above T-4, especially in a child who already has some degree of respiratory distress. In a normal child, however, respiratory depression does not occur unless the block extends up to the cervical dermatomes and paralyses the diaphragm. This complication can occur following administration of excessive doses or volumes of the local anaesthetic, especially via the thoracic epidural route or following inadvertent intrathecal injection. Immediate tracheal intubation and mechanical ventilation will maintain the vital functions until spontaneous breathing is restored.
c) Urinary retention. Opioids used in the epidural or intrathecal space can cause urinary retention. Bladder catheterisation is frequently necessary to avoid this adverse effect.
d) Total spinal anaesthesia. In the case of inadvertent perforation of the dura mater there is a danger that some or all of the local anaesthetic will be injected into the subarachnoid space, resulting in extensive spinal anaesthesia; the main consequence of this is respiratory arrest within a few seconds.
e) Inadvertent subcutaneous or intramuscular injection. This complication can occur with any type of block procedure, but happens most commonly when the caudal approach is used. Injection of the local anaesthetic subcutaneously would only lead to failure of the technique.

Systemic complications

a) Central nervous system and cardiac toxicity. Owing to their pharmacological effects local anaesthetics have potential cerebral and cardiac toxicity, which

becomes clinically evident in the case of inadvertent intravascular injection, massive overdose or accumulation (continuous infusion of normal dose of local anaesthetic). The availability of new local anaesthetics, levoenantiomers such as ropivacaine and levobupivacaine, can reduce this risk thanks to the reduced toxicity of these two drugs.

b) Allergic reactions. Allergy to local anaesthetics is rare, especially with preservative-free amino-amides.

Conclusions

Regional anaesthesia is a very effective way of providing effective analgesia to paediatric patients. Most of the techniques currently available are both easy and safe, which allows their extensive use in children. However, like all powerful therapies, regional block procedures are not free of adverse effects; the potential for complications must be carefully checked preoperatively. Selection of local anaesthetics, insertion routes and block procedures in association with appropriate and careful monitoring would prevent any major undesirable issues and allow regional anaesthesia to be a safe and effective tool for use in overcoming pain with minimal morbidity.

References

1. Fox MA, Webb RK, Singleton R et al (1993) The Australian Incident Monitoring Study. Problems with regional anaesthesia: an analysis of 2000 incident reports. Anaesth Intensive Care 21:646-649
2. Giaufré E, Dalens B, Gombert A (1993) Epidemiology and morbidity of regional anaesthesia in children. A one-year prospective survey of the French Language Society of Paediatric Anaesthesiologists (ADARPEF). Anesth Analg 83:904-912
3. Bonoli P, Grillone G, Fossa S et al (1995) Le complicanze in anestesia pediatrica. A cura e per l'iniziativa del gruppo di studio SIAARTI per l'anestesia e la terapia intensiva in età infantile. Minerva Anestesiol 61:115-125
4. Selby IR, Rigg JD, Faragher B (1996) The incidence of minor sequelae following anaesthesia in children. Paediatr Anaesth 6:293-302
5. Tiret L, Nivoche Y, Hatton F (1988) Complications related to anaesthesia in infants and children: a prospective study of 40240 anaesthetics. Br J Anaesth 61:263-269
6. Ivani G (ed) (2001) Paediatric regional anaesthesia. A practical approach. SEE, Florence
7. Dalens B (1993) Anesthésie locorégionale de la naissance à l'age adulte. Pradel, Paris
8. Ivani G, Conio A, Papurel G et al (2001) 1000 consecutive blocks in children: how to manage them safely. Reg Anesth Pain Med 26:93-94
9. Ivani G, Lampugnani E, Torre MA (1998) Comparison of ropivacaine with bupivacaine for paediatric caudal block. Br J Anaesth 81:247-248
10. Bosemberg AT, Thomas J, Lopez T et al (2001) Plasma concentration of ropivacaine following a single-shot caudal block of 1, 2 or 3 mg/kg in children. Acta Anaesthesiol Scand 45:1276-1280
11. Dalens B, Ecoffey C, Joly A et al (2001) Pharmacokinetics and analgesic effect of

ropivacaine following ilioinguinal/iliohypogastric nerve block in children. Paediatr Anaesth 11:415-420
12. Ivani G, De Negri P, Conio A et al (2002) Comparison of racemic bupivacaine, ropivacaine and levobupivacaine for paediatric caudal anaesthesia. Effects on postoperative analgesia and motor blockade. Reg Anesth Pain Med 27:157-161
13. De Negri P, Ivani G, Visconti C et al (2001) The dose-response relationship for clonidine added to a postoperative continuous epidural infusion of ropivacaine in children. Anesth Analg 93:71-76
14. Guinard JP, Borboen M (1993) Probable venous air embolism during caudal anesthesia in a child. Anesth Analg 76:1134-1135
15. Schwartz N, Eisenkraft JB (1993) Probable venous air embolism during epidural placement in an infant. Anesth Analg 76:1136-1138
16. Sethna NF, Berde CB (1993) Venous air embolism during identification of the epidural space. Anesth Analg 76:925-927
17. Jackson KE, Rauck RL (1991) Suspected venous air embolism during epidural anaesthesia. Anesthesiology 74:46-49
18. Goldman LJ (1995) Complications in regional anaesthesia. Paediatr Anaesth 5:3-9
19. Busoni P, Messeri A (1995) Loss of resistance technique to air for identifying the epidural space in infants and children. Use an appropriate technique! Paediatr Anaesth 5:396-399
20. Dohi S, Naito H, Takahashi T (1979) Age-related changes in blood pressure and duration of motor block in spinal anaesthesia. Anaesthesiology 50: 319-323
21. Duckles SP, Banner W Jr (1984) Changes in vascular smooth muscle reactivity during development. Annu Rev Pharmacol Toxicol 24:65-93

Chapter 56

Home ventilation in paediatric patients with chronic respiratory failure

B. Fauroux

Noninvasive positive pressure ventilation (NPPV) is a promising technique in children. First, a number of diseases leading to chronic respiratory failure in childhood, such as neuromuscular diseases, abnormalities of the airways, the chest wall and/or lungs, or disorders of ventilatory control, are primarily disorders that lead to alveolar hypoventilation, which can be improved by a ventilatory assistance. As such, oxygen therapy *alone* is not only usually ineffective in relieving symptoms, but has also been shown to be dangerous, and it can lead to a marked acceleration of carbon dioxide (CO_2) retention [1-3]. Secondly, by definition, NPPV is a noninvasive technique that can be applied on demand, and preferentially at night, causing much less morbidity, discomfort and disruption to social and family life than a tracheostomy.

Nonetheless, NPPV is probably underused in children because its application is technically more difficult in infants and young children. Few physiological studies have been performed in this age group; the optimal ventilatory mode and setting for each medical condition in which it could be used have not been defined; and the criteria that justify the initiation of NPPV are most often based on consensus reports focused on neuromuscular diseases [4-6]. Several recent physiological studies do, however, provide a rationale for NPPV in some paediatric diseases that are responsible for alveolar hypoventilation [7, 8].

Home use of NPPV has become much more widespread in recent years. We will discuss the different paediatric conditions for which NPPV could be proposed, the potential benefits of NPPV, and the practical organisation of home care in the young patients concerned.

Paediatric conditions that can be improved by NPPV

The ability to sustain spontaneous ventilation can be viewed as a balance between neurological mechanisms controlling ventilation together with ventilatory muscle power on one hand and the respiratory load, determined by lung, thoracic and airway mechanics, on the other (Fig. 1). Significant dysfunction of any of these three components of the respiratory system may impair the ability to take efficacious breaths spontaneously. In normal children, central respiratory drive and ventila-

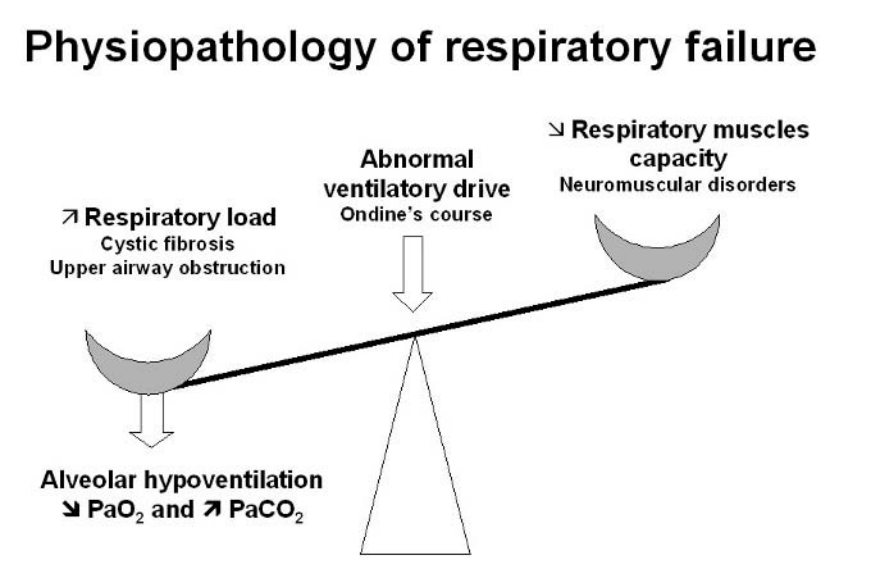

Fig.1. Spontaneous ventilation is the result of a balance between neurological mechanisms controlling ventilation together with ventilatory muscle power on one side, and the respiratory load, determined by lung, thoracic and airway mechanics, on the other. If the respiratory load is too high and/or ventilatory muscle power or central respiratory drive is too low, ventilation may be inadequate, resulting in alveolar hypoventilation with hypercapnia and hypoxaemia

tory muscle power exceed the respiratory load, and they are thus able to sustain adequate spontaneous ventilation. However, if the respiratory load is too high and/or ventilatory muscle power or central respiratory drive is too low, ventilation may be inadequate, resulting in hypercapnia. Chronic ventilatory failure, then, is the result of an imbalance that cannot be spontaneously corrected in the respiratory system, in which ventilatory muscle power and central respiratory drive are inadequate to overcome the respiratory load. If these abnormalities cannot be corrected by medical treatment, the child will benefit from long-term ventilatory support.

Disorders characterised by a ventilatory muscle weakness

In most cases, the respiratory muscles are not spared in patients with a neuromuscular disease. In neuromuscular disorders, elastic load and respiratory muscle weakness are responsible for a rapid shallow breathing leading to chronic CO_2 retention [9]. Ventilatory muscle weakness may be present at birth (spinal muscular atrophy), develop later in the course of the disease (Duchenne muscular dystrophy), or be acquired (myopathy, spinal cord injury). Generally, respiratory muscle weakness involves inspiratory muscle weakness, which results in inability to inspire fully with consequent hypoventilation resulting in inadequate gas exchange.

Expiratory muscle weakness is frequently observed, causing an inability to cough and predisposing to pulmonary infection and recurrent atelectasis. Some co-morbidities can precipitate alveolar hypoventilation or respiratory failure. Indeed, in individuals in whom vertebral and respiratory muscle weakness is present before spinal growth is complete, thoracic scoliosis often complicates the clinical picture. These children with ventilatory muscle weakness often do not have patent parenchymal lung disease, so that they are good candidates for long-term home NPPV.

Disorders characterised by an increase in respiratory load

Upper or lower airway obstruction or chest wall deformity are paediatric diseases that cause an increase in respiratory load. Obstructive sleep apnoea (OSA) is less common in children than in adults. The pathophysiology is also different with the predominant role of enlarged tonsils and adenoids [10]. Airway obstruction is usually relieved after adenotonsillectomy [11], and persistence of sleep disturbance after surgery is observed in under 20% of cases. Other causes of upper airway obstruction can cause severe alveolar hypoventilation in young children, such as laryngomalacia, tracheomalacia, Pierre Robin syndrome, cystic lymphangioma and some rare congenital disorders of the face, such as pyknodysostosis [7]. In these infants, alveolar hypoventilation can persist after adenotonsillectomy, especially during sleep. Indeed, because of small lung volumes and the progressive maturation of sleep stages, infants are particularly susceptible to the cardiovascular consequences of increased upper airway resistance during sleep. We have shown that the respiratory effort, assessed by the esophageal (PTPes) and diaphragmatic (PTPdi) pressure time product, of young children with upper airway obstruction is greatly increased during wakefulness [7]. NPPV successfully relieves the additional load imposed on the respiratory muscles. This translates into a significant increase in tidal volume (Vt), a decrease in respiratory rate and a significant improvement in diurnal and nocturnal gas exchange [7].

Cystic fibrosis (CF) is the most common genetic disease in the Caucasian population. Most of the morbidity and mortality is due to the involvement of the lungs, which is characterised by progressive airflow obstruction as a result of mucus plugging and inflammation within the bronchial walls, and destruction of the lung parenchyma secondary to bronchiectasis. In children and young adults with advanced stable pulmonary CF disease, as lung disease progresses, as assessed by a fall in the forced expiratory volume in 1 s (FEV_1), there is an increase in the respiratory muscle load, as assessed by the increases in PTPes, PTPdi and the elastic work of breathing [12]. As a result, the patients develop a compensatory mechanism involving a rapid shallow breathing pattern in an attempt to reduce the increase in load. Although this breathing strategy maintains the level of ventilation, the partial arterial carbon dioxide pressure ($PaCO_2$) then rises, so that the efficiency of the respiratory muscle pump to clear CO_2 declines. NPPV, by relieving the load on the respiratory muscles, improves alveolar hypoventilation and thus gas exchange. This explains why NPPV is as effective as oxygen therapy in improving arterial oxygenation, but significantly more effective than oxygen therapy in decreasing $PaCO_2$ [3, 13].

Chest wall abnormalities such as severe scoliosis, kyphosis or thoracic dystrophy are among the chest wall abnormalities that can cause restrictive disease severe enough to require long-term NPPV [14]. The prognosis of these children depends on the severity, the type and the evolution of the disease.

Disorders characterized by failure of the neurological control of ventilation

Disorders of neurological control of breathing that are so severe as to cause chronic respiratory failure are uncommon to rare. Congenital central hypoventilation syndrome (Ondine's curse) is the most common presentation in childhood and is characterised by failure of autonomic control of breathing [15]. Hypoxia and hypercapnia worsen during sleep. NPPV has been tried in older children who sustain adequate ventilation during wakefulness but require ventilatory assistance only during sleep [16-18]. Failure of NPPV requires ventilatory support via a tracheostomy.

A recent study collated experience with domiciliary NPPV in children in France [19]. An anonymous cross-sectional national study was performed based on a postal questionnaire sent to all specialist centres utilising domiciliary NPPV for chronic respiratory failure. Patients aged <18 years and receiving long-term home NPPV were included in the study. Detailed information was obtained from 102 patients supervised by 15 centres: 4 of the 15 centres were caring for 84% of patients. Several (7%) of the patients were under 3 years old, 35% were between 4 and 11 years of age and 58% were over 12 years. Underlying diagnoses included neuromuscular disease (34%), OSA and/or craniofacial abnormalities (30%), cystic fibrosis (17%), congenital hypoventilation (9%), scoliosis (8%) and other disorders (2%). NPPV was started because of nocturnal hypoventilation (67%), acute exacerbation (28%) and/or failure to thrive (21%). This observational study showed the relatively low number of paediatric patients receiving home NPPV in a country with wide experience in this technique, supporting the fact that the technique is probably underused in this age group.

Criteria for initiation of NPPV

The most widely accepted indication for NPPV is diurnal hypercapnia [6]. NPPV is also indicated when acute exacerbations caused by bronchitis or pneumonia precipitate acute respiratory failure [6]. Ideally, however, NPPV should be initiated before an acute exacerbation, which is not an optimal situation for starting such a treatment from either the physiological or the psychological aspect. There is also wide agreement that clinical symptoms attributable to nocturnal hypoventilation, such as broken sleep, daytime hypersomnolence, excessive fatigue and morning headache should be considered very important when the decision on whether to initiate NPPV has to be made. These symptoms warrant a polysomnographic sleep study to document nocturnal hypoventilation. In addition, when NPPV is decided on, its effects on diurnal $PaCO_2$, sleep, growth and neuropsychological deve-

lopment, such as improved alertness, attention/concentration, and behaviour/mood, are crucial factors in children and merit further investigation [20, 21].

Current guidelines have been published, but precise criteria for starting NPPV are only available for patients with Duchenne myopathy [4, 5]. A recent study suggests that arterial blood gases should be performed in patients with Duchenne myopathy when FEV_1 falls below 40% of the predicted value and that polysomnography should be considered when $PaCO_2$ is ≥45 mmHg [20]. There is a negative correlation between $PaCO_2$ and survival [22], and ventilatory support should be considered in Duchenne myopathy when daytime $PaCO_2$ exceeds 6.0 kPa (45 mmHg) [5]. NPPV administered during sleep is associated with a decrease in awake $PaCO_2$ despite a further decline in ventilatory capacity (VC) [20]. It appears reasonable to consider NPPV in Duchenne muscular dystrophy only when patients develop daytime hypercapnia or symptomatic nocturnal hypercapnia [5].

There are no published guidelines or recommendations for patients with OSA and cystic fibrosis. For both these groups of patients, diurnal hypercapnia is a reasonable indication for NPPV. When diurnal hypercapnia is not present a sleep study is recommended in case of failure to thrive or excessive fatigue, because clinical symptoms of nocturnal hypoventilation can be subtle, especially in infants.

Contraindications, side-effects and limits of NPPV

NPPV is generally preferred over invasive mechanical ventilation as first-line therapy for chronic respiratory failure. However NPPV is contraindicated in some circumstances [23] (Table 1). NPPV is also contraindicated in the case of recent pneumothorax, which can occur in patients with advanced cystic fibrosis affecting the lungs. In this population, nasal polyps are common and should be treated before the initiation of NPPV.

Side-effects are common. They are caused by the interface and the delivery of positive pressure. In our series, skin lesions, ranging from transient erythema to permanent skin necrosis, attributable to the nasal mask, were observed in 53% of the 40 patients during their routine 6-month follow-up in our department. In young children, there is also a potential risk of facial deformity, such as facial flattening and maxillary retrusion caused by the pressure on growing facial structures from the mask. These potential side-effects justify the systematic follow-up of children receiving NPPV by a paediatric maxillofacial specialist. Abdominal distension is an uncommon problem that can be lessened by switching to a PS ventilator or decreasing the V_T on a volume-targeted ventilator [11].

Table 1. Contraindications for NPPV (From [23])

Relative contraindications	Severe swallowing impairment Inadequate family/caregiver support Need for full-time ventilatory assistance
Absolute contraindications	Intractable upper airway obstruction Intractable secretion retention Inability to cooperate Inability to achieve adequate peak cough flow, even with assistance Inability to fit mask

Ventilatory modes and interfaces for children

Ventilatory modes

The ventilatory mode and the ventilator settings that are most appropriate for each specific condition remain matters of debate. Moreover, developments in the specific equipment available for therapy are linked more closely to industrial ability and capacity than to the publication of clear indications recognised in scientific trials.

Since the original publication by Sullivan et al. [24], nasal CPAP has become the treatment of choice for the treatment of obstructive events during sleep [11, 25]. Upper airway patency is maintained with nasal CPAP by a pneumatic splinting effect. In addition, it has been demonstrated that CPAP reduces the work of breathing in patients with flow limitation. In such patients, CPAP overcomes the inspiratory threshold imposed by intrinsic PEEP and pneumatically splints the airways to prevent dynamic collapse during exhalation. Thus, while the main indication for CPAP is OSA, it is also advisable in obstructive lung disease, when intrinsic positive end-expiratory pressure (PEEPi) increases the work of breathing. In this way, this ventilatory mode has proved its efficacy in increasing exercise tolerance in patients with cystic fibrosis, with a positive correlation between the efficacy of the CPAP and the severity of the lung disease assessed by the percentage of decrease in FEV_1 [26]. However, because upper airway loading with complete or partial obstruction and PEEPi are not the sole mechanisms of hypoventilation, CPAP would be insufficient in patients with respiratory function abnormalities.

Volume-targeted ventilation is characterised by the delivery of a fixed, predetermined V_T. Thus, the main advantage of assisted control/volume-targeted (AC/VT) ventilation is that a guaranteed minimal V_T is delivered, but this can result in detrimentally high inspiratory airway pressures, causing discomfort and poor tolerability. Although many of the volume-targeted ventilators have no leak-compensation mechanisms, this mode is suitable for patients with neuromuscular diseases, in whom the ventilator acts as a substitute for the weakened respiratory muscles, which are unable to trigger the ventilator. However, a relatively high back-up rate (two to three breaths lower than the patient's spontaneous respiratory rate) is required to avoid nocturnal desaturations, and as a consequence many

patients adopt a controlled mode without triggering the ventilator. In addition, the inspiratory triggers of these ventilators are not very sensitive, which is another factor justifying the use of a relatively high back-up rate [27]. The settings generally recommended are a V_T of 10–15 ml/kg and a frequency two or three breaths slower than the child's spontaneous breathing rate [6]. These ventilators designed for home use are relatively easy to move about. Technologically, they are not as sophisticated as hospital ventilators. Another limitation of AC/VT devices is that when infants and children acquire superadded infection these ventilators may not be able to ventilate them adequately. Furthermore, few of them are capable of operating within certain limits (i.e. V_T <50–100 ml).

Pressure support (PS) is a more recent mode of ventilation. This ventilatory mode is pressure targeted, and each breath is triggered and terminated by the patient and supported by the ventilator; the patient can control his/her respiratory rate, inspiratory duration (T_I) and V_T [28]. This explains the relative ease in adapting to, and the greater comfort and synchrony of, this mode. In contrast to volume-targeted ventilation, V_T is not predetermined but depends on the level of PS, the inspiratory effort of the patient and the mechanical properties of the patient's respiratory system. During use of this mode, since there are no mandatory breaths present, an in-built low-frequency back-up rate is used to prevent episodes of apnoea. Furthermore, because the breaths are triggered by the patient, the sensitivity of the trigger is crucial. The sensitivity of the inspiratory triggers of the different ventilators designed for the home varies, but some have triggers as sensitive as those of intensive care devices [29]. Because during PS inspiratory muscle activity may influence respiratory frequency and V_T, this ventilatory mode is generally proposed for patients who can breathe spontaneously for substantial periods of time and require mainly nocturnal ventilation.

Bi-level PPV is the combination of pressure support (PS) and PEEP, permitting an independent adjustment of expiratory positive airway pressure (EPAP) and inspiratory positive airway pressure (IPAP). In this condition upper airway obstruction and/or work of breathing induced by PEEPi are prevented by EPAP, and PS can thus easily be triggered by the patient. This ventilatory mode has been used in children with OSA, cystic fibrosis [30, 31] and neuromuscular disease [30-33].

The interfaces

The necessity for an interface specifically designed for children is a significant technical limitation of NPPV in paediatric patients. In young children, nasal masks are preferred because they have less static dead space, are less claustrophobic and allow communication and expectoration more easily than full-face masks do. However, few masks suitable for children are commercially available. This short coming is even more significant in the case of infants. Most often, NPPV is thus restricted to a few highly specialised paediatric centres that have the facilities to manufacture custom-made masks for infants and children who cannot use commercially available ones.

Benefits of NPPV

Improved survival

The major benefit of NPPV is the improved survival, although this has only been demonstrated in patients with neuromuscular diseases. Indeed, a recent study evaluated the effect of NPPV on survival in patients with Duchenne muscular dystrophy in Denmark between 1977 and 2001 [34]. While the overall incidence remained stable at 2.0 per 10^5, the prevalence rose from 3.1 to 5.5 per 10^5, mortality fell from 4.7 to 2.6 per 100 years at risk and the prevalence of ventilator use rose from 0.9 to 43.4 per 100. Ventilator use is probably the main reason for this dramatic increase in survival.

No comparable improvement in survival has been demonstrated for lung diseases such as cystic fibrosis or for OSA.

Improved nocturnal hypoventilation

The effect that is most obvious in the paediatric population is the correction of nocturnal hypoventilation. During sleep, certain key alterations in respiratory and upper airway function and ventilatory responses lead to a degree of nocturnal hypoventilation even in normal subjects, causing a rise of up 3 mm Hg (0.4 kPa) in $PaCO_2$ in adults [35]. Because sleep is an at-risk period in patients with chronic respiratory insufficiency and also for practical reasons, NPPV is preferentially performed during the night, but daytime mechanical ventilation in awake adult patients has been reported to be just as effective as nocturnal mechanical ventilation in reversing chronic hypercapnia [36].

Change in pulmonary mechanics

The physiological changes in the compliance of the lungs and the chest wall play a crucial part in the normal development of the lung. It would be an important advantage if we knew whether long-term NPPV in infants and young children could preserve near-normal chest wall compliance, both in children with a too-stiff chest, due to chest deformity, for example, and in those with neuromuscular disease, who are exposed to ankylosis in the costosternal and costovertebral joints and to gradual stiffening of the rib cage because of a breathing at smaller VT and greater respiratory frequency.

Chronic hypoventilation can alter the dynamic or static compliance of the lung. The majority of observations in patients with neuromuscular disease have shown a significant reduction in pulmonary compliance. The measurements recorded in these patients have been of dynamic compliance reflecting abnormalities in airways rather than a true change in the elastic properties of the lungs. Specific compliance, relating static expiratory compliance to total lung capacity, is normal in patients with respiratory muscle weakness. Atelectasis could explain the hypoxaemia due to the ventilation-perfusion mismatch.

One major concern in paediatric patients is the effect of chronic hypoventilation on lung growth and, as a logical consequence, the effect of NPPV in promoting or preserving physiological lung and chest wall growth in the developing child. To our knowledge, this has not been studied.

Effect on quality of life

Every 'new' long-term treatment should be associated with a significant improvement of quality of life in patients with a chronic disease. Most surprisingly, very few studies have evaluated the effect of NPPV on quality of life. A recent French study evaluated the social and psychological impact of invasive and noninvasive home mechanical ventilation in 52 adult patients (mean age 25±5 years) with Duchenne muscular dystrophy [37]. Although the patient group was not compared with a control group, the self-estimated quality of life of these patients was good, and higher than expected by the healthcare givers. In paediatric patients, the impact of NPPV on the quality of life and family organisation is also an important aspect. Such studies are clearly warranted in the future.

Organisation of home care

Requirements for home care

The major advantage of NPPV is that it can be applied at home, combining greater potential for psychosocial development and family functioning with lower costs. The use of home NPPV requires appropriate diagnostic procedures, appropriate titration of the ventilator, cooperative and well-informed and trained family members and careful, well-organised follow up. Prior to discharge, the child's respiratory status should have been stable for several days at least with the actual ventilator and circuit he or she will be using at home. Settings on a home ventilator do not provide the same ventilation in the child as the same settings on a hospital ventilator, and the efficacy of home equipment must be evaluated in each child prior to discharge home.

Once the child is at home, with continuing growth ventilator settings must be evaluated to ensure adequate gas exchange, with recordings of pulse oximetry (SaO_2), transcutaneous partial arterial oxygen pressure ($PtcO_2$) and transcutaneous partial arterial carbon dioxide pressure ($PtcCO_2$) on a regular basis. Although the optimal frequency for these evaluations has not been determined, they should generally be performed more frequently in infants and small children who are growing rapidly. Polysomnographic evaluations are recommended as a diagnostic tool before the initiation of NPPV and then as a control test of the efficacy of NPPV before discharge home with the ventilator and again as a surveillance test during an overnight hospital admission during follow-up. Extrapolation from a polysomnographic evaluation performed during daytime naps

should be made with care, because they do not always reflect what happens during the night.

Routine and emergency services must be available. Providers/home care equipment technicians and nurses should make home visits at least once monthly to perform preventive maintenance and check on ventilator function. VT, rate, oxygen concentration if necessary, pressures and alarms should be calibrated and their function checked. Evaluation of compliance should be systematically checked by counters on the equipment that determine the amount of time the ventilator is effectively used, and not only how long it is turned on.

Additional therapies

Oxygen therapy at home must be justified on the basis of individually determined medical necessity, as determined by appropriate physiological monitoring, such as SaO_2 during periods of sleep, wakefulness, feeding and physical activity and arterial blood gases. CO_2 should be minimised first by ventilator use before oxygen therapy is considered, especially for patients with neuromuscular disorders and OSA. It is important to remember that supplemental oxygen is *not* a replacement for assisted ventilation in patients who hypoventilate.

Systematic humidification of the ventilator gas is not necessary for NPPV because of the respect of the upper airway. However, nasal intolerance because of excessive dryness can resolve after humidification of the ventilator gas.

Children are frequently undernourished when they start NPPV. Adequate nutrition is critical for growth and development of the lungs and the chest wall. Nutritional support via a nasogastric tube is frequently necessary during the first weeks or months. This can be performed by fashioning a port in a custom-made nasal mask if gastrostomy feeding is not planned. In infants, discoordination of the swallowing mechanisms is frequent and swallowing function should be evaluated to assess the risk of pulmonary aspiration. Many patients also have associated gastro-oesophageal reflux, which may require medical treatment, and eventually surgical correction. This can be combined with a gastrostomy if necessary.

Psychological aspects

It is essential that the child, age permitting, and the parents should have the opportunity to discuss the NPPV therapy before it is started. Discussion should start long enough before the anticipated need to allow the child and the family to evaluate the options thoroughly and to discuss their feelings. While NPPV is essentially regarded as the first choice, being a noninvasive therapy, nonetheless it still represents an objective element reflecting a further step in the severity of the child's disease. It is crucial to determine short-term and intermediate-term goals of NPPV with the child and the family, to explain the principles of NPPV and to underline the fact that NPPV will adapt to the child and not vice versa. A wide range of ventilators and masks are available, and both child and family should be made

aware that great care will be taken to choose the most appropriate equipment and settings. The final objective is for NPPV to translate into greater wellbeing and a better quality of life, with a total adherence of the child and his/her family.

Conclusions

In conclusion, NPPV is increasingly being used in children and infants. Unfortunately, in this age group the therapy is generally used on an empirical basis. Paediatricians, physiologists, nurses, physiotherapists and technicians should combine forces to determine the physiological effects of NPPV more accurately, especially those on the respiratory muscles, the respiratory compliance and growth, and the central drive, the appropriate timing of initiating, and most importantly, the benefits in terms of psychoneurological development and quality of life.

References

1. Masa J, Celli B, Riesco J et al (1997) Noninvasive positive pressure ventilation and not oxygen may prevent overt ventilatory failure in patients with chest wall disease. Chest 112:207-213
2. Gay P, Edmonds L (1995) Severe hypercapnia after low-flow oxygen therapy in patients with neuromuscular disease and diaphragmatic dysfunction. Mayo Clin Proc 70:327-330
3. Gozal D (1997) Nocturnal ventilatory support in patients with cystic fibrosis: comparison with supplemental oxygen. Eur Resp J 10:1999-2003
4. Robert D, Willig TN, Paulus J (1993) Long-term nasal ventilation in neuromuscular disorders: report of a Consensus Conference. Eur Respir J 6:599-606
5. Rutgers M, Lucassen H, Kesteren RV et al (1996) Respiratory insufficiency and ventilatory support. 39th European Neuromuscular Centre International workshop. Neuromuscul Disord 6:431-435
6. Anomymous (1998) Management of pediatric patients requiring long-term ventilation. Chest 113:322S-336S
7. Fauroux B, Pigeot J, Polkey MI et al (2001) Chronic stridor caused by laryngomalacia in children.Work of breathing and effects of noninvasive ventilatory assistance. Am J Respir Crit Care Med 164:1874-1878
8. Fauroux B, Pigeot J, Isabey D et al (2001) In vivo physiological comparison of two ventilators used for domiciliary ventilation in children with cystic fibrosis. Crit Care Med 29:2097-2105
9. Misuri G, Lannini B, Gigliotti F et al (2000) Mechanism of CO_2 retention in patients with neuromuscular disease. Chest 117:447-453
10. Croft CB, Brockbank MJ, Wright A et al (1990) Obstructive sleep apnea in children undergoing routine tonsillectomy and adenoidectomy. Clin Otolaryngol 15:307-314
11. Guilleminault C, Pelayo R, Clerk A et al (1995) Home nasal continuous positive airway pressure in infants with sleep-disordered breathing. J Pediatr 127:905-912
12. Hart N, Polkey MI, Clément A et al (2002) Changes in pulmonary mechanics with increasing disease severity in children and young adults with cystic fibrosis. Am J Respir Crit Care Med 166:61-66

13. Milross MA, Piper AJ, Norman M et al (2001) Low-flow oxygen and bilevel ventilatory support. Effects on ventilation during sleep in cystic fibrosis. Am J Respir Crit Care Med 163:129-134
14. Simonds AK, Ward S, Heather S et al (2000) Outcome of paediatric domiciliary mask ventilation in neuromuscular and skeletal disease. Eur Respir J 16:476-481
15. Gozal D (1998) Congenital central hypoventilation syndrome: an update. Pediatr Pulmonol 26:273-282
16. Ellis ER, McCauley VB, Mellis C et al (1987) Treatment of alveolar hypoventilation in a six-year-old girl with intermittent positive pressure ventilation through a nose mask. Am Rev Resp Dis 136:188-191
17. Nielson DW, Black PG (1990) Mask ventilation in congenital central alveolar hypoventilation syndrome. Pediatr Pulmonol 9:44-45
18. Zaccaria S, Braghiroli A, Sacco C et al (1993) Central hypoventilation in a seven year old boy. Long-term treatment by nasal mask ventilation. Monaldi Arch Chest Dis 48:37-38
19. Fauroux B, Boffa C, Desguerre I et al (2003) Long-term noninvasive mechanical ventilation for children at home: a national survey. Pediatr Pulmonol 35:119-125
20. Hukins CA, Hillman DR (2000) Daytime predictors of sleep hypoventilation in Duchenne muscular dystrophy. Am J Respir Crit Care Med 161:166-170
21. Rains JC (1995) Treatment of obstructive sleep apnea in pediatric patients. Clin Pediatr 34:535-541
22. Phillips M, Smith P, Carrol N et al (1999) Nocturnal oxygenation and prognosis in Duchenne muscular dystrophy. Am J Respir Crit Care Med 160:198-202
23. Hill NS (2002) Ventilator management for neuromuscular disease. Semin Respir Crit Care Med 23:293-305
24. Sullivan CE, Issa FG, Berthon-Jones M et al (1981) Reversal of obstructive sleep apnea by continuous positive airway pressure applied through the nares. Lancet 1:862-865
25. Waters WA, Everett FM, Bruderer JW et al (1995) Obstructive sleep apnea: the use of nasal CPAP in 80 children. Am J Respir Crit Care Med 152:780-785
26. Henke KG, Regnis JA, Bye PTP (1993) Benefits of continuous positive airway pressure during exercise in cystic fibrosis and relationship to disease severity. Am Rev Resp Dis 148:1272-1276
27. Fauroux B, Louis B, Hart N et al (2004) The effect of back-up rate during non-invasive ventilation in young patients with cystic fibrosis. Intensive Care Med (in press)
28. Brochard L, Pluskwa F, Lemaire F (1987) Improved efficacy of spontaneous breathing with inspiratory pressure support. Am Rev Resp Dis 136:411-415
29. Lofaso F, Brochard L, Hang T et al (1996) Home versus intensive care pressure support devices. Experimental and clinical comparison. Am J Respir Crit Care Med 153:1591-1599
30. Padman R, Lawless S, Von Nessen S (1994) Use of BiPAP by nasal mask in the treatment of respiratory insufficiency in pediatric patients: preliminary investigation. Pediatr Pulmonol 17:119-123
31. Caronia CG, Silver P, Nimkoff L et al (1998) Use of bilevel positive airway pressure (BIPAP) in end-stage patients with cystic fibrosis awaiting lung transplantation. Clin Pediatr 37:555-559
32. Robertson PL, Roloff DW (1994) Chronic respiratory failure in limb-girdle muscular dystrophy: successful long-term therapy with nasal bilevel positive airway pressure. Pediatr Neurol 10:328-331
33. Guilleminault C, Philip P, Robinson A (1998) Sleep and neuromuscular disease: bilevel positive airway pressure by nasal mask as a treatment for sleep disordered breathing in patients with neuromuscular disease. J Neurol Neurosurg Psychiatr 65:225-232

34. Jeppesen J, Green A, Steffensen BF et al (2003) The Duchenne muscuar dystrophy population in Denmark, 1977-2001: prevalence, incidence and survival in relation to the introduction of ventilator use. Neuromuscul Disord 13:804-812
35. Gothe B, Altose MD, Goldman MD et al (1981) Effect of quiet sleep on resting and CO_2 stimulated breathing in humans. J Appl Physiol 50:724-730
36. Schönhofer B, Geibel M, Sonneborn M et al (1997) Daytime mechanical ventilation in chronic respiratory insufficiency. Eur Resp J 10:2840-2846
37. Raphael JC, Dazord A, Jaillard P et al (2002) Indices de satisfaction des patients atteints d'une dystrophie muculaire de Duchenne de Boulogne et ventilés à domicile. Rev Neurol 158:453-460

Chapter 57

Decision-making in paediatric extracranial trauma

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Introduction and epidemiology

Injury continues to be the most common cause of death and disability in children and can be considered as the most serious health care problem in this population [1-3] (Table 1). Paediatric trauma represents 15% of overall traumatology. Most frequently, the patient presents with head injury, isolated or associated, while extracranial injury accounts for 15% of the cases. Blunt trauma is definitely the most common finding (95%) [4]. Ninety percent of paediatric injuries are caused by falls and vehicular crashes, the latter being also the most common cause of death, regardless whether the child is a passenger, a cyclist or a pedestrian. Other important causes of death are drowning, house fires and homicides. Falls are a very common cause of injury, but they infrequently result in death. These data suggest that the most important intervention to reduce morbidity and mortality from trauma in the paediatric population (also dramatically reducing medical care costs) is to implement prevention measures; however, proven strategies are grossly underutilized [5-8].

Table 1. Mortality statistics: most common causes of death for age groups

0 - 1 month	Prematurity and congenital defects
1 mo - 1 year	SIDS
1 - 15 years	Trauma

The priorities of assessment and management of the injured child are the same as in the adult, but the unique anatomic characteristics of children require special consideration [9]:

1. Multiple organ injury must be considered as the rule rather than the exception: the smaller body mass of children means close proximity of multiple organs and a greater force applied per unit body area.
2. Internal organ damage is frequently seen without overlying bony fracture, because of incomplete calcification of the skeleton.
3. Hypothermia may develop very quickly compared to in an adult.
4. Psychological and long-term effects on the injured child are a challenge that should not be underestimated, as they may dramatically affect the quality of life of the child and even of his/her family for years afterward [10-12]. Half of injured children with an Injury Severity Score (ISS) =4 do have long-term sequelae [13].

5. Pain is less tolerated in infants than in adults.
6. Equipment of the appropriate size must be readily available. A useful guide in choosing the correct equipment and drugs dosage in the emergency department is the Broselow Paediatric Resuscitation Measuring Tape, which is associated with colour-coded materials [14].

Rapid assessment of the traumatic injuries is imperative to formulating an appropriate plan. Several methods may be used to determine the overall injury to a child, including the Paediatric Trauma Score (PTS) [15, 16], the ISS [17], and the Modified Injury Score (MIS) [18]. More recently, the New Injury Severity Score (NISS) has been proposed and validated by Sullivan et al. [19].

Initial management

The overall goal of initial management is to avoid the so-called triad of death: hypothermia, acidosis, coagulopathy. In the presence of the triad, it is useless to perform definitive surgical repair. Multiply injured children should therefore be managed with a three-stage "damage-control approach" [20, 21], a term coined in the early 1990s by Rotondo et al. [22, 23].

The goal of the first stage is to prevent ongoing damage as rapidly as possible. It consists of rapid identification of areas of exsanguinations, and transport to the operating room. Focused surgery is carried out in order to control haemorrhage and alleviate contamination. Definitive reconstruction is delayed; insteas, rapid, simple closure (sometimes abdominal packing and closure of the wound with loose retention sutures) and immobilization of fractures without definitive reduction or set are performed.

The second stage involves transfer to the ICU for further resuscitation and stabilisation. The goals are rewarming, optimising haemodynamics, supporting ventilation, correcting the coagulopathy, and reversing the acidosis. Prevention and/or treatment of abdominal compartment syndrome [24, 25], with particular attention to the related cardiorespiratory and renal effects, should be carried out. In addition, injury identification (tertiary survey) should be refined. This stage may be quite protracted and complicated, and usually requires invasive monitoring.

When the child is stabilized definitive surgery and reconstruction is indicated. In this third stage of the damage control approach, packs are removed, tissues are debrided, and repair can proceed in a controlled fashion. Definitive repair and fracture reduction can be performed.

In the following, some important differences in the management of different aspects of trauma in adult and paediatric patients are discussed.

Airway and breathing

As in adults, establishing and/or maintaining a patent airway is the first priority in the management of the injured child, since failure to do this is the most common

cause of cardiac arrest [9]. Head and concomitant facial injuries are common and may represent a challenge for the anaesthesiologist, while airway injuries are less common in the paediatric population. Other problems may result from the likelihood of a full stomach, and the possible presence of foreign bodies in the airway. Alignment of the spinal column may be difficult due to the larger occiput, so that it may be necessary to put a layer of padding beneath the entire torso. Spine immobilization usually involves a rigid backboard, head blocks or towels, and a rigid collar. Spinal injury may be occult and the increased laxity of cervical supporting ligaments results in decreased cervical stability. Therefore, cervical injury must always be suspected [26].

If the child needs to be tracheally intubated, preoxygenation is particularly important due to reduced oxygen reserve in the paediatric patient. Initially, orotracheal intubation via direct laryngoscopy is preferred [27]. A rapid sequence intubation technique with Sellick manoeuvre is indicated [28, 29] (Table 2). The use of atropine sulfate to ensure an adequate cardiac rate should be considered. Surgical cricothyroidotomy is rarely indicated for the infant or small child; if absolutely necessary, it should be performed with a surgical approach. Tracheostomy may be required in individuals who have severe disruption of the craniofacial skeleton as well as blood filling of the airway [30]. When needed, tracheotomy should not be removed unless an endoscopic evaluation of the airway confirms the resolution of airway compromise. Nevertheless, laryngeal stenosis is not a frequent complication in these patient because primary laryngeal trauma does not generally accompany craniofacial skeletal injury and patients with primary craniofacial trauma typically do not require intubation for long periods of time [31]. Flexible fibre-optic endoscopy may be necessary for intubation in the acute period if tracheotomy is not immediately available. When needed, as in airway disruption

Table 2. Rapid sequence induction

1) Preoxygenation			
2) Manual in-line axial traction			
3) Cricoid pressure (not too early)			
4) Atropine 0.1-0.5 mg			
5) Induction of anaesthesia:	Head injury	Lidocaine	1.5-2 mg·kg^{-1}
		Alfentanil	15-30 mg·kg^{-1}
	Normovolaemia	Propofol	2-3 mg·kg^{-1}
		Pentothal	4 mg·kg^{-1}
		Midazolam	0.3 mg·kg^{-1}
	Hypovolaemia	Midazolam	0.1 mg·kg^{-1}
		Ketamine	1-2 mg·kg^{-1}
6) Muscle relaxants: vecuronium 0.1-0.3 mgl·kg^{-1}, rocuronium 0.6-1.2 mg·kg^{-1}, cisatracurium 0.25-0.3 mg·kg^{-1}. The use of succinylcholine is still controversial			
7) Orotracheal intubation with cuffed/uncuffed tube			
8) Gentle hyperventilation			
9) Release cricoid pressure			

or in expected difficult airway, fibre-optic intubation may be difficult especially in small children. Microlaryngoscopy and bronchoscopy may be useful in establishing an airway when visualisation is compromised. A comprehensive review on trauma airway management has been recently published by Langeron [32].

Circulation and shock

Injury in childhood frequently results in significant blood loss. However, a reduction in blood pressure is physiologically prevented in children by vasoconstriction and increasing heart rate. Therefore, blood pressure by itself is not a reliable end point for assessing the adequacy of resuscitation [33]. A narrowed pulse pressure is a sign of blood loss of about 30-45%. Furthermore, once hypotension occurs, it often represents a blood loss >45% and cardiovascular collapse may follow rapidly, often accompanied by bradycardia [9]. Signs and symptoms of hypovolaemia and shock to be considered are tachycardia, poor skin perfusion, skin mottling, cold extremities, capillary refill >2 s, compromised level of consciousness and reduced urinary output. Normal urinary output is 2 $ml \cdot kg^{-1} \cdot h^{-1}$ in the newborn and in infants up to 1 year, 1.5 $ml \cdot kg^{-1} \cdot h^{-1}$ in the toddler and 1 $ml \cdot kg^{-1} \cdot h^{-1}$ in the older child through adolescence.

Early goal-directed resuscitation is recommended. Fluids are administered in boluses of 20 $ml \cdot kg^{-1}$. Aggressive fluid resuscitation often requires 40-60 $ml \cdot kg^{-1}$ but the needs may even be much higher. No significant differences between colloids and crystalloids have been demonstrated, although colloids appeared to be more effective in restoring normal pulse pressure in the group of patients with narrowest pulse pressure [34]. Total blood volume in children can be estimated as 80 ml/kg. It is important to notice that, when using crystalloids to replace blood loss, the 3:1 rule can be applied in children as well as in adults. Blood (10 $ml \cdot kg^{-1}$ bolus) may be administered in case of failure to improve after >50 $ml \cdot kg^{-1}$ of crystalloids in 1 h [35]. In the absence of specific studies for the paediatric population, the target of haemoglobin concentration is reasonably set at 10 mg/dl. Prompt involvement of a surgeon is a must in case of suspected continuous blood loss, particularly when the child proves to be unresponsive to fluid therapy and shows rapid deterioration. Care must be taken to use all available measures to avoid hypothermia (such as heaters, thermal blankets, warmed fluids and inhaled gases).

This approach requires a good venous access, which is often difficult to establish in children [36]. The peripheral percutaneous route should be the first choice, while femoral veins should be avoided except in emergency due to the risk of thrombosis and even ischemic limb loss. Moreover, femoral vein cannulation may exacerbate intra-abdominal vascular injuries. In children less than 6 years of age, intra-osseous infusion may be considered to start fluid resuscitation if two attempts of percutaneous access fail [37]. However, it should be discontinued as soon as a peripheral or central access has been established. Central venous cannulation may be indicated. Internal jugular cannulation is relatively contraindicated in patients with suspected cervical spine injury because it may require manipulation of the neck [38].

As in adults, vasopressors and inotropes should be used only after adequate fluid resuscitation have failed to stabilize the patient, and the causes of fluid-refractory shock must be promptly considered (continuous bleeding with the need of immediate surgical haemostasis, pericardial tamponade, tension pneumothorax, haemothorax, association with septic shock).

Therapeutic end points are capillary refill <2 s, normal pulses with no differential between peripheral and central pulses, warm extremities, return to normal skin colour, increased pulse pressure (>20 mm Hg), urine output >1 $ml \cdot kg^{-1} \cdot h^{-1}$, normal mental status, decreased lactate and increased base deficit, and superior vena cava or mixed venous oxygen saturation >70%. Cardiac index (when measured) should range between 3.3 and 6.0 $l \cdot min^{-1} \cdot m^{-2}$ with normal perfusion pressure (mean arterial pressure-central venous pressure) for age. Hepatomegaly is often the first sign of fluid overloading [34].

Finally, paediatric patients and especially infants are at risk for hypoglycaemia when they depend on intravenous fluids. Frequent monitoring and an appropriate glucose administration is advisable. There are no studies in children that show a benefit from insulin therapy to obtain a rigid control of glycaemia.

Coma

Coma may follow head injury but also multiple organ injury and hypoperfusion due to direct trauma or shock. The evaluation of the neurological status of the child is a fundamental step of the initial assessment. As discussed above, an improvement in mental status is one of the most important signs of adequate resuscitation. The Glasgow Coma Scale (GCS) has been modified for the paediatric age, as reported in Table 3.

In the initial evaluation and management of multiple trauma patients, care must be taken to utilize a correct psychological approach. At all times in paediatric resuscitation, one must be aware that the child will have anxiety related to procedures and parental separation. In addition to the child's emotional needs, parental concerns must be addressed, and communication with the parents should be established quickly [39]. Particular attention must also be paid to provide adequate pain control in order to prevent an exaggerated stress response to physical injuries, mainly related to catecholamine release.

Injury of the upper airway

Injuries of the upper airways are relatively uncommon [40] but potentially life-threatening in children and require prompt diagnosis and intervention [41]. The size of the airway is obviously smaller in the paediatric population, and airway disruptions are less tolerated in children than in adults. Laryngotracheal injuries can be caused either by external or internal factors. External causes may be divided into blunt trauma, penetrating wounds, or iatrogenic (at the time of delivery or due

Table 3. Modified Glasgow Coma Scale. Modified from [42]

Activity		Adults	Paediatric
Best eye response (E)	4	Spontaneous	Spontaneous
	3	To verbal stimulation	To verbal stimulation
	2	To pain	To pain
	1	None	None
Best verbal response (V)	5	Oriented	Coos or babbles (normal activity)
	4	Confused	Irritable, continually cries
	3	Inappropriate words	Cries to pain
	2	Nonspecific words	Moans to pain
	1	None	None
Best motor response (M)	6	Follows commands	Infant moves spontaneously or purposefully
	5	Localises pain	Infant withdraws from touch
	4	Withdraws from pain	Infant withdraws from pain
	3	Flexion in relation to pain	Abnormal flexion to pain for an infant (decorticate response)
	2	Extension in relation to pain	Extension to pain (decerebrate response)
	1	None	None

to tracheostomy). Internal causes may be iatrogenic (intubation, endoscopy, etc.), thermal, chemical and mechanical.

Blunt trauma is the most common cause of external trauma of the upper airway.

The trachea and larynx in infants and small children are located higher in the neck, normally protected by the relatively large head and mandible, which take the majority of the impact. The laryngeal skeleton is made up of a soft cartilage, and laryngeal fractures are less common than in adults. The most narrow point is at the level of the cricoid cartilage (C_3), in contrast to the adult larynx which is narrowest at C_7.

Blunt laryngeal trauma can result in several different types of injuries, such as mucosal oedema with subsequent haematoma of the true vocal cords, lacerations, arytenoid cartilage dislocation, cricothyroid disruption, laryngotracheal separation (more common in younger patients) and vocal cord paralysis, the latter being a challenge for decannulation. Laryngeal fractures, although uncommon, can occur and may range from simple to comminute fractures. Once an airway injury has been recognised, a careful examination of all closely related structures is vital (oesophagus, cervical spine, great vessels) [31].

Evaluation

Whenever possible, fibre-optic endoscopy should be performed before intubation in order to evaluate the nature and severity of injury, and to exclude laryngotracheal separation, which may cause the tube to be positioned in the soft tissues of the neck. However, if respiratory distress is present, intervention is necessary before there is complete assessment of the injury. If endoscopic evaluation is not feasible, microlaryngoscopy, bronchoscopy and possibly tracheostomy are recommended.

When permitted by the clinical situation, a complete history and clinical examination should be performed before securing the airway. Key points are understanding the mechanism of trauma and recognising some important clinical features, such as changes in voice (hoarseness), pain on swallowing or speaking, presence of dysphagia, stridor, dyspnoea, haemoptysis, subcutaneous emphysema (which reveals disruption of some part of the aerodigestive system), oedema, crepitations, evidence of bone fractures, or loss of the thyroid or cricoid prominence [43] If the child remains stable, laryngoscopy should be performed (or, if not feasible, a mirror examination), together with head and neck radiographic evaluation. The cervical spine must be evaluated as well. CT scans are usually not necessary but can be useful in the case of suspected vocal cord haematomas, slight arytenoid dislocation or poor vocal cord mobility, in which the exclusion of other gross abnormalities may lead to conservative treatment. When an oesophageal laceration is suspected, a barium oesophogram may be done.

Treatment

When a surgical intervention is prospected, tracheostomy is indicated. Cricothyroidotomy should be avoided in all laryngotracheal injuries because it may aggravate the injury [44]. In case of cricothyrotomy, this should be converted to tracheostomy after stabilization. The major risk of intubation in the setting of laryngeal trauma is dislodging the distal end of a fractured larynx [45].

Depending on the severity of injury, the patient should be only observed and monitored; full endoscopic evaluation may be performed in order to assess the need for surgical repair. Serial endoscopic evaluation may be also helpful for monitoring the degree of airway obstruction over time. Early intervention in laryngeal trauma will minimise the risk of infection and long-term sequelae, such as laryngeal and tracheal stenosis. It is important to remember that airway obstruction and consequent respiratory distress may occur rapidly in children because of the loose connective tissue in the larynx and the relatively small size of the airway, especially in case of oedema or haematoma formation. Administration of steroids and racemic epinephrine as necessary may be helpful [31].

Chest trauma

Thoracic injuries are less frequent in children than in adults, accounting for approximately 10% of total admissions to Trauma Centres [46], but they are characterized by high lethality, especially when combined with head or abdominal injury [47]. Furthermore, more than two-thirds of children with chest injury have been shown to have other organ system injuries. Blunt trauma is the most common mechanism, but in adolescence penetrating trauma is not rare [48]. The specific injuries caused by thoracic trauma in the child are identical to those encountered in the adult, although the frequencies of occurrence of those injuries are somewhat different due to the anatomy of the child's chest. The greater flexibility of the thoracic cage in young children permits transmission of the force of impact to the internal organs. As a result, pulmonary contusions are more common, whereas bony fractures occur less frequently in children than in adults. In children, the presence of rib fractures is a sign of a high-energy trauma, and multiple rib fractures are associated with a high mortality [49]. As the bony rib cage ossifies, fractures and flail segments become more common. The same could be applied to the thoracic spinal column, and younger patients may present with spinal cord injuries without plain film abnormalities (in this case RMN may be diagnostic). Pneumothorax may develop in several ways and sometimes is asymptomatic, nevertheless its recognition is fundamental to avoid cardiopulmonary problems. Injuries of the mediastinal organs are much less common than in adults [50], while haemothorax has a prevalence of 13% in blunt chest trauma [51]. Myocardial dysfunction, although rare, may follow cardiac contusion. The oesophagus is a well-protected organ and its lesions are very rare except for penetrating wounds. Blunt diaphragmatic rupture occurs in 0.4% of pateints [52], but when diagnosed the incidence of involvement of other organs (especially liver and spleen) is very high (up to 78%) [50].

A study by Holmes et al. [53] showed that predictors of thoracic injury in children with blunt thoracic trauma include low systolic blood pressure, elevated respiratory rate, abnormal results on thoracic examination, abnormal chest auscultation findings, femur fracture, and a GCS score of less than 15.

Pulmonary contusion

Pulmonary contusion is the most common injury due to thoracic trauma in paediatric patients. Although children and adults differ in regard to injury mechanism, overall injury severity, associated injuries, and outcomes are quite similar [54]. Findings include alveolar haemorrhage, consolidation, and oedema. Chest radiograph is diagnostic in the majority of patients [55]. It may be difficult to initially differentiate contusion from aspiration pneumonia. CT scans are useful to evaluate the severity and guide management. Complications are common and include pneumonia (20%) and ARDS (3-20%), but death directly attributable to pulmonary contusion is rare [50, 56]. Children have a diminished functional residual capacity and higher oxygen consumption per unit body mass. Therefore hypoxaemia may develop rapidly.

Treatment

Treatment of paediatric thoracic injuries does not differ from those of adults. For this reason, only a few specific considerations will be proposed [50].

Rib fractures are treated with supportive measures, such as use of pain medication and, when the child is old enough to participate, incentive spirometry and deep breathing measures. Priorities are the prevention of atelectasis and pneumonia. Prompt drainage of intrathoracic collections of air or fluid that may limit pulmonary expansion may facilitate a more rapid return to normal physiology.

Flail rib segments, or multiple contiguous ribs with more than two points of fracture, are rare in children, but they are often associated with significant respiratory embarrassment. Ineffective respiration may result from paradoxic motion of the affected segment. Treatment is similar to simple rib fracture with the addition of measures such as epidural anaesthesia, positive-pressure ventilation, and occasional operative fixation.

Haemothorax requires prompt drainage of blood to avoid chronic atelectasis, ventilation/perfusion mismatch, and pneumonia due to organization of the haematoma. Thoracotomy is rarely required even in the setting of penetrating injuries (4-5%) [57].

In pulmonary contusion, the requirement for mechanical ventilation varies from 0 to 35%, but is less than in adults despite the diminished functional residual capacity. Therapeutic measures include fluid restriction, oxygen, pain control, incentive spirometry and prevention of atelectasis. Extracorporeal oxygenation has been rarely used.

Antibiotic use in the context of chest injury remains controversial.

Abdominal and pelvic trauma

Trauma to abdomen and pelvis represent 10% of injury in the paediatric age [58]. Spleen is the organ most frequently involved, followed by liver, intestine, and pancreas. Renal trauma is rare and may be complicated by pathologic lesions of the urinary tract, which must be suspected in case of gross haematuria with a minimal-force blunt abdominal trauma [59]. However, some authors have found significant renal injury even with minimal haematuria or normal urinanalysis [60]. Most renal injuries are treated conservatively and do not require surgical intervention. Pelvic fractures may be difficult to diagnose due to the frequent association with other distracting injuries, and may cause of retroperitoneal or intra-abdominal haemorrhages. Fatal blood loss from pelvic fractures is extremely rare (0-2%) [61]. Disruption of the pelvis suggests a high-impact injury [62].

The most common mechanism of abdominal injury in children is blunt trauma primarily due to motor vehicles or bicycle crashes and falls. Penetrating injuries are less common and require immediate evaluation by a surgeon. A combination of hypotension and penetrating trauma requires prompt surgical intervention.

Assessment

Physical findings suggestive of intra-abdominal injury include abrasions and contusion of the abdominal wall, e.g. seatbelt sign, abdominal tenderness and distension. The conscious child may be difficult to evaluate due to uncooperative behaviour, especially when frightened by the event. Almost all infants and young children who are stressed and crying will swallow large amounts of air, making evaluation even more difficult. Decompression of the stomach by inserting a gastric tube should be a part of the resuscitation phase. Orogastric intubation is preferred in infants. Decompression of the urinary bladder also facilitates abdominal evaluation. Rectal examination can be very useful.

Haemodynamically unstable patients with distension of the abdomen require surgical intervention immediately after completion of primary and secondary surveys, as already described in the "damage-control approach". In less critically injured patients, the evaluation should be deepened. Radiographic examination of chest, pelvis and cervical spine (lateral) should be done to identify possible associated injuries, massive gastric distension and intraperitoneal air and to verify the positioning of the gastric tube [9]. Haemoglobin concentration test should be performed, and blood also sent for cross-match. Some studies have also shown the utility of serum AST/ALT and urinanalysis in the evaluation of intra-abdominal injury [63-65]. Serum amylase and lipase have been proposed as markers of pancreatic injury, but the data are controversial [66-68].

Ultrasonography is widely used in adults to evaluate abdominal trauma. Data on the paediatric population are still few, but a recent study of 313 children by Soudack M et al. [69] showed that focused assessment by sonography in trauma (FAST) is an effective tool in screening paediatric trauma patients [69]. Nonetheless, it is not recommended as an alternative to CT scanning.

CT scanning has been the standard of care for evaluating the haemodynamically stable paediatric patient since the mid-1980s and can clearly identify injuries to spleen, liver, kidney, pancreas and retroperitoneum [70]. CT scanning has also been recently proposed for the evaluation of pelvic fractures and associated injuries [71]. Identification of intestinal injuries may be more difficult and requires a combination of strong clinical suspicion, careful evaluation of CT scans and serial physical examinations [72]. Both oral and intravenous contrast should be used. It is important to remember that a conscious child usually requires sedation.

Diagnostic peritoneal lavage (DPL) can be used to detect intra-abdominal bleeding in the hypotensive child, especially when ultrasonography is not readily available. The technique is the same as in adults but the risk of iatrogenic damage of the abdominal organs is higher due to the thinner abdominal wall. Retroperitoneal organs cannot be evaluated reliably by this technique. However, the presence of blood in the peritoneum (whether confirmed by CT, DPL or FAST) is not itself mandatory for celiotomy in a child. By contrast, the presence of leukocytosis, faeces, vegetable fibres, and/or bile in the lavage mandates celiotomy.

Nonoperative management

Nonoperative management of paediatric patients with blunt abdominal trauma is the current standard [73, 74]. The rationale for this approach is based on the fact that injury to the spleen, liver, and kidneys causes a bleeding that is usually self-limiting. As noted above, the presence of intraperitoneal blood on CT, DPL, or ultrasound does not necessarily mandate a celiotomy. Celiotomy is restricted to those patients that cannot be haemodynamically normalised by primary fluid resuscitation. Despite this, abdominal trauma is still considered a surgical disease [75, 76]: nonoperative management of visceral injuries is decided by a surgeon, who also decides whether to operate. Continuous involvement and repeated examinations by a surgeon are mandatory while paediatric intensive-care facilities are made available to the patient.

Most pelvic fractures can be successfully managed nonoperatively; the need for surgical intervention is more frequent for associated injuries. However, a long-term review is indicated because of delayed complications in children due to their further growth and development [61].

Spleen and liver injury

The spleen is the most commonly involved organ in abdominal trauma in children, and nonoperative management is successful in more than 90% of patients [77]. Contrast-enhanced CT scanning is approximately 95% sensitive and specific in detecting splenic injury [78]. However, the presence of contrast blush on CT may be insufficient to determine the need for intervention [79, 80]. Indications for surgical intervention are haemodynamic instability, rapid deterioration or evidence of associated hollow viscus injury. In children with spleen trauma managed nonoperatively, 10-23% require blood transfusion. The goal of nonoperative management is to avoid postsplenectomy infection, most often caused by *Streptococcus pneumoniae,* and in general preservation of splenic function [81]. Signs and symptoms of spleen injury include Kehr's sign (referred pain to the left shoulder due to diaphragmatic irritation), left-upper-quadrant abrasion, distension or tenderness. Injury grade and the presence of associated injuries are associated with an increased indication for splenic operation [82, 83].

Liver injuries are usually more severe than in adults [84] but they can be successfully treated with nonoperative management in 85-90% of patients. Symptoms do not substantially differ from those of splenic injury. In addition, elevated transaminase levels are highly suggestive for hepatic trauma [63-65]. Diagnosis is made by CT scanning, but the CT-scan grade of injury alone is not predictive of outcome. Haemodynamic instability and/or peritoneal signs require rapid intervention. In case of intervention, focused surgery to control haemorrhage is preferred rather than large hepatic resection, and definitive intervention is delayed.

Other visceral injuries

Small bowel injury is not very frequent but can be caused by seatbelt. The child may present with a transverse midabdominal ecchymosis, abdominal pain, and back pain. CT scan alone is not a reliable tool and diagnosis require a high level of suspicion especially in patients with seatbelt signs and intraperitoneal free fluid in the absence of solid-organ injury. A seatbelt can also cause mesenteric disruption (that may lead to ischaemic insult and delayed stricture and perforation), rupture of the bladder and duodenal perforation.

Duodenal and pancreatic injury are relatively uncommon and are caused in children more often by bicycle handlebars (blunt epigastric trauma). For duodenal injury, as well as for pancreatic lesions without a major ductal injury, treatment with bowel rest, nasogastric suction and parenteral nutrition is often successful. By contrast, any rupture or perforation of a hollow viscus is an indication for operative intervention. All these injuries can be misdiagnosed because of vague early symptoms and difficult interpretation of radiological findings [58].

Muscoloskeletal trauma

Muscoloskeletal injuries are an important cause of long-term morbidity and disability in children, because of the unique anatomy and physiology of the immature skeleton. Bone growth occurs by membranous bone formation in flat bones and by endochondral ossification in long bones. In the long bones, the physes, located between the metaphysis and the epiphysis, are the weakest structures – until skeletal maturity. In fact, they are even more vulnerable than ligaments and thus can be frequently damaged in trauma. Physeal injuries must be carefully treated to avoid the risk of physeal arrest and subsequent angular deformity or limb length inequality.

The immature, pliable nature of bones in children may lead to a so-called greenstick fracture. Such fractures are incomplete, with angulation maintained by cortical splinters on the concave surface [9]. An adequate radiological assessment is fundamental to fully evaluate these injuries.

Open fractures usually derive from a high-energy trauma and lead to soft-tissue damage that is often prioritised in trauma management. Irrigation and debridement, with removal of necrotising and contaminated tissue, is the key point of the initial treatment and should be urgently performed. However skeletal stabilisation is important to prevent further damage of soft-tissues.

One possible complication of musculoskeletal trauma is compartment syndrome. Symptoms include pain disproportional to the extent of injury, pain at passive movement, paresthesias, and pulselessness. However, even in the presence of a pulse a compartment syndrome cannot be excluded. Intracompartmental pressure can be measured especially in unconscious patients. The treatment is fasciotomy.

Vascular injuries are relatively rare in children [85] and usually are caused by supracondylar distal humerus fractures, distal femur fractures, knee dislocations,

proximal tibia fractures, open tibial shaft fractures, and displaced pelvic fractures. As for compartment syndrome, the presence of a pulse does not exclude an injury. Doppler and sometimes an angiogram are indicated when arterial injury is suspected. In each case, the surgeon is responsible for balancing the benefits and risks of a revascularisation [86].

Fat embolism is rare but not impossible in children, and must be suspected when a patient with multiple bone injuries presents with tachycardia, hypoxemia, dyspnoea, axillary petechiae and sensorial changes as well as pulmonary infiltrates at a radiogram.

Blood loss associated with long-bone and pelvic fractures is proportionately greater in children than in adults and may lead to haemodynamic instability.

Stabilisation of fractured extremities in splints is required after secondary survey, while definitive treatment and stabilisation is delayed. Injuries that require a more urgent treatment include the above mentioned compartment syndrome, vascular injuries, open fractures, but also some irreducible joint dislocations, which are associated with a high risk of vascular lesions (tibiofemoral) or bone ischaemia (hip, talus) [87].

Cervical spine and spinal cord injuries

Paediatric spinal cord injury is a relatively uncommon problem, responsible for approximately 2-5% of all spinal cord injuries [88]. However, evaluation of cervical spine and spinal cord injuries may be challenging in children. Spinal cord injuries may occur even in the absence of fractures, especially in younger children. This condition is called spinal cord injury without obvious radiographic abnormality (SCIWORA). In children <8 years old, 80% of spinal cord injuries occur in the cervical spine. By contrast, Reddy et al. [89] found that the distribution of fractures in the spine reported in the literature is quite variable. As in adults, children may present with neurogenic shock. Difficulties in alignment and protection of the column have already been described. The role of steroids in children is controversial. Current recommendation in adults is administration of an initial bolus of methylprednisolone of 30 $ml \cdot kg^{-1}$, followed by an infusion of 5.4 $mg \cdot kg^{-1} \cdot h^{-1}$ for 24 to 48 h, but there are no specific recommendations for paediatric patients.

In children who have experienced trauma and who are not alert and nonconversant, or who have neurological deficit, midline cervical tenderness, or painful distracting injury, or are intoxicated, it is recommended that anteroposterior and lateral cervical spine X-rays be obtained before cervical spine clearance. In children >9 years of age, also an open-mouth cervical spine x-rays should be done. Dynamic films may be useful when the suspicion of instability remains after static X-rays, or to exclude gross ligamentous instability. CT scanning is used to exclude occult fractures and to have a better definition of fractures, especially since some regions are not adequately seen with plain X-rays [90]. It is important to remember that a negative CT scan does not exclude the presence of an instability, since SCIWORA may be present especially in children <8 years of age. Magnetic resonance imaging (MRI) has become quite useful in the evaluation of spinal cord injuries and some

centres use it as the standard for cervical clearance, due to the possibility of SCIWORA [91]. MRI is a valuable and cost-efficient method in the evaluation of potential spinal cord injury, especially in obtunded children or children with equivocal plain radiographs [92]. It is very sensitive at detecting ligamentous disruption and instability. Nevertheless, the routine use of MRI is associated with serious problems in an emergency, especially regarding resuscitation and monitoring during the procedure, as well as the immediate availability of the MRI equipment or 24 h a day.

The basic principles of treatment are the same as in adults. Timing of decompression and surgical intervention are controversial, but an important consideration to be made in children is concern about future growth.

Anaesthesia in the paediatric trauma patient

Emergency intervention is required in less than 30% of the paediatric trauma events. No evidence can be found for the administration of anaesthesia procedures in the multiple trauma paediatric patient. General anaesthesia is most commonly selected although local and regional anaesthesia techniques can be used for minor procedures.

Preparation of the patient with multiple trauma injuries

During anamnesis, the mechanism of trauma, pre-existing pathologies and time of last meal should be evaluated. Full stomach preparation is recommended when specific data are not available.

The diagnostic information (X-rays, CT scans, laboratory tests, etc.) should be reviewed. Spinal column protection with in-line stabilization of the neck should be established when spinal cord injury has not been excluded.

An intravenous access should be obtained before induction. Possibilities vary from a peripheral vein to a central vein. The intraosseus route (children <6 years) or a surgical approach are valid alternatives (see above).

Physical re-examination should focus on the ABCs of resuscitation. Evaluation of the adequacy of oxygenation with pulse oxymetry and ventilation by auscultation and capnography will provide a rapid assessment of the airway and breathing. If patients arrive without controlled ventilation, then intubation should proceed following the indication previously discussed. Adequate fluid replacement with iso-osmolar fluids is indicated and haemodynamic instability should be treated as previously described. The level of consciousness is determined according to the modified GCS (Table 3).

Whenever possible an informed consent should be obtained from parents or guardian.

Laboratory studies to evaluate the PaO_2, $PaCO_2$, electrolytes, glucose, haematocrit, and coagulation parameters should be obtained, and conditions should be treated appropriately. With ongoing blood loss and transfusion or clinical evidence

of coagulopathy, additional testing should be performed regularly. Lactate levels and pH of the arterial blood gas can be used to evaluate the adequacy of resuscitation [93].

Monitoring

Electrocardiography, pulse oxymetry, noninvasive blood pressure, capnography, and temperature are standard monitoring techniques. Invasive blood pressure and central venous pressure (CVP) measurements are recommended to evaluate haemodynamic status. If CVP is not rapidly available, an estimate of the intravascular volume status can be assessed by examining the systolic pressure variation on the arterial pressure tracing with positive-pressure ventilation. Systolic pressure variation less than 5 mm Hg indicates minimal volume depletion.

In children with insignificant bladder trauma, a urinary catheter should be placed to decompress the bladder, improve surgical exposure and allow for intraoperative detection of haematuria and measurement of urine output.

Pulmonary artery catheter may be considered when there is concern about cardiac dysfunction or pulmonary hypertension.

Maintenance anaesthesia

Administration of anaesthetic agents is based upon patient conditions. Patients who are hypotensive and hypovolaemic will require insignificant amounts of anaesthesia until bleeding is controlled and haemodynamic stability is achieved.

Inhalation agents (isoflurane, sevoflurane, desflurane) can be titrated according to haemodynamic effect. The use of volatile anaesthetics is advantageous in a trauma setting because they can be easily and quickly reversed if the patient becomes suddenly hypotensive.

Nitrous oxide increases the volume of any air-filled space, such as a pneumothorax, and therefore should be used carefully in the setting of trauma patients.

Thiopental and propofol can be used but they may cause more peripheral vasodilation and are not as easily titratable as the volatile anaesthetics.

Narcotic agents (fentanyl, sufentanil) and benzodiazepines can be administered in small incremental doses. Remifentanil, an ultrashort-acting narcotic, should be used cautiously due to the frequent occurrence of a profound reduction in blood pressure and heart rate.

Long-acting nondepolarising muscle relaxants (pancuronium, vecuronium) should be administered to patients not expected to be extubated at the end of the procedure. Atracurium and mivacurium cause relatively short-lived histamine release and should be avoided in hypotensive patients.

Application of warming methods is essential to maintain or increase body temperature [29].

In younger children the use of infusion pumps reduces the risk of fluid overload. Baseline fluid requirements in children are 4 $ml \cdot kg^{-1} \cdot h^{-1}$ for the first 10 kg, 2

$ml \cdot kg^{-1} \cdot h^{-1}$ for each kg between 10 and 20 kg and 1 $ml \cdot kg^{-1} \cdot h^{-1}$ for each kilo over 20 kg. For example, an 18-kg child would require 10x4=40 plus 8x2=16 for a total of 56 $ml \cdot kg^{-1} \cdot h^{-1}$. Aggressive fluid treatment in hypovolaemic shock has been previously described.

Close clinical control during the postoperative period in the ICU is usually the rule in multiple trauma patients.

References

1. Schalamon J, v. Bismarck S, Schober PH et al (2003) Multiple trauma in pediatric patients. Pediatr Surg Int 19: 417–423
2. Van der Sluis CK, Kingma J, Eisma WH et al (1997) Pediatric polytrauma: short-term and long-term outcomes. J Trauma 43:501–506
3. Berry FA (1990) Perioperative anesthetic management of the pediatric trauma patient. Crit Care Clin 6(1):147-163
4. Orliaguet G, Lejay M (1999) Pediatric Trauma Patients. Curr Opin Crit Care 5:506-510
5. Osmond MH, Brennan-Barnes M, Shephard AL (2002) A 4-Year Review of Severe Pediatric Trauma in Eastern Ontario: A Descriptive Analysis. J Trauma 52(1):8-12
6. Dowd MD, Keenan HT, Bratton SL (2002) Epidemiology and prevention of childhood injuries. Crit Care Med. 30 (Suppl 11):S385-S392
7. Wheatley J, Cass DT (1989) Traumatic deaths in children: the importance of prevention. Med J Aust 150(2):72-78
8. Boswell WC, Boyd CR, Scheffner D et al (1996) Prevention of pediatric mortality from trauma: are current measures adequate? South Med J 89(2):218-220
9. ACS Committee on Trauma (1997) Advanced Trauma Life Support for Doctors. Student Course Manual. American College of Surgeons, Chicago.
10. Gill AC (2002) Risk Factors for Pediatric Posttraumatic Stress Disorder After Traumatic Injury. Arch Psychiatr Nurs 16(4):168-175
11. Winston FK, Kassam-Adams N, Garcia-Espana F et al (2003) Screening for risk of persistent posttraumatic stress in injured children and their parents. JAMA 290(5):643-649
12. Winston FK, Kassam-Adams N, Vivarelli-O'Neill C et al (2002) Acute Stress Disorder Symptoms in Children and Their Parents After Pediatric Traffic Injury. Pediatrics 109(6):e90
13. Vladka S, Poenaru D, Dueck A (2000) Long-term disability after trauma in children. J Pediatr Surg 35:684–687
14. Shah AN, Frush K, Luo X et al (2003) Effect of an intervention standardization system on pediatric dosing and equipment size determination: a crossover trial involving simulated resuscitation events. Arch Pediatr Adolesc Med 157(3):229-236
15. Tepas JJ 3rd, Mollitt DL, Talbert JL et al (1987) The pediatric trauma score as a predictor of injury severity in the injured child. J Pediatr Surg 22(1):14-18
16. Letts M, Davidson D, Lapner P (2002) Multiple trauma in children: predicting outcome and long-term results. Can J Surg 45(2):126-131
17. Baker SP, O'Neill B, Haddon W Jr et al (1974) The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. J Trauma 14(3):187-196
18. Mayer T, Matlak ME, Johnson DG et al (1980) The modified injury severity scale in pediatric multiple trauma patients. J Pediatr Surg 15(6):719-726

19. Sullivan T, Haider A, DiRusso SM et al (2003) Prediction of mortality in pediatric trauma patients: new injury severity score outperforms injury severity score in the severely injured. J Trauma 55(6):1083-1087
20. Scalea T (2002) What's New in Trauma in the Past 10 Years. Int Anesthesiol Clin 40(3):1-17
21. Mattox KL (1997) Introduction, background, and future projections of damage control surgery. Surg Clin North Am 77:753–759
22. Rotondo MF, Zonies DH (1997) The damage control sequence and underlying logic. Surg Clin North Am 77(4):761-777
23. Rotondo MF, Schwab CW, McGonigal MD et al (1993) 'Damage control': an approach for improved survival in exsanguinating penetrating abdominal injury. J Trauma 35(3):375-382
24. Morken J, West MA (2001) Abdominal compartment syndrome in the intensive care unit. Curr Opin Crit Care 7:268–274
25. Raeburn CD, Moore EE, Biffl WL et al (2001) The abdominal compartment syndrome is a morbid complication of post injury damage control surgery. Am J Surg 182:542–546
26. Patel JC, Tepas JJ III, Mollitt DL et al (2001) Pediatric cervical spine injuries: Defining the disease. J Pediatr Surg 36:373–376
27. Tobias JD (1996) Airway management for pediatric emergencies. Pediatr Ann 25:317-328
28. Moynihan RJ, Brock-Utne JG, Archer JH et al (1993) The effect of cricoid pressure in preventing gastric insufflation in infants and children. Anesthesiology 78(4):652-656
29. Ross AK (2001) Pediatric trauma. Anesthesia management. Anesthesiol Clin North America. 19(2):309-337
30. Granholm T, Farmer DL (2001) The surgical airway. Respir Care Clin North Am 7:13–23
31. Myer CM 3rd (2004) Trauma of the larynx and craniofacial structures: airway implications. Paediatr Anaesth 14(1):103-106.
32. Langeron O (2000) Trauma Airway Management. Curr Opin Crit Care 6:383-389
33. Schwaitzberg SD, Bergman KS, Harris BH (1988) A pediatric trauma model of continuous hemorrhage. J Pediatr Surg. 23(7):605-609
34. Dellinger RP, Carlet JM, Masur H et al (2004) Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med 32(3):858-873
35. Wetzel RC, Burns RC (2002) Multiple trauma in children: critical care overview. Crit Care Med 30(Suppl 11):S468-S477
36. Kanter RK, Zimmerman JJ, Strauss RH et al (1986). Pediatric emergency intravenous access. Evaluation of a protocol. Am J Dis Child 140(2):132-134
37. Macgregor DF, Macnab AJ (1990) Intraosseous fluids in emergencies. Pediatrics 85(3):386-387
38. White JR, Dalton HJ (2002) Pediatric trauma: postinjury care in the pediatric intensive care unit. Crit Care Med 30(Suppl 11):S478-S488
39. Shemesh E, Keshavarz R, Leichtling NK et al (2003) Pediatric emergency department assessment of psychological trauma and posttraumatic stress. Psychiatr Serv 54(9):1277-1281
40. Holinger PA, Schild JA (1972) Pharyngeal, laryngeal and tracheal injuries in the pediatric age group. Ann Oto Rhinol Laryngol 81:538–545
41. Kadish H, Schunk J, Woodward GA (1994) Blunt pediatric laryngotracheal trauma: case reports and review of the literature. Am J Emerg Med 12(2):207-211
42. Davis RJ (1987) Head and spinal cord injury. In: Roger M (ed) Textbook of Pediatric Intensive Care. Williams & Wilkins, Baltimore, Maryland, p 658
43. O'Connor PJ, Russell JD, Moriarty DC (1998) Anesthetic implications of laryngeal trauma. Anesth Analg 87(6):1283-1284

44. Granholm T, Farmer DL (2001) The surgical airway. Respir Care Clin N Am 7(1):13-23
45. Lichenstein R, Gillette DL (2002) An unusual presentation of stridor: blunt pediatric laryngotracheal trauma. J Emerg Med 22(4):375-378
46. Stafford PW, Harmon CM (1993) Thoracic trauma in children. Curr Opin Pediatr 5(3):325-332
47. Black TL, Snyder CL, Miller JP et al (1996) Significance of chest trauma in children. South Med J 89(5):494-496
48. Peterson RJ, Tepas JJ 3rd, Edwards FH et al (1994) Pediatric and adult thoracic trauma: age-related impact on presentation and outcome. Ann Thorac Surg 58(1):14-18
49. Garcia VF, Gotschall CS, Eichelberger MR et al (1990) Rib fractures in children: a marker of severe trauma. J Trauma 30(6):695-700
50. Bliss D, Silen M (2002) Pediatric thoracic trauma. Crit Care Med 30(Suppl 11):S409-415
51. Nakayama DK, Ramenofsky ML, Rowe MI (1989) Chest injuries in childhood. Ann Surg 210(6):770-775
52. Barsness KA, Bensard DD, Ciesla D et al (2004) Blunt diaphragmatic rupture in children. J Trauma 56(1):80-82
53. Holmes JF, Sokolove PE, Brant WE et al (2002) A clinical decision rule for identifying children with thoracic injuries after blunt torso trauma. Ann Emerg Med 39(5):492-499
54. Allen GS, Cox CS Jr, Moore FA et al (1997) Pulmonary contusion: are children different? J Am Coll Surg 185(3):229-233
55. Bonadio WA, Hellmich T (1989) Post-traumatic pulmonary contusion in children. Ann Emerg Med 18(10):1050-1105
56. Davis SL, Furman DP, Costarino AT Jr (1993) Adult respiratory distress syndrome in children: associated disease, clinical course, and predictors of death. J Pediatr 123(1):35-45
57. Inci I, Ozcelik C, Nizam O et al (1996) Penetrating chest injuries in children: a review of 94 cases. J Pediatr Surg 31:673–676
58. Gaines BA, Ford HR (2002) Abdominal and pelvic trauma in children. Crit Care Med 30(Suppl 11):S416-423
59. Chopra P, St-Vil D, Yazbeck S (2002) Blunt renal trauma-blessing in disguise? J Pediatr Surg 37(5):779-782
60. Nguyen MM, Das S (2002) Pediatric renal trauma. Urology 59(5):762-766
61. Chia JP, Holland AJ, Little D et al (2004) Pelvic fractures and associated injuries in children. J Trauma 56(1):83-88
62. Silber JS, Flynn JM, Koffler KM et al (2001) Analysis of the cause, classification, and associated injuries of 166 consecutive pediatric pelvic fractures. J Pediatr Orthop 21:446–450
63. Holmes JF, Sokolove PE, Brant WE et al (2002) Identification of children with intraabdominal injuries after blunt trauma. Ann Emerg Med 39:500-509
64. Hennes HM, Smith DS, Schneider K et al (1990) Elevated liver transaminase levels in children with blunt abdominal trauma: A predictor of liver injury. Pediatrics 86:87–90
65. Puranik SR, Hayes JS, Long J et al (2002) Liver enzymes as predictors of liver damage due to blunt abdominal trauma in children. South Med J 95:203–206
66. Jobst MA, Canty TG Sr, Lynch FP (1999) Management of pancreatic injury in pediatric blunt abdominal trauma. J Pediatr Surg 34:818–823
67. Nadler EP, Gardner M, Schall LC et al (1999) Management of blunt pancreatic injury in children. J Trauma 47:1098–1103
68. Adamson WT, Hebra A, Thomas PB et al (2003) Serum Amylase and Lipase Alone Are Not Cost-Effective Screening Methods for Pediatric Pancreatic Trauma. J Pediatr Surg 38:354-357

69. Soudack M, Epelman M, Maor R et al (2004) Experience with focused abdominal sonography for trauma (FAST) in 313 pediatric patients. J Clin Ultrasound 32(2):53-61
70. Kane NM, Cronan JJ, Dorfman GS et al (1988) Pediatric abdominal trauma: Evaluation by computed tomography. Pediatrics 82:11–15
71. Guillamondegui OD, Mahboubi S, Stafford PW et al (2003) The utility of the pelvic radiograph in the assessment of pediatric pelvic fractures. J Trauma 55(2):236-239
72. Meyer PG (1999) Critical care management of severe paediatric trauma: a challenge for anaesthesiologists. Paediatr Anaesth 9(5):373-376
73. Partrick DA, Moore EE, Bensard DD et al (2000) Operative management of injured children at an adult level I trauma center. Trauma 48(5):894-901
74. Cochran A, Mann NC, Dean JM et al (2004) Resource utilization and its management in splenic trauma. Am J Surg 187(6):713-719
75. Acierno SP, Jurkovich GJ, Nathens AB (2004) Is pediatric trauma still a surgical disease? Patterns of emergent operative intervention in the injured child. J Trauma 56:960-966
76. Tepas JJ 3rd, Frykberg ER, Schinco MA et al (2003) Pediatric trauma is very much a surgical disease. Ann Surg 237(6):775-780
77. Upadhyaya P (2003) Conservative management of splenic trauma: history and current trends. Pediatr Surg Int 19(9-10):617-627
78. Minarik L, Slim M, Rachlin S et al (2002) Diagnostic imaging in the follow-up of nonoperative management of splenic trauma in children. Pediatr Surg Int. 18(5-6):429-431
79. Nwomeh BC, Nadler EP, Meza MP et al (2004) Contrast extravasation predicts the need for operative intervention in children with blunt splenic trauma. J Trauma 56(3):537-541
80. Lutz N, Mahboubi S, Nance ML et al (2004) The significance of contrast blush on computed tomography in children with splenic injuries. J Pediatr Surg 39(3):491-494
81. Mooney DP (2002) Multiple trauma: liver and spleen injury. Curr Opin Pediatr 14(4):482-485
82. Mooney DP, Forbes PW (2004) Variation in the management of pediatric splenic injuries in New England. Trauma 56(2):328-333
83. Potoka DA, Schall LC, Ford HR (2002) Risk factors for splenectomy in children with blunt splenic trauma. J Pediatr Surg 37(3):294-299
84. Wakeman C, Beasley S, Pearson S et al (2003) Liver injury in children: causes, patterns and outcomes. N Z Med J 116(1178):U515
85. Shaker IJ, White JJ, Signer RD (1976) Special problems of vascular injuries in children. J Trauma 16:863–867
86. Harris LM, Hordines J (2003) Major vascular injuries in the pediatric population. Ann Vasc Surg 17(3):266-269
87. Musgrave DS, Mendelson SA (2002) Pediatric orthopedic trauma: principles in management. Crit Care Med 30(Suppl 11):S431-S443
88. Reynols R (2000) Pediatric spinal injury. Curr Opin Pediatr 12(1):67-71
89. Reddy SP, Junewick JJ, Backstrom JW (2003) Distribution of spinal fractures in children: does age, mechanism of injury, or gender play a significant role? Pediatr Radiol 33: 776–781
90. [No authors listed] (2002) Management of pediatric cervical spine and spinal cord injuries. Neurosurgery. 50(Suppl 3):S85-S99
91. Frank JB, Lim CK, Flynn JM et al (2002) The efficacy of magnetic resonance imaging in pediatric cervical spine clearance. Spine 27(11):1176-1179
92. Flynn JM, Closkey RF, Mahboubi S et al (2002) Role of magnetic resonance imaging in the assessment of pediatric cervical spine injuries. Pediatr Orthop 22(5):573-577
93. Lee LA, Sharar SR, Lam AM (2002) Perioperative head injury management in the multiply injured trauma patient. Int Anesthesiol Clin 40(3):31-52

Chapter 58

Developments in the treatment of postoperative pain in paediatrics

P. Busoni, A. Messeri

Pain treatment in children is a rather large and complicated topic, which has recently been further developed and enriched by interesting research studies that have been reported in the medical literature. We therefore decided to restrict this paper to postoperative pain control and the problems related to procedural pain.

The undertreatment of children who are in pain following surgery has been recognised. Inadequate treatment of neonates and babies was widespread earlier. However, the 1990s saw a change in physicians' perceptions of neonatal pain and refinement of modern analgesic techniques for use in children [1].

The increased understanding of the neurophysiology of pain and the concept that inadequate treatment of pain can have an impact on outcome and lead to long-term behavioural changes have prompted anaesthetists to study new techniques of pain management in children. In addition, developments are currently in train in clinical pain services, with new, sophisticated analgesia delivery devices and monitoring protocols.

A multimodal approach using locoregional anaesthesia combined with opioids and nonsteroidal anti-inflammatory drugs (NSAIDs) or paracetamol is now widely accepted. The emotional component of pain must also be addressed in all aspects of paediatric practice, and it must be recognised that there is a place for instinctive comforting measures, distraction techniques and new nonpharmacological treatments, all of which should be applied to complement safe and effective use of analgesic drugs.

Pharmacological analgesia

Paracetamol

Paracetamol is widely used to reduce fever and for analgesia. It acts through inhibition of cyclo-oxygenase and is thought to have an analgesic effect on NMDA receptors in the spinal chord. The pharmacodynamics of paracetamol analgesia have not yet been adequately described in humans, and the therapeutic range for analgesia is not well established. Little or no analgesia is obtained below plasma levels of 10 $\mu g\ ml^{-1}$. Paediatric studies using paracetamol 10 $mg\ kg^{-1}$ orally have shown no

more analgesic effect than placebo in children undergoing myringotomy [2].

Anderson et al. [3] gave each of 100 children who were scheduled for tonsillectomy paracetamol, 40 mg kg^{-1}, by the oral or the rectal route. After 50 min the plasma concentration was measured and compared with the degree of analgesia achieved. Anderson demonstrated increasing numbers of patients with satisfactory analgesia as plasma concentrations increased, with a ceiling effect at 25–30μg ml^{-1}.

The peak analgesic effect of paracetamol is not seen until 1 h after its peak plasma concentration is reached. There is evidence for this in terms of the relationship between plasma and cerebrospinal fluid (CSF) paracetamol concentrations. The central analgesic effect is therefore attributed to the ability of paracetamol to cross the blood barrier in high concentrations [4].

The rectal and oral routes of administration are both commonly used in children. A maximum daily dose of 90 mg kg^{-1} day^{-1} is widely accepted as safe [5]; 60 mg kg^{-1} day^{-1} is recommended in neonates [6].

However, there is little published information on which dosing regimen best maintains therapeutic levels. Paracetamol is commonly given in a dose of 10–15 mg kg^{-1} every 4 h p.o. and 15–20 mg kg^{-1} every 4 h rectally.

In neonates the hepatic glucuronide process is not yet mature, and they are capable of forming the reactive intermediate that causes hepatocellular damage, despite a comparatively low level of cytochrome P450 system. However, the rate constant for the sulfation metabolic pathway is larger in neonates than in adults and is the most important route of metabolism.

Anderson et al. conclude that a rectal loading dose of 40 mg kg^{-1} followed by 30 mg kg^{-1} every 12 h by the same route or an oral loading dose of 30 mg kg^{-1} followed by 20 mg kg^{-1} every 8 h p.o. will achieve concentrations of 10–20 mg l^{-1} [7]. However, high doses of paracetamol have to be used for it to be effective, and the problem of cumulative toxicity with repeated dosing has not yet been addressed in neonates. Morton [8] therefore concludes that caution is required when the current dosage maxima are applied for longer than 72 h.

Nonsteroidal anti-inflammatory drugs

The main benefits of NSAIDs in minor, moderate and severe pain derive from an opioid-sparing effect, and they can also be used constructively as a component in a multimodal approach to enhance the quality of analgesia by combining drugs with central and peripheral effects. However, the clinical use of NSAIDs in the perioperative period is sometimes limited for fear of upsetting haemostasis, as they inhibit thromboxane-A2 production with a consequent decrease in platelet function. The effect of NSAIDs on clinical bleeding tendency is difficult to quantify, and generally haemostasis remains below the upper limits found in healthy patients.

Intraoperative use of rectal diclofenac (1 mg kg^{-1}) in children 1–10 years of age has been shown to provide a lower level of postoperative analgesia than 1 ml kg^{-1} of caudal bupivacaine 0.25%, but better pain control in the late recovery phase. The incidence of side-effects is similar for diclofenac and bupivacaine group, being low after either [9].

Ketorolac is a NSAID that is effective in providing postoperative pain relief in most patients. It has been administered i.v. (0.5 mg kg^{-1}) and i.m. (1 mg kg^{-1}); it has been shown to cause a significant reduction in opioid requirements and to shorten the duration of stay in hospital with no evidence of increased bleeding [10].

Opioids

The use of opioids for extended surgery is well established in the paediatric population. Patient-controlled analgesia (PCA) and nurse- or parent-controlled analgesia (NCA) are opioid delivery systems that allow the patient to receive a preset amount of the opioid at preselected intervals. PCA can be used in children as young as 5–6 years of age; when children have control over their own analgesia this has considerable psychological benefits. Kerschlbaum et al. [11] report that the range of patients receiving opioids can be increased with NCA.

Recent studies have focused on the prevention of side-effects, such as postoperative nausea and vomiting (PONV), with PCA morphine [12–15]. Routine prophylactic antiemetic treatment seems to be advisable during paediatric PCA.

Tramèr et al. have [12] shown that droperidol is effective in preventing PONV during adult PCA, but the use of droperidol in children still requires investigation [13]. Other antiemetic agents may be a more appropriate choice. Kokinsky et al. [14] report that a single bolus of diyrazine, a phenothiazine, when anaesthesia is induced leads to a significant reduction of vomiting. It has been demonstrated that tropisetron, a long-acting 5-hydroxytryptamine-3 receptor antagonist, can reduce vomiting during PCA in children [15].

Busoni et al. [16] have shown that dexamethasone reduces the incidence of vomiting when administered i.v. to children for common paediatric operations, and this protective effect should be studied with a view to preventing nausea during the use of PCA. During adult PCA, ketamine has been found to reduce the incidence of PONV [17]. This approach has not yet been studied in children.

Tolerance and respiratory depression are other important side-effects of opioid use. In adults, it may be safe to use ketamine to reduce tolerance [18] and respiratory depression during opioid administration [19]. These findings indicate that the inclusion of small doses of ketamine in a balanced analgesic programme may be an interesting field for future paediatric pain research.

In summary, opioids are effective, but cause side-effects; a multimodal approach to analgesia works best and offers the chance of lower doses of these agents and more rapid weaning from them.

Nonpharmacological methods

Recent research in paediatric pain control strongly suggests that use of relaxation, mental imagery and play can help children to control their pain. Armstrong et al. [20] have demonstrated that there is a role for play in preparation for paediatric anaesthesia. Play therapy can be an effective method of providing tangible infor-

mation about the surgical experience and simultaneously attenuating a child's fantasies and fears about the surgery.

For Bowmer [21], play is a simple way of helping a child to deal with the painful world of hospital and to master situations that might otherwise be overwhelming. The results are rewarding in terms of happier, less anxious, children, parents and medical staff.

Local and regional anaesthesia

The development of locoregional anaesthesia is the result of anatomical studies and of improved understanding and safety of the local anaesthetics in use. In particular, there is increasing interest in peripheral nerve blocks achieved by way of the single-shot technique or by continuous infusion. The continuous infusion method has been developed in adult patients for orthopaedic surgery, and as yet the literature includes little information on its use in paediatric patients [22].

Ropivacaine is a widely used local anaesthetic with a wider margin of safety for paediatric patients. Ropivacaine 0.2% appears to be optimal in terms of producing adequate analgesia with an acceptable degree of motor block; the use of ropivacaine 0.3% is associated with a high incidence of motor block and minimal improvement in postoperative pain relief relative to ropivacaine 0.2% [23]. Higher concentrations of ropivacaine than 0.3% demonstrably provide a lesser degree of motor blockade than equivalent volumes and concentrations of bupivacaine [24].

When a longer duration of anaesthesia with no motor block is needed, clonidine, 2 $\mu g\ kg^{-1}$, or preservative-free ketamine, 0.5 $mg\ kg^{-1}$, will prolong analgesia [25, 26].

However, the main advantage of ropivacaine is its excellent safety profile. It has been successfully used in children, infants and neonates in continuous infusion through a lumbar epidural catheter, although pharmacokinetic data are limited to patients over 3 months old [27].

Levobupivacaine is a new local anaesthetic. It is a single-isomer formulation (*S*[–]-enantiomer of bupivacaine) that is thought to have lower toxicity than compounds with racemic formulae. Studies in human volunteers confirm that it has a smaller arrhythmogenic, and a less negative inotropic, effect than bupivacaine [28]. In recent studies in a paediatric population, levobupivacaine has been used for peripheral and central blocks. It reduced the need for rescue analgesia, providing effective analgesia and a less intense motor block than bupivacaine [29]. The lower toxicity of bupivacaine thus gives a wider safety margin in daily clinical practice, both for single-shot administration and for continuous infusion in paediatric patients.

Conclusions

A lot of new and advanced methods are now available to allow paediatric anaesthetists to provide adequate pain treatment to children. The authors believe that a

multimodal approach to analgesia is the best. Local and regional anaesthesia are commonly used to treat early postoperative pain, combined with systemic drugs given in the appropriate dosages by modern delivery systems. Titration of analgesics against the results of regular reassessment of analgesia is effective. The 'acute pain service' is an institutional way of coordinating analgesic management and is the best way to advance the cause of ensuring comprehensive provision of safe pain control for all children.

Procedural pain is frequently encountered in children, either during an emergency or during disease management. Invasive procedures are known to be the most painful and traumatic events experienced by children. Although procedure-related pain is an acute, short-lived experience, it is accompanied by a great deal of fear and anxiety. For example, researchers have reported that bone marrow aspirations/biopsies and lumbar punctures are perceived as extremely painful by children with cancer. Previous studies have shown that children do not adapt to the discomfort associated with intrusive procedures, but experience greater levels of anxiety with repeated painful experiences. Children often experience symptoms such as depression, insomnia and anorexia before a clinic or hospital visit that will involve a procedure. The consensus among professionals caring for children with cancer supports a developmental approach to managing pain associated with procedures in children with cancer. The goal is to provide comfort and support during all procedures experienced by the child with cancer.

This overview addresses the following questions:

- What will influence the choice of therapy?
- Which procedures are included?
- Are therapeutic interventions supported by efficacy and safety data?
- Is there any evidence to support combining drugs and nonpharmacological techniques?
- How can the risk of analgesia-related complications be reduced?

What will influence the choice of therapy?

Many factors influence the therapy selected. These include the expected intensity and duration of pain, the age of the child at any previous unpleasant experience, whether the need results from an emergency, what the environment is like and the human resources available. Even in the case of similar procedures, therapeutic interventions sometimes vary considerably even in the same country. In a Swedish nationwide survey of pain treatment in paediatric oncology, lumbar punctures were performed under general anaesthesia in half of the institutions taking part and without general anaesthesia in the remaining centres. The expected intensity and duration of pain depends on the procedure involved and on the patient. Even a simple venous puncture can be described as the worst pain for some children. There is evidence that young children experience more distress and warrant more consideration than older children subjected to similar procedures. Safety considerations are essential when painful procedures are to be managed in remote loca-

tions. Education of nursing staff and of physicians without specialist training in anaesthesiology is a key issue in improving the safety of analgesia-sedation techniques.

Which procedures are included?

'Procedural pain' includes pain caused by many different procedures and situations. The procedures involved ranged from simple phlebotomy to invasive procedures involving serious risks should the patient move in response to the painful stimulus.

Are therapeutic interventions supported by efficacy and safety data?

Procedures can be divided into three categories in terms of pain and/or discomfort:
- Minor (venipuncture, Port-a-cath puncture, intravenous cannulation)
- Moderate (lumbar puncture, bone marrow aspiration)
- Major (fracture reduction, endoscopy)

For minor and moderate procedures 50% nitrous oxide and local anaesthetics, used alone or in combination, have clearly proved their effectiveness and safety. Other oral, intravenous/intramuscular agents of many chemical groups are currently in use. However, although many practitioners have anecdotal practice patterns that they believe are highly successful, the literature does not clearly support any one practice pattern over others.

Is there any evidence to support combining drugs and nonpharmacological techniques?

A wide range of behavioural and cognitive techniques has been found to be efficacious in helping children to cope with acute procedural pain. Many existing interventions and assessment tools are reasonably easy to use, allowing practitioners to identify the children who will be most vulnerable to pain and to reduce pain-related distress significantly in these children. However, the degree to which cognitive-behavioural management can be applied is limited in a child who is very young or has already been severely traumatised. The availability of expert practitioners is also limited in many centres.

How can the risk of analgesia-related complications be reduced?

Large surveys of adverse events encountered during procedural sedation have been reported in the past. In studies involving midazolam-fentanyl- and propofol-fentanyl-based regimens respiratory adverse event rates of 5–10% have been observed.

In contrast, the incidence of serious adverse events is around 1% with such agents as low-dose i.v. ketamine or nitrous oxide.

Prevention of procedural pain should be a priority for all physicians. Premixed nitrous oxide, local anaesthetics and low-dose i.v. ketamine share the same advantageous safety profile and are useful for most minor and moderately extensive procedures. The combination of hypnotics and opioids requires close monitoring and should be reserved for trained physicians. Cognitive behavioural therapies are a valuable adjunct that can be applied to reduce procedure-related distress and should be used whenever possible. Organisation and education are essential to reduce the potential hazards associated with unintentionally deep sedation. The published guidelines should be followed to minimise the incidence of severe adverse events [30].

References

1. De Lima J, Lloyd-Thomas AR, Howard RF et al (1996) Anesthetists' perception of and prescribing for infant and neonatal pain. BMJ 313:787-792
2. Watcha MF, Ramirez-Ruiz M, White PF et al (1992) Perioperative effect of oral ketorolac and acetaminophen in children undergoing bilateral myringotomy. Can J Anaesth 39:649-654
3. Anderson B, Kunagasundarum S, Woollard G (1996) Analgesic efficacy of paracetamol in children using tonsillectomy as a pain model. Anaesth Intensive Care 24:669-673
4. Piguet V, Desmeules J, Dayer P (1998) Lack of acetaminophen ceiling effect on R-III nociceptive flexion reflex. Eur J Clin Pharmacol 53:321-324
5. Anderson JB (1998)What we don't know about paracetamol in children. Paediatr Anaesth 58:451-460
6. Alder Hey Hospital (1998) Guidelines on the management of pain in children, 1st edn. Alder Hey Hospital, London
7. Anderson JB, Holford NHG, Woollard GA (1997) Paracetamol kinetics in neonates. Anaesth Intensive Care 25:721-722 (A)
8. Morton NS, Arana A (1999) Paracetamol-induced fulminant hepatic failure in a child after 5 days of therapeutic doses. Paediatr Anaesth 15:43-46
9. Moores MA, Wandless JG, Fell D (1990) Paediatric postoperative analgesia. A comparison of rectal diclofenac with caudal bupivacaine after inguinal herniotomy. Anaesthesia 45:156-158
10. Gunter JB, Varughese AM, Harrington JF et al (1995) Recovery and complications after tonsillectomy in children: a comparison of ketorolac and morphine. Anesth Analg 81:1136-1141
11. Kerschbaum G, Altmeppen J, Funk W, Taeger K(1998) Parent controlled analgesia in a 3-year-old boy after traumatic amputation. Anaesthesist 47:238-242
12. Tramèr MR, Walder B (1999) Efficacy and adverse effect of prophylactic antiemetics during patient controlled analgesia therapy: a quantitative systematic review. Anesth Analg 88:1354-1361
13. Habre W, Wilson D, Johnson CM (1999) Extrapyramidal side-effects from droperidol mixed with morphine for patient-controlled analgesia in two children. Paediatr Anaesth 9:362-364
14. Kokinsky E, Thomberg E, Nilsson K et al (1999) Postoperative nausea and vomiting in

children using patient-controlled analgesia: the effect of prophylactic intravenous dixyrazine. Acta Anaesthesiol Scand 43:191-195
15. Ang C, Habre W, Sims C (1998) Tropisetron reduces vomiting after tonsillectomy in children. Br J Anaesth 80:761-763
16. Busoni P, Crescioli M, Agostino R et al (2000) Vomiting and common paediatric surgery. Paediatr Anaesth 10:639-643
17. Adriaenssens G, Vermeyen KM, Hoffmann VLH et al (1999) Postoperative analgesia with i.v. patient-controlled morphine: effect of adding ketamine. Br J Anaesth 83:393-396
18. Lauretti GR, Lima ICPR, Reis MP et al (1999) Oral ketamine and transdermal nitroglycerin as analgesic adjuvants to oral morphine therapy for cancer pain management. Anesthesiology 90:1528-1533
19. Persson J, Scheinin H, Hellstrom G et al (1999) Ketamine antagonises alfentanil-induced hypoventilation in healthy male volunteers. Acta Anaesthesiol Scand 43:744-752
20. Armstrong TSH, Aitken HL (2000) The developing role of play preparation in paediatric anaesthesia. Paediatr Anaesth 10:1-5
21. Bowmer N (2002) Therapeutic play and the impact on anxiety in hospitalized children. Ky Nurse 50:15-20
22. Sciard D, Matuszczak M, Gebhard R et al (2001) Continuous posterior lumbar plexus block for acute postoperative pain control in young children. Anesthesiology 95:1521-1523
23. Bosenberg A, Thomas J, Lopez T et al (2002) The efficacy of caudal ropivacaine 1, 2 and 3 mg × l(-1) for postoperative analgesia in children. Paediatr Anaesth 12:53-58
24. Da Conceincao MJ, Coehlo L (1998) Caudal anaesthesia with 0.375% ropivacaine or 0.375% bupivacaine in paediatric patients. Br J Anaesth 80:507-508
25. De Negri P, Ivani G, Visconti C et al (2001) How to prolong postoperative analgesia after caudal anaesthesia with ropivacaine in children: *S*-ketamine versus clonidine. Paediatr Anaesth 11:679-683
26. Ivani G, De Negri P, Conio A et al (2000) Ropivacaine-clonidine combination for caudal blockade in children. Acta Anaesth Scand 44:446-449
27. Hansen TG, Ilett KF, Lim SI et al (2000) Pharmacokinetics and clinical efficacy of long-term postoperative epidural ropivacaine infusion in children. Br J Anaesth 85:347-353
28. Bardsley H, Gristwood R, Baker H et al (1998) A comparison of the cardiovascular effects of levobupivacaine and rac-bupivacaine following intravenous administration to healthy volunteers. Br J Clin Pharmacol 46:245-249
29. Ivani G, De Negri P, Conio A et al (2001) Levobupivacaine vs ropivacaine vs bupivacaine in pediatric caudal anesthesia (abstract). ASA Annual Meeting, abs Anesthesiology
30. Vanhelleputte P, Nijs K, Delforge M et al (2003) Pain during bone marrow aspiration: prevalence and prevention. J Pain Symptom Manage 26:860-866

TRAUMA AND EMERGENCY SYSTEM

Chapter 59

Prehospital care: triage and primary survey

O. Predescu, A. Baker

Trauma is one of the main causes of critical illness and death in the whole world and is also the leading cause of death in the first four decades of life; it is an epidemic disease of society.

European versus American emergency medical system

The main difference between the two emergency medical systems consists in the fact that in the Anglo-American system the patient is brought to the doctor, while in the Franco-German system, the doctor is brought to the patient. Emergency patients, like the trauma patients, are treated by the emergency physicians and paramedics at the scene and during transport in the European system, compared with the American system where the treatment is applied in the emergency department. In North America, the paramedics apply the medical principles of an emergency department physician, while in the Franco-German system the doctor at the scene acts as a intensive care unit extender, having also the potential of the more accurate prehospital triage [1].

In North-America, the initial call for trauma is via the police or fire department; who are trained to provide basic life support, including cardiopulmonary resuscitation, keeping the airways open, bag-valve-mask ventilation and manual tamponade of external bleeding sites. Emergency medical technicians and paramedics extract trauma victims from the accident site, immobilize them for transport and provide advanced life support manoeuvres. The distance, geography, logistics and patient condition determine the method of transport and the first and second destination. For example, if the patient is profoundly unstable haemodynamically, it may be better to stop at the nearest hospital to begin stabilization before transportation to the certified trauma centre, where the trauma team leader, the anaesthetist or the intensivist, the emergency physician, neuroradiologist, neurosurgeon, general surgeon and orthopaedist should already be in the emergency room.

In Europe, physicians arrive at the scene of the accident with the ambulance. Improved resuscitation and survival to discharge has been reported when cardiac arrest is managed by doctors from 1% to 13% in a Danish study [2]. However, the presence of the physicians and their very early start of advanced trauma support at the field site seems not to improve the outcome compared with the patients who

were immediately transported to the trauma centre, where procedures can be performed safely and effectively [3].

Epidemiology

The three main causes of major trauma are motor vehicle accidents, firearms and falls. Motor vehicles accidents in United States resulted in 3,033,000 injuries, 42,116 fatalities and 500,000 hospitalizations in 2001. Young adults are at the highest risk of fatal and non-fatal injuries due to car accidents. Their death, hospitalization and emergency department visiting rates are double the rates for all the other ages. The highest death rate due to motor vehicle injury is in New Zeeland (63 per 100,000), followed by the United States with 41 per 100,000. Males die from motor vehicle accidents more than twice as often as females in the 15-44 age group [4, 5]. Gun-related death affects males and young people; for the 10-24 year age group, firearms are the second leading cause of death [4]. Falls account for less than 8% of deaths due to trauma; the greatest risk is in the very young and in the elderly, being more severe in the latter group. The profile of injuries in Canada is provided by the National Trauma Registry; 48% of all reported severe injuries were related to motor vehicle accidents and 42% of all reported deaths were car accident related. [6]

Trauma deaths occur in a tri-modal distribution: an immediate period, accounts for more than half of all trauma death and occurs at the scene as a result of severe brain, spinal cord, heart or major vessel injuries. Research, trauma care excellence and functional trauma system cannot lower the incidence of these deaths. The other half of the deaths is almost equally divided in the early and the late period. The early period regards death appearing in the first few hours of injury. The continuous improvement of the prehospital care of trauma patients is aimed at reducing early death by applying effective and rapid advanced trauma life support (ATLS) manoeuvres. Late deaths regard trauma deaths that occur days or weeks after the injury, mainly owing to multiple system organ failure and sepsis [7]. Because death is related to the severity of injury, a reduction in morbidity and mortality related to trauma would be possible mainly with an efficient prevention program.

Trauma care system

The trauma care system is an organized approach designed to provide the acutely injured patient with personnel, facilities and equipment for rapid initial and optimal treatment within a defined geographic area [4]. The trauma system is based on field triage guidelines enabling the delivery of patients to the designated trauma centre. There are clinical and operational components of a trauma care system:

Public education and injury prevention aim to eliminate the trauma incidents.

Human resources regard the qualified personnel running the system – physicians, nurses and emergency medical technicians.

Prehospital care has a direct effect on survival. The paramedics in the prehospital system evaluate the patients at the scene and report patients' status using mechanistic, anatomic and physiological criteria for entering the trauma system. The grade of care that paramedics should deliver at the scene and during transport is controversial. Prehospital care includes airway management, external bleeding control, immobilization of the spine, needle decompression of suspected tension pneumothorax and immobilizing the major fractures of limbs.

Communication between components of the trauma care system is very important for obtaining optimal trauma care.

Medical directions may be "off line" in terms of protocols to be applied by paramedics, concerning triage, treatment, transport, or "on line", provided by the hospital physician.

Triage – the adaptation of the patient need to the system resources. The result of the triage should be that the critically injured patient reaches the trauma centre promptly and safely.

Transport – the choice of the transport mode is made on what is the best for the patient in terms of time to definitive care.

Trauma care centres, level I or the tertiary care hospitals represent the leader in the system with optimal trauma care, quality improvement, education and research. *Level II* trauma centres are also able to provide complete treatment for trauma patients, but do not have educational and research programs. *Level III* has the role of stabilizing and initial resuscitation measures for major trauma patients. *Level IV* has the role of assuring initial care and they should have well functioning protocols for rapid transfer of the patients [4, 8].

A reduction of 9% in the mortality rate in regions where trauma care system functions has been demonstrated, which means that thousand of lives would be saved if the system were available universally [8]. The principles involved in the initial assessment of a patient with a major trauma are well established by the American College of Surgeons in the ATLS guidelines or by the Australasian College of Surgeons in The Early Management of Severe Trauma guidelines.

Prehospital care – Triage

One of the most well known recent disasters necessitating well defined triage criteria was the September 11, 2001 attack. In only one day New York City had more than 7,000 victims needed to be seen and evaluated primarily in three hospitals; 550 of them required admission [9].

The whole medical triage process is based on classification, determining priorities and assessing the best treatment. Within a trauma system, triage involves the process of identifying which patient needs to be sent to the designated trauma centre.

Under-triage occurs when the patient's injury is underestimated; the delay in diagnosis and treatment is potentially life-threatening. Over-triage means that the patient's injuries were overestimated; this patient will probably be sent to the trauma

centre without medical indications. Both cases increase the morbidity and mortality of the trauma patients [10], although over-triage is safer than under-triage [11].

There are triage criteria determining whether a given patient requires emergency medical serivces transport to the hospital or an alternative. The first step in triage is measurements of the vital signs (systolic blood pressure <90, respiratory rate <10 or >29) and of the level of consciousness (Glasgow coma score <13) followed by anatomical and mechanism of injury assessment, age of the patient and preexisting conditions such as history of cardiac or pulmonary disease and environmental factors – all of this being described in a triage system's field criteria, and having impact on morbidity and mortality. The ideal triage system will direct the most severe trauma patient to the most appropriately staffed hospital and transport the other patients with less severe injuries to hospitals in the geographic area. It seems that faster transport to the hospital, such as transporting the severe blunt trauma patient by helicopter emergency trauma medical system into a Level I trauma centre, markedly reduces mortality [12, 13]. In the case of large natural or manmade disaster the triage laws are governed by the principle that the treatment of the population must have priority over the individual's treatment. In accordance with the available resources and the numbers and types of causalities, this means that some possible salvageable patients may not be treated [10].

The prehospital phase implies outcome measurements based on hospital admission, critical events, death and diagnosis. The outcome assessment is based on classical trauma scores.

Based of the general medical principle – first, do no harm – there are debates and concerns whether or not to start resuscitative manoeuvres in the field and how extensive they should be. Because of the most probable causes of early death in trauma, paramedics are focused on relieving airway obstruction and maintenance of the airways, control of external bleeding and management of shock, prevention of deterioration of an unstable spine by immobilization of the patient, prevention of secondary brain injury and transport to the closest trauma centre.

Manoeuvres such as in-field endotracheal intubation, which is not a therapeutic standard for paramedics in prehospital care, is more often encouraged by trauma systems. A comparison of prehospital and hospital data in trauma patients conclude that there is a decreased risk of fatal outcome in the in-field intubated patients with blunt injuries and low Glasgow coma score [14]. Airway protection is often the single most important therapy to be administrated at a scene and endotracheal tube placement could be a lifesaving manoeuvre. There are, however, potential detrimental effects of in-field intubation so further well designed statistical studies should be performed to resolve this question [15].

Intravenous crystalloid administration in prehospital period care is recommended in patients with blunt injuries; aggressive intravenous fluid administration is indicated only in patients with penetrated injuries and shock and when the transport will last more than 30 min [5]. There is major controversy in the literature related to timing, volume and type of fluid used for resuscitation in the trauma patient and the general conclusion is, again, that further large prospective randomized trials are needed to establish standards [16-20].

The indication for fluid resuscitation in haemorrhagic shock are restoring the plasma volume, restoring the microcirculatory flow and assuring adequate oxygen delivery. The injured hypovolaemic patient needs to have reversal of hypovolaemia and control of haemorrhage. The ATLS guidelines do not specify which should be done first but lactated Ringer's solution is the crystalloid of choice in class II haemorrhages or higher in the prehospital settings, delivered through two large bore peripheral intravenous cannulae. The recommended infusion volume is related to the 3:1 ratio, but probably a ratio of 10:1 would be more appropriate for crystalloid replacement because of the ongoing haemorrhage, capillary leak and decreased serum oncotic pressure. An initial bolus of 1-2 L of Ringer's lactate or normal saline is the routine [21].

Special consideration should be given to in-field fluid resuscitation of traumatic head injury [22]. Secondary brain injury related to hypotension (systolic blood pressure <90 mmHg) and hypoxaemia (PaO_2 <60 mmHg or apnea or cyanosis in field) significantly increases the morbidity and mortality. The primary objective of fluid resuscitation in these patients is to minimize secondary brain injury related to hypotension by using adequate resuscitation measures for maintaining a normal cerebral perfusion pressure and avoiding brain oedema. Another challenge in field resuscitation is for the patients with spinal cord injury that can have haemorrhagic shock associated sometimes with neurogenic shock that will maintain the hypotension in spite of aggressive fluid resuscitation.

Another area of investigation is the hypertonic saline (7.5% NaCl or 3% NaCl) [23-26] resuscitation of the patients with hypotension and traumatic brain injury. There are many advantages of the hypertonic solutions over the isotonics: a small volume of hypertonic solution is as effective as a large volume of isotonic solutions in expanding plasma volume and enhancing cardiac output. Hypertonic saline increases perfusion of the microcirculation by selective arteriolar vasodilatation and by decreasing swelling of the red blood cells and the endothelium; it also markedly decreases the inflammatory response, specifically the neutrophil cytotoxicity. The benefits of hypertonic saline in patients with closed traumatic brain injury is that it decreases the intracranial pressure. Other hypertonic and oncotic solutions studied in traumatic brain injury are hypertonic saline/dextrane (HDS: 7.5% NaCl + 6% dextran 70 or 4.5% dextran) [27-29].

The prehospital care providers have the earliest opportunity to start the treatment for diminishing the effects of secondary brain injury. There are defined brain-oriented standards for basic, advanced and prolonged life support aiming to maintain a normal blood pressure, adequate oxygenation and maintaining normocapnia or achieving an $EtCO_2$ of 30-35 mmHg when high intracranial pressure signs are present [30, 31], and cooling of the head and trunk [32-34]. Other studies [35, 36], however, have not yet shown a benefit in outcome in patients treated with early mild hypothermia.

On the debate of colloids versus crystalloids in fluid resuscitation, the Cochrane 2004 review analysis concluded that there is no evidence from randomized controlled trials that resuscitation with colloids reduces the risk of death compared with crystalloids. The Cochrane analysis also concluded that there are not

enough data as to whether the hypertonic solutions are better than isotonic crystalloids.

A potential prehospital treatment for decreasing the need for massive crystalloid administration could be earlier administration of blood, in particular red blood cells. However blood products administration is not part of in-field trauma life support measures, probably based on the limited supply of stored blood and the potential adverse effects related to blood product transfusion. Haemoglobin-based oxygen carriers seem to be a promising therapy. Further, for quick in-field haemorrhage control in hypothermic, coagulopathic and acidotic patients, rVIIa may be a candidate [37].

Another possible future approach of the patient with haemorrhagic shock could be the induction of suspended animation [38, 39] – defined as a profound cooling of the whole body for the protection and preservation of the organism for up to 2 hours of no flow (cardiac arrest) or low flow (shock) status allowing the transport of the patient and the control of bleeding and followed by delayed resuscitation.

The initial evaluation and initiating of adequate supportive therapy of a polytraumatized, multiple injured person is a challenging task and every minute can make a difference between life and death. There is no gold-standard for the triage system in part because there are no consensus definitions for major trauma. Probably the most important aspect of prehospital care is to efficiently and rapidly organize either the definitive therapy or transfer to a trauma centre able to provide definitive therapy.

Primary survey

Principles involved in the initial assessment (primary survey) of the patient with major trauma are those outlined by the American College of Surgeons in their ATLS guidelines. Usually this occurs in the hospital phase, the place of action being the emergency department. It is performed by the trauma team.

The aim of the primary survey is to identify and immediately treat life-threatening injuries and is defined by the mnemonic formula ABCDE: airway control and stabilization of cervical spine, breathing (work and efficacy), circulation and control of external bleeding, disability or neurological status and exposure or undressing of the patient, while also protecting from hypothermia. The primary survey continues with monitoring (with urinary catheter and gastric tube insertion) and x-rays. Initial resuscitation films should be limited to a lateral cervical spine film, anterior-posterior chest x-ray and an antero-posterior pelvis film, although the body computed tomography scan for the multiple injured trauma patient (haemodynamically stable) is now routine in many institutions. For intra-abdominal bleeding detection, the focused assessment with sonography for trauma (FAST) or diagnostic peritoneal lavage are mandatory screening studies for the patient in shock. During the primary survey, while making clinical assessment, performing intervention following an ABC protocol, an initial working diagnosis should be established.

Secondary survey

The secondary survey represents a complete reassessment of the patient; it formally begins after completing the primary survey by stabilizing the life-threatening injuries. It includes a detailed history, a complete physical examination "from head to toe", additional indicated x-rays or other specialized studies (CT, angiography) and laboratory tests. The AMPLE history should include information about allergies, past medication history, past medical history, last meal and full description of the events leading to injury and hospital admission. The mechanism of injury is very important regarding the apparition of occult injuries missed at the first clinical examination. Pain and distracting injuries also increase the risk of unidentified lesions. During this stage of trauma care, the patient should be continuously monitored: cardiac rhythm, pulse oxymetry, end-tidal carbon dioxide monitoring, frequent blood pressure measures, mental status exam, and clinical assessment of peripheral perfusion.

During the secondary survey, the ABCDE of the patient should be constantly reevaluated and ongoing diagnostic and therapeutic plans should be formulated and updated. If at any time during the secondary survey the patient's clinical status deteriorates, the rescuer should return to the elements of the primary survey. Once the patient has had the acute life-threatening injuries stabilized during the primary survey and has had the major injuries identified during the secondary survey stage, the patient should have priorities set for definitive therapeutic management.

The ideal system for management of trauma it is still controversial, especially concerning prehospital care and the geographical aspects related to trauma care delivery [40]. The trauma care system seems to work well in urban regions, but there are still organizational problems in rural regions. Telemedicine – the use of tele-conferencing and tele-consultation – may play an important role in providing educational programs, real-time medical consultation and tele-radiology hoping to improve the care of the trauma patients in the future [41]. For the trauma patient it is very important to receive the right care at the right time and in the right place.

References

1. Dick W (2003) Anglo-American vs. Franco-German emergency medical system. Prehospital and Disaster Medicine 18:29-37
2. Frandsen F, Nielsen JR, Gram L (1991) Evaluation of intensified prehospital treatment in out-of-hospital cardiac arrest: survival and cerebral prognosis – the Odense Ambulance study. Cardiology 79:256-264
3. Lieberman M, Mulder D, Lavoi A (2003) Multicenter Canadian Study of Prehospital Trauma Care. Annals of Surgery 237:153-160
4. Mattox K, Feliciano D, Moore E (2000) Trauma. 4th edn, McGraw-Hill, New York
5. Richards C, Mayberry J (2004) Initial management of the trauma patient. Crit Care Clin 20:1-11
6. Kortbeek J, Buckley R (2003) Trauma care system in Canada. Injury Int J Care Injured 34:658-663

7. Alexander R, Proctor H (1993) ATLS Instructor manual, American College of Surgeons, Chicago
8. Hoff W, Schwab C (2004) Trauma system development in North America. Clinical orthopaedics and related research 422:17-22
9. Hoey B, Schwab C (2004) Level I center triage and mass casualties. Clinical orthopaedics and related research 422:23-29
10. Frykberg E (2002) Medical management of disaster and mass casualities from terrorist bombing: how can we cope. J Trauma 53:201-212
11. Cone D, Benson R, Schmidt T (2004) Field triage system: methodologies from the literature. Prehospital Emergency Care 8:130-137
12. Biewener A, Aschenbrenner U, Rammelt S (2004) Impact of helicopter transport and hospital level on mortality of polytrauma patients. J Trauma 56:94-98
13. Thomas S (2004) Helicopter emergency medical services transport outcomes literature. Prehospital Emergency Care 8:322-333
14. Arbabi S, Jurkovich G, Wahl W (2004) A comparison of prehospital and hospital data in trauma patients. J Trauma 56:1029-1032
15. Bochicchio GV, Scalea TM (2003) Is field intubation useful? Curr Opin Crit Care 9:524-529
16. Shafi S, Kauder D (2004) Fluid resuscitation and blood replacement in patients with polytrauma. Clinical Orthopaedics and Related Research 422:37-42
17. Boldt J (2004) Fluid choice for resuscitation of the trauma patient:a review of the physiological, pharmacological, and clinical evidence. Can J Anesth 51:500-513
18. Revell M, Greaves I, Porter K (2003) Endpoints for fluid resuscitation in hemorrhagic shock. J Trauma 54:S63-S67
19. Rizoli S (2003) Crystaloids and colloids in trauma resuscitation:a brief overview of the current debate. J Trauma 54:S82-S88
20. Kramer G (2003) Hypertonic resuscitation:physiologic mechanisms and recommendation for trauma care. J Trauma 54:S89-S99
21. Werdan K, Schuster HP (2004) Schock in der Prähospital- und Hospitalphase. Internist 45:257-276
22. Rouxel J, Tazarourte K, Le Moigno S (2004) Prise en charge préhospitalière des traumatisés crâniens. Ann Fr Anesth Réanim 23:6-14
23. Bunn F, Tasker R, Akpa E (2004) Hypertonic versus isotonic crystalloid for fluid resuscitation in critically ill patients. The Cochrane Library 2, John Wiley & Sons
24. Anderson P, Schierhout G, Roberts I (2004) Colloids versus crystalloids for fluid resuscitation in critically ill patients. The Cochrane Library 2, John Wiley & Sons
25. Chiara O, Pelosi P, Brazzi L (2003) Resuscitation from hemorrhagic shock: experimental model comparing dextran and hypertonic saline solution. Crit Care Med 31:1915-1922
26. Bhardwaj A, Ulatowsky J (2004) Hypertonic saline solutions in brain injury. Curr Opin Crit Care 10:126-131
27. Cooper J Myles P, McDermott F (2004) Prehospital hypertonic saline resuscitation of patients with hypotension and severe traumatic brain injury. JAMA 291:1350-1357
28. Wade CE, Grady JJ, Kramer GC (1997) Individual patient cohort analysis of the efficacy of hypertonic saline/dextran in patients with traumatic brain injury and hypotension. J Trauma 42:S61-S65
29. Alpar EK, Killampalli VV (2004) Effect of hypertonic dextran in hypovolemic shock: a prospective clinical trial. Injury, Int J Care Injured 35:500-506
30. David JS, Cresta MP, Souab A (1999) Traumatismes crâniens graves: effets de la ventilation mécanique préhospitalière sur la capnie. Ann Fr Anesth Réanim 17:398-402

31. Lal D, Weiland S, Newton M (2003) Prehospital hyperventilation after brain injury: a prospective analysis of prehospital and early hospital hyperventilation pf the brain-injuried patient. Prehospital Disaster Med 18:20-23
32. Layon J, Gabrielli A, Friedman W (2004) Textbook of neurointensive care. Saunders, Philadelphia
33. Chestnut R (2004) Management of brain and spine injuries. Crit Care Clin 20:25-55
34. Kabon B, Bacher, A Spiss C (2003) Therapeutic hypothermia. Best Pract Res Clin Anest 17:551-568
35. Clifton G (2004) Is keeping cool still hot? An update on hypothermia in brain injury. Curr Opin Crit Care 10:116-119
36. Clifton G, Miller E, Choi S (2001) Lack of effect of induction of hypothermia after acute brain injury. N Engl J Med 344:556-563
37. Moore F, McKinley B, Moore E (2004) The next generation in shock resuscitation. The Lancet 363:1988-1996
38. Tiesherman S (2003) Trauma fluid resuscitation in 2010. J Trauma 54:S231-S234
39. Tisherman S (2004) Suspended animation for resuscitation from exsanguinating hemorrhage. Crit Care Med 32 :S46-S50
40. Nathens AB, Brunet FP, Majer RV (2004) Development of trauma systems and effect on outcomes after injury. Lancet 363:1794-1801
41. Smith SR (2001) Telemedicine and Trauma Care. South Med J 94:825-829

Chapter 60

Spine and spinal cord trauma

O. Predescu, A. Baker

Case Thirty-One

Title: Instruction concerning a dislocation in a vertebra of [his] neck.

Examination: If thou examinest a man having a dislocation in a vertebra of his neck, shouldst thou find him unconscious of his two arms (and) his two legs on account of it, (and) urine drops from his member without his knowing it; his flash has received wind; his two eyes are bloodshot; it is a dislocation of a vertebra of his neck extending to his backbone which causes him to be unconscious of his two arms (and) his two legs. If, however, the middle vertebra of his neck is dislocated, it is an emissio seminis which befalls his phallus.

Diagnosis: Thou shouldst say concerning him: "One having a dislocation in a vertebra of his neck, while he is unconscious of his two legs and his two arms, and his urine dribbles. An aliment not to be treated." [1, 2]

This is the first spinal injury related document dating back to the time of the ancient Egyptian Imhotep (2640 BC), and contained in what is now known as the Edwin Smith papyrus. It is a textbook of surgery describing in detail and systematically the examination, diagnosis, treatment and prognosis of clinical cases like vertebral subluxations and dislocations as well as quadriplegia and paraplegia in patients with upper and lower cervical spine injuries.

For almost 4,600 years acute spinal cord injury has been one of the most traumatic, disabling and devastating conditions for individuals, medical staff and society in general.

Epidemiology and demographics

Traumatic spinal cord injury is one of the major causes of morbidity in developed countries [3]. The National Spinal Cord Injury Statistical Center at the University of Alabama reported in 2002 that 250,000 Americans were suffering from spinal cord injuries, of which 52% are considered paraplegic and 47% tetraplegic [4]. The annual incidence of spinal cord injury (SCI), excluding those who die at the scene of the accident, is of approximately 40 cases per million population or approximately 11,000 new cases each year. Eighty-two percent of patients are male, but it seems that the 4:1 ratio has been decreasing over the last few years [5]. The average age of the spinal cord injured person is 31 years and 56% of injuries occur in patients

between 16 and 30 years old. SCI are most commonly caused by motor vehicle accidents (37%), acts of violence (28%), falls (21%), are sport-related (6%) or have other causes (8%). The most rapidly increasing cause of injuries is due to violence – from 13.9% in 1973-1977 to 21.8% in 1994-1998 [5]; motor vehicle accident injuries are decreasing in number.

Clinical findings in spinal cord injury

The clinical picture of the acute spinal cord injury has remained almost the same as the description offered by the ancient Egyptians. The clinical examination depends on the pattern of the spinal cord injury. A complete spinal cord transection syndrome, if the level of injury is high cervical, is clinically characterized by respiratory insufficiency, tetraplegia, complete anaesthesia below the affected level, ileus, bowel retention, delayed gastric emptying and abdominal distension (symptoms that characterize spinal shock), and hypothermia, hypotension and bradycardia (neurogenic shock – occurring more commonly in injuries above T6). The spinal shock is due to axonal and cellular dysfunction, ionic conduction shift, spinal inhibitory pathways and hyperpolarization of caudal motor nerves, lasting for a period of hours to days.

An incomplete spinal cord injury, depending on the location of the lesion, can be described as an anterior cord syndrome, caused by compression of the lateral corticospinal and spinothalamic tracts, but preserving the posterior tract, with complete motor loss below the lesion and preservation of deep touch, position and vibration sensation. The central cord syndrome is caused by a central injury of the cord and affects the lower motor neurons and the tracts that decussate at that level, with a more severe loss of power in the upper extremities compared with the lower extremities and with a variable altered sensation. Brown-Séquard syndrome, or hemisection of the cord, is characterized by loss of motor power, position and vibratory sense on the side of the injury and loss of temperature sensation on the other side. Touch is only slightly impaired. Posterior syndrome cord results in the loss of the sense of position, while cauda equina syndrome is characterized by symmetrical motor and sensory loss of bladder and bowel control.

The severity of injury is best described by the American Spinal Injury Association impairment scale. International standards for neurological and functional classifications of SCI assess motor function in 10 muscle groups (arm, C5-T1; legs, L2-S1) and sensation (light, touch and pinprick) in 28 dermatomes (C2-S4/5) on both sides of the body.

Pathophysiology

The mechanism of spinal cord injury involves two stages. Primary spinal cord injury, directly related to trauma, involves compression or traction forces as well as distraction, laceration or shear forces on the spinal cord which are caused by the

initial impact, the resulting bone fragments and persisting compression. It is also possible that the impact can lead to severe ligamentous injuries only without evidence of affected bones, with spontaneously dislocated and reduced spinal cord. [6] The most frequent injury levels is the cervical level C1 to C1-T7, accounting for 55%; the remaining 45% is equally divided between T1-T11, T11-L2 and L2-S5. Diving injuries in particular occur in the cervical region because of increased mobility of this region, smaller vertebrae and reduced ligamentous and muscular strength of stabilization structures. SCI arises from different types of vertebral column injuries. The distribution of column injuries which cause cord injury is fracture-dislocation (40%), burst fractures (30%), compression fractures (10%) and dislocations alone (5%). Spinal cord injuries without obvious radiological abnormality or evidence of trauma account for 15% of cases [3].

Primary injury tends to affect mainly the central grey matter, probably because it is softer and because of its greater vascularisation [6-8]. Secondary spinal cord injury is a cascade of self-perpetuating biochemical and cellular events leading to neuronal death. There are many mechanisms and theories proposed to explain secondary spinal cord insult [7, 9].

The vascular theory follows the evidence that there are systemic and local changes that occur in spinal cord blood flow after acute spinal cord injury [10]. Ischaemic events start in the central grey matter immediately after the injury, spreading to the surrounding white matter and become progressively worse if they remain untreated [7]. The cause of this ischaemia can be the vasospasm due to the direct mechanical trauma or liberation of vasoactive amines. Posttraumatic haemorrhages or thrombosis may promote ischaemia. Glutamate, the major excitatory neurotransmitter in the central nervous system (CNS) seems to be involved, being excessively released after injury. The spinal cord swells and occupies the entire spinal canal at the level of injury. When the cord swelling exceeds the venous pressure, blood flow autoregulation is impaired exacerbating ischaemia. Systemic hypotension further decreases spinal cord blood flow, and hypertension does not necessarily improve blood flow, and may in fact aggravate the oedema. The loss of autoregulation starts at the same time as the ischaemic events, around 60-90 min after the injury and persists for more than 24 h [7]. The period of reduced perfusion is followed by a "luxury perfusion" stage. This hyperaemia tends to exacerbate injury and cellular death due to the increased production of oxygen free radicals and nitric oxide during the reperfusion period [6]. Acute spinal cord injury is one of the causes of neurogenic shock characterized by decreased vascular sympathetic tone and unopposed vagal tone, decreased systemic vascular resistence and decreased cardiac output, leading to hypotension and bradycardia.

Electrolyte imbalance is found in injured cells as they lose the integrity of the neuronal membrane and permit extracellular ions to enter the cell. Changes in sodium, potassium, calcium and water concentration gradient between the cell and the extracellular fluid causes tissue swelling. The injured cells will release breakdown products such as prostaglandins, leukotrienes, toxic levels of excitatory amino acids and free radicals. The increased vascular permeability for protein leads to vasogenic oedema and regional blood flow declines. The blood-brain barrier is

altered and local tissue reperfusion will lead to haemorrhagic infarction and further damage to cells. Inflammatory cell infiltration and glial reaction begins at the periphery of the lesion. Macrophages will eventually remove debris, resulting in cystic cavitations in the spine. Apoptosis may occur as a result of changes in the cells resulting in axonal demyelination. Apoptosis occurs around the lesion as well as in the ascending and descending white matter tracts [7]. Neurotransmitter accumulation, including serotonin, catecholamines, and acetylcholine as well as inflammation and endogenous opioids are other contributors to secondary injury mechanisms.

Management Principles

The care and the treatment of persons suspected of suffering from SCI begins with the emergency medical system personnel. Firstly, physicians must diagnose early, relieving cord compression and correcting evident misalignments of the spine, concomitant with the ATLS resuscitation protocols. Secondly, they must minimize cellular-level damage, a complex neuroprotective approach. Thirdly, they must stabilize the vertebrae to prevent further injury. All first aid personnel must be trained in the fundamental aspects of spinal cord injury resuscitation, with attention to homeostasis, including normotension, normoxia, prevention of hypothermia and spinal misalignment.

Prevention of re-injury to the spinal cord by stabilization of segments with abnormal motion – application of a rigid collar and a backboard are primary measures which should be done at the scene. Any movement of the patient during transport is performed with strict head alignment. The optimal prehospital management of the SCI patient includes four specific goals: initial resuscitation, immobilization of the patient, extrication from the place of injury and early transportation to hospital [11].

Therapeutic interventions, while overlapping, can be thought of in three main periods [12]: the first 8 h post injury is the period for reducing the initiation of secondary injury and any effects of these secondary injuries. The second period is in the first few days and is dedicated to the intensive care unit (ICU) treatment of the different organ insufficiencies and providing surgical stabilization of the spine; the third treatment period addresses sequellae after the establishment of the definitive lesion.

Critical Care

Respiratory insufficiency and pulmonary dysfunction are common especially if the injury is at the cervical level [13]. With higher cervical spinal injury, above C_3, the patient will have almost total muscle paralysis. Such patients do not cough, tidal volumes are very low, reduction in vital capacity and inspiratory capacity. They can have glosopharyngeal breathing for a short period of time, using the tongue,

cheek, pharyngeal and laryngeal muscles to bring air into the trachea [14, 15]. These patients will experience hypoxaemia, which can exacerbate the spinal cord ischaemia following trauma, so they need early intubation and mechanical ventilation. The bronchial hygiene protocol for tetraplegia secondary to cervical spinal cord injury include [15]: stabilization of the spinal column every 2 h for position changing in the bed, deep breathing manoeuvres, assisted cough, bronchodilators, fibre-optic bronchoscopy if there is persistent atelectasis, and frequent monitoring of pulmonary mechanics [16].

Intubation of the spinal cord injured patient is a challenge for health care professionals. The safest procedure seems to be awake fibre optic intubation, or nasotracheal intubation if there are no other contraindications, but also oro-tracheal intubation can be safely performed with manual in-line stabilization of the column. Hyperextension of the neck should be avoided to prevent further spinal stenosis and spinal cord compression. Airway securing can be facilitated by using muscle relaxant drugs. The use of succinylcholine carries the increased risk of hyperkalaemia due to potassium loss via a proliferation of extrajunctional receptors usually starting 2-4 days after injury.

Cardiovascular instability is directly correlated to the severity of SCI. Hypotension is common after acute SCI. It usually responds to volume repletion, but some patients require vasopressors for maintaining a systolic pressure above 100 mmHg. Episodic hypotension unrelated to hypovolaemia appears in 68% of patients with severe cervical injuries [14]. Invasive haemodynamic monitoring in the ICU for acute SCI patients is very useful because it allows early identification and prompt treatment of cardiac dysfunction and haemodynamic instability. If the infusion of 1-2 L of intravenous fluids fails to increase the blood pressure to normal levels, there may be the need of increasing cardiac output; but because the cardiac accelerator fibres have been interrupted in cervical and upper thoracic lesions, the heart is not able to increase the heart rate; an α and β adrenergic drug such as dopamine or norepinephrine should be used for increasing the sympathetic tone and offering chronotropic positive effects [17]. What normal blood pressure means regarding spinal cord perfusion pressure is not very well established, but it seems that aggressive volume resuscitation to a mean arterial pressure of at least 85 mmHg improves spinal cord perfusion and neurological outcome after spinal cord traumatic injury [17, 18].

The patient with acute SCI is at increased risk of thromboembolic disease, pulmonary embolism or deep venous thrombosis. Patients with SCI have a threefold greater risk of developing venous thrombembolism than other trauma patients. The use of compressing devices from the first day and low molecular weight heparin 3 days after the accident appears to be safe[17].

Treatment possibilities for limitation of secondary injury

Specific pharmacological intervention for preventing secondary injury and neuroprotection is still a very controversial subject. The National Acute Spinal Cord

Injury Studies, NASCIS I, II in 1990 and III in 1997 were meant to evaluate the efficacy of methylprednisolone, the required dose and timing, and to compare methylprednisolone with tirilazad mesylate – a nonglucocorticoid inhibitor of lipid peroxidation (NASCIS III) [19, 20]. The last study concluded that treatment with methylprednisolone, with a loading dose of 30 mg/kg intravenously is beneficial when given within 8 h of injury. When the loading dose is given within 3 h of injury, then 5.4-mg/kg intravenous continuous infusion is recommended. Patients receiving the loading dose between 3 to 8 h will have the same dose, but for 48 h. Corticoids are thought to act as an neuroprotective agent, inhibiting lipid peroxidation, and so preserving Na, K homeostasis, attenuating glutamate release, preserving aerobic metabolism, preserving calcium homeostasis and inhibiting calpain-mediated cytoskeletal damage [21]. The study conclusion about tirilazad was that there is no rational for using it in the treatment of SCI [22].

Some of the conclusions of NASCIS II and III have been challenged on the basis of a lack of compelling data, statistical analysis and clinical significance to the patient. In addition, the overall safety of steroids with respect to serious complications, such as increased septic complications, pneumonia, respiratory failure, urinary tract infection and hyperglycaemia [21, 23] and possible lethality after this corticoid dose administration [23, 24], may not have received sufficient analysis. As such, while some centres consider this standard therapy, others still consider it investigational.

The gangliosides are present in high concentration in the CNS, mainly in the cell membrane. GM-1 ganglioside accelerates neurite growth and stimulates nerve regeneration. There is some evidence that it accelerates recovery from acute SCI in severe incomplete injuries. Both GM-1 ganglioside and methylprednisolone are recommended as treatment options only in recently published guidelines.

Several other pharmacological agents have been studied, each of them targeting different pathophysiological mechanisms of the secondary posttraumatic spinal cord injury. None has emerged yet as standard therapy [25]. Thyrotropin-releasing hormone may antagonize auto-destructive factors such endogenous opioid, leukotrienes, excitatory amino acids, and may augment spinal blood flow, restore ionic balance and reduce lipid degradation, but its use is still under research. It has been shown that the level of the endogenous antioxidants – vitamins A, E, C, Se – is decreased after SCI so the antioxidants may be a possible treatment in the future. The calcium channel blocker nimodipine has been investigated based on the observations that the intracellular increase in calcium levels is involved in toxic neuronal cell death. Magnesium, Na channel blocker, K channel blocker, N-methyl-d-aspartate receptor agonists, modifiers of apoptosis, erythropoietin are some of the investigated future treatment options [26-29].

Another therapeutic question is what is the ideal temperature for the SCI patient. Similar to that for brain injuries, animal studies for SCI [30] show that mild systemic hypothermia is neuroprotective and may have beneficial effects on the outcome, but further studies should be done for establishing when hypothermia must be applied, and for how long.

The third therapeutic approach in SCI is stabilizing the vertebrae to prevent

further injury. The benefit of surgical treatment for unstable injuries include a decrease in hospital length of stay and a decrease in the complication appearing during prolonged immobilization, as well as enabling an earlier start of the rehabilitation programme [31].

The best timing for surgery is still under investigation. Guidelines for the management of acute cervical spine and spinal cord injury state that there are not yet sufficient data to declare standards, but there are recommendations [12]: immobilization of the patient at the scene with cervical collar and back-board, use of the American Spinal Injury Association classification to assess the neurological and functional status of the spinal cord, a standard radiological assessment for cervical spinal trauma – three view cervical spine series plus computed tomography; dynamic flexion-extension x-ray or magnetic resonance imaging for discontinuing the collar in awake patients with normal radiological and computed tomography images, but with neck pain. Standards include prophylactic treatment of thromboembolism, rotating beds, pneumatic compressing stockings and appropriate spinal column stabilization. Surgery for urgent decompression in the presence of bilateral facet dislocation and incomplete spinal cord injury with neurological deteriorating patient is class III evidence. Early surgery does not increase the complication rate after ASCI, and the ideal timing for surgery needs further randomized trial [32-34].

Four thousand six hundred years ago physicians, priests and magicians worked together in the art of healing. More advanced and more scientific than in ancient Egyptian times, SCI treatment remains a field of much creative research potential.

References

1. Encyclopaedia Britannica – online content
2. Wilkins R, Smith E (1964) Cyber Museum of Neurosurgery, Surgical Papyrus. Journal of Neurosurgery 21:240-244
3. Sekhon L, Fehlings M (2001) Epidemiology, demographics, and pathophysiology of acute spinal cord injury. Spine 26:S1-S11
4. The University of Alabama National Spinal Cord Injury Statistical Center – (2002)
5. Nobunaga AI, Go BK, Karunas RB (1999) Recent demographic and injury trends in people served by the Model Spinal Cord Injury Systems. Archive of Physical Medicine and Rehabilitation 80:1372-1382
6. Koyanagi I, Iwasaki Y, Hida K (2000) Acute cervical cord injury without fracture or dislocation of the spinal column. J Neurosurg (Spine)1 93:15-20
7. Tator C, Fehlings M (1991) Review of secondary injury theory of acute spinal cord trauma with emphasis on vascular mechanisms. Journal of Neurosurgery 75:5-7
8. Dumont R, Okonkwo D, Hulbert RJ (2001) Acute spinal cord injury, part I: pathophysiologic mechanisms. Clinical Neuropharmacology 24:254-264
9. McDonald J, Sadowsky C (2002) Spinal-cord injury. The Lancet 359:417-425
10. Tator C, Izumi K (1997) Vascular mechanism in the pathophysiology of human spinal cord injury. Journal of Neurosurgery 86:483-49
11. Wardrope J, Locker T (2004) Risk assessment for spinal injury after trauma. BMJ 328:721-723

12. Edmond P (2004) Measurements in spinal cord injury. Spine 42:209-210
13. Hadley M (2002) Management of acute spinal cord injuries in an intensive care unit or monitored setting. Neurosurgery 50:S51-S57
14. Ball P (2001) Critical care of spinal cord injury. Spine 26:S27-S30
15. Levi L, Wolf A, Belzberg H. (1993) Hemodynamic parameters in patients with acute cervical cord trauma: description, intervention and prediction of outcome. Neurosurgery 33:1007-1017
16. Singhal A, Baker A, Fehlings M (2003) Spinal cord injury management, in Andrews B (ed) Intensive care in neurosurgery. Thieme, New York, pp 137-141
17. Mansel JK, Norman JR. (1990) Respiratory complication and management of spinal cord injuries. Chest 97:1446-1453
18. Vale FL, Burns J, Jackson AB (1997) Combined medical and surgical treatment after acute spinal cord injury; results of a prospective pilot study to assess the merits of aggressive medical resuscitation and blood pressure measurement. J Neurosurg 87:239-246
19. Bracken M, Shepard M, Holford T (1998) Methylprednisolone or tirilazad mesylate administration after acute spinal cord injury: 1 year follow up. J Neurosurg 89:699-706
20. Bracken M, Holford T (2002) Neurological and functional status 1 year after acute spinal cord injury: estimates of functional recovery in National Acute Spinal Cord Injury Study II from results to modeled in National Acute Spinal Cord Injury Study III. J Neurosurg (Spine 3) 96:259-266
21. Hurlbert RJ, Moulton R (2002) Why do you prescribe methylprednisolone for acute spinal cord injury? A Canadian perspective and position statement. Can J Neurol Sci 29:236-239
22. Hurlbert RJ (2000) Methylprednisolone for acute spinal cord injury: an inappropriate standard of care. J Neurosurg (Spine 1) 93:1-7
23. Hugenholtz H, Cass DE, Dvorak MF (2002) High-dose methylprednisolone for acute closed spinal cord injury – only a treatment option. Can J Neurol Sci 29:227-235
24. Benzel E (2002) Commentary on National Acute Spinal Cord Injury Study III. J Neurosurg (Spine 3) 96:257-258
25. Hall E (2001) Pharmacological treatment of acute spinal cord injury: how do we build on past success? The Journal of Spinal Cord Medicine 24:7-11
26. Brewer K, Hardin JS (2004) Neuroprotective effects of nicotinamide after experimental spinal cord injury. Academic Emergency Medicine; 11:125-130
27. Dumont R, Verma S, Okonkwo D (2001) Acute spinal cord injury, part II: contemporary pharmacotherapy. Clinical Neuropharmacology 24:265-279
28. Kaptanoglu E, Solaroglu I, Okutan O (2004) Erythropoietin exerts neuroprotection after acute spinal cord injury in rats: effect on lipid peroxidation and early ultrastructural findings. Neurosurg Rev 27:113-120
29. Shibuya S, Miyamoto O, Janjua NA (2004) Posttraumatic moderate systemic hypothermia reduces TUNEL positive cells following spinal cord injury in rat. Spinal Cord 42:29-34
30. Pollard M, Apple D (2003) Factors associated with improved neurologic outcomes in patients with incomplete tetraplegia. Spine 28:33-38
31. Tator C, Fehlings M, Thrope K (1999) Current use and timing of spinal surgery for management of acute spinal cord injury in North America: result of a retrospective multicenter study. J Neurosurg (Spine 1) 91:12-18
32. Fehlings M, Tator C (1999) An evidence-based review of decompressive surgery in acute spinal cord injury: rationale, indications, and timing based on experimental and clinical studies. J Neurosurg (Spine 1) 91:1-11

33. Fehlings M, Sekhon L, Tator C (2001) The role and timing of decompression in acute spinal cord injury; what do we know?, what we should do? Spine 26:S101-S110
34. Muraszko K (2003) What's new in neurological surgery. J Am Coll Surg 196:919-925

Chapter 61

Treatment of acute pneumothorax in the field

G. Berlot, D. Massarutti, E. Carchietti

The occurrence of pneumothorax (PNX) in trauma patients represents a potentially lethal injury that can sometimes be hard to recognise at the scene but at the very same time relatively easy to treat even in the out-of-hospital setting. Actually, although no precise data are available, it has been estimated that in our region the incidence of PNX exceeds 80 cases/million inhabitants/year [1]. The most frequent cause is traffic accidents; however, the incidence likely underestimates the real frequency of PNX, as: (a) previous studies demonstrated than abnormal air collections were present in as many as 40% of patients with blunt chest injuries and in virtually all patients with penetrating injuries; and (b) its occurrence can go unnoticed in patients dying on the scene or immediately thereafter, before the implementation of any diagnostic work-up [2]. Independent of this consideration, it appears that: (a) PNX is present, with different degrees of severity, in a substantial number of trauma patients; (b) it can, within minutes, result in decompensation, especially in mechanically ventilated patients, leading to the development of cardiovascular collapse, which may be attributed to other causes; and (c) it represents a cause of death that is relatively easy to prevent, provided that it is recognised early and treated rapidly . Guidelines for the treatment of spontaneous PNX have been issued [3], but they apply only partially in the extra-hospital environment. Recently, the treatment of traumatic PNX as well as of other life-threatening thoracic injuries has been significantly modified due to the development of both new devices and diagnostic techniques; as a result, several different approaches have been recommended [4].

Pathophysiology of PNX

Basically, in circumstances associated with trauma, air can penetrate the pleural space through two different routes [5]:

a. From a breakdown of the lung and/or of the tracheobronchial tree following a blunt trauma, causing a rapid increase in intrathoracic pressure that overcomes the distensibility of the tissues involved. A peculiar form of PNX is caused by air collection initially developing in the mediastinum and distally spreading into the pleural or pericardial space via the broncho-vascular sheaths [6, 7].
b. From a penetrating wound of the chest wall. This kind of PNX may be associated with extensive tissue damage and blood loss, and carries a substantial risk of

late infections [4].

Beside these causes, in trauma patients as well as in other critically ill patients, PNX can also occur following certain therapeutic manoeuvres, such as central-vein cannulation, thoracentesis, and as a consequence of elevated transpulmonary pressure associated with an inappropriately high volume and/or pressure, as determined by the use of intermittent positive pressure ventilation (IPPV) or positive end-expiratory pressure (PEEP).

Independent of the cause, the presence of air in the pleural space is associated with a number of consequences involving both respiratory and cardiovascular function. First, it reduces or totally abolishes the subatmospheric (negative) pressure existing within the pleura. The underlying mechanisms differ between spontaneously breathing and mechanically ventilated patients. During spontaneous breathing, even a minimal defect of the lung and/or of the airways can cause a consistent escape of air into the pleural space due to a sucking effect exerted by the negative pressure of the latter. The leak of air due to this mechanism will cease when pressures are equilibrated. When IPPV or PEEP is applied, air is driven outside the airways during inspiration, setting the stage for a more rapid cardiorespiratory decompensation than that which occurs during spontaneous breathing. Second, the increased intrapleural pressure causes the lung to collapse, leading to a loss of gas-exchanging surface and to the development an intrapulmonary shunt. Moreover, in the spontaneously breathing patient, a partially collapsed lung causes an ineffective ventilation, as an amount of air moves to and from the other lung without participating in respiration, ultimately leading to the development of hypoxaemia possibly associated with hypercapnia. In head trauma patients, conditions are particularly relevant for the development of secondary brain injury [8]. Third, the increased intrapleural pressure exerts a dual effect on the circulation: initially, the loss of pleural negativity causes a reduced venous return, which can be further aggravated by a concomitant hypovolaemia. Later on, if enough pressure develops inside the pleural space, the mediastinum is displaced toward the contralateral side, leading to a kinking of the venae cavae (Fig. 1). Finally, different direct negative actions of tension PNX on the heart have been hypothesised, including clockwise rotation of the heart around its longitudinal axis and acute right ventricular overload related to the increased pulmonary vascular resistances. In extreme cases, a reduction of the coronary blood flow related to the elevation of intrapleural pressure has been demonstrated as well [9].

The pathophysiologic disturbances associated with PNX may not be present in the initial phase, especially in subjects with good cardiac and respiratory reserve; however, it must be recalled that these can be overcome in minutes, making a high index of suspicion necessary.

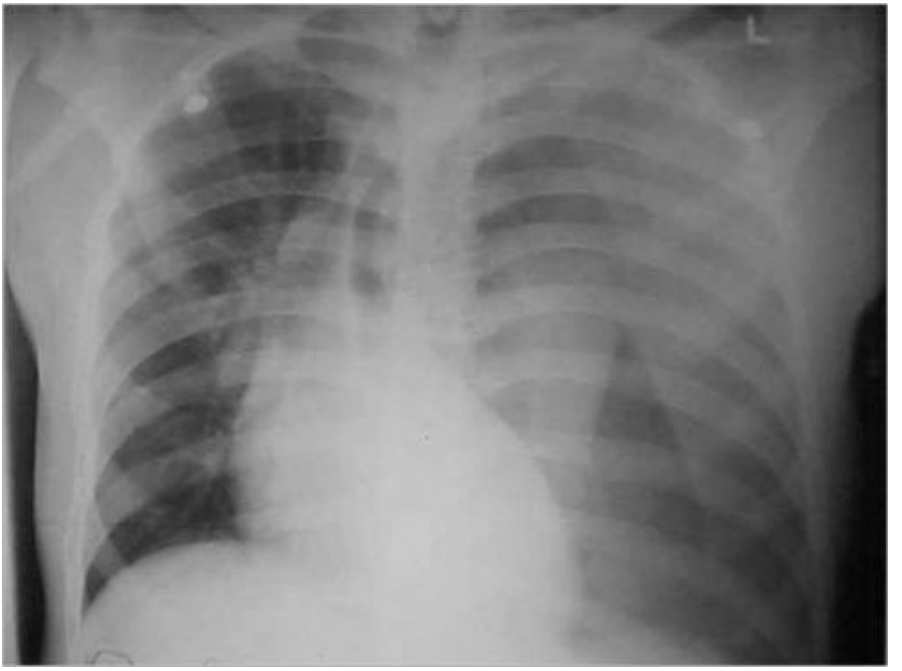

Fig. 1. Hypertensive pneumothorax: the mediastinum is massively displaced rightward (see text)

Diagnosis

The clinical diagnosis of PNX is based on a constellation of signs and symptoms primarily related to the above-described pathophysiologic derangements of the involved functions (Table 1). Unfortunately, some of them (i.e. tachycardia, arterial hypotension) are rather unspecific in trauma patients whereas others, albeit more specific, are hard to recognise in a noisy and messy out-of-hospital setting (i.e. unilateral reduced breath sounds). Moreover, as stated above, in young and healthy spontaneously breathing patients the clinical picture can be silent even in the presence of a PNX (Fig. 2). However, this situation can rapidly change especially when an IPPV or PEEP is applied. This appears particularly relevant in patients with suspected PNX as: if they must be intubated and mechanically ventilated due

Table 1. Signs and symptoms suggestive of pneumothorax in patients with blunt injury

Physical examination	Cardiovascular signs	Respiratory signs
Cyanosis	Tachycardia	Tachypnea, dyspnea
Subcutaneous emphysema	Hypotension	Increased percussion note
Flail chest	Pulsus paradoxus	Decreased breath sounds
Presence of ruptured ribs		Asymmetry of the chest wall

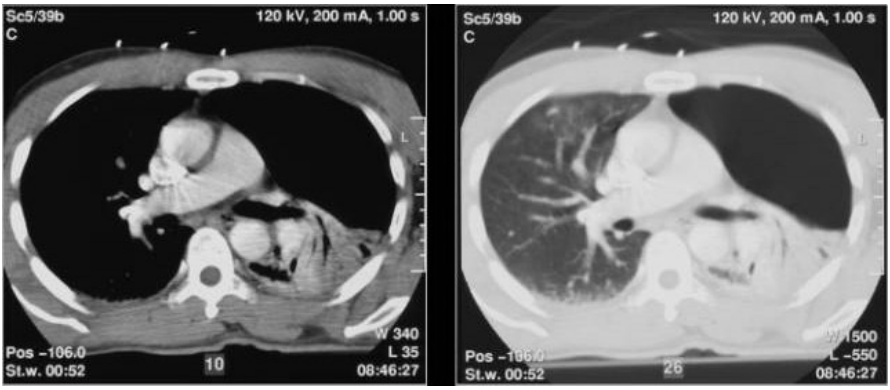

Fig. 2. Male, 31-years-old, road accident; a wide collection of air is present in the left hemithorax where the lung is totally collapsed (*right*). Clinical data do not reflect the underlying conditions. GCS=15, respiratory rate (spontaneous) =18 bpm; arterial pressure 135/80 mmHg; heart rate 115 beats per min; SpaO2=98 at FIO2 0.4. The scan was obtained approximately 45 min after the accident. The pneumothorax is not clearly appreciable if an inappropriate window is selected (*left*)

to reasons other than chest trauma (i.e. head injury) they can collapse in a very short time, e.g. during the transport, when the diagnosis can be even more difficult due to the movements of the helicopter or ground ambulance, the lack of space and other factors negatively reducing diagnostic capabilities. The very same factors also make any therapeutic procedure more difficult.

A time-honoured approach consists of explorative puncture of the pleural space, at the second intercostal space on the midaxillary line, with a saline-filled syringe attached to a large-bore needle [4]. The appearance of bubbles in the syringe documents the presence of air. This diagnostic procedure is biased by a number of confounding factors potentially leading to a false-negative diagnosis, including the thickness of the chest wall. which can be deeper than the needle used (Fig. 3), and filling of the indwelling canula with blood clots and debris. In thin subjects, the exploratory puncture itself can cause PNX.

Thus, it appears that in these circumstances the diagnosis of a highly suspected PNX can be reliably made on the basis of simple physicals signs, including crepitus from ruptured ribs and asymmetric expansion of the thorax. More specific signs, such as subcutaneous emphysema, usually appear later on and confirm the diagnosis.

The radiologic diagnosis can be elusive and misleading as well, for a variety of reasons. First, chest X-rays (CXs) of trauma victims are usually taken with a portable apparatus and with the patient in the supine instead of in the upright position. The latter, along with a lateral view, is indicated in ambulatory patients as it allows better visualisation of air that has collected in apicolateral locations. Unfortunately, in the supine position air collects in the anterior and inferior recesses, where it is harder to recognise [2,10]. Despite these limitations, CX can supply some clues as to the existence of a PNX, including an abnormally deep

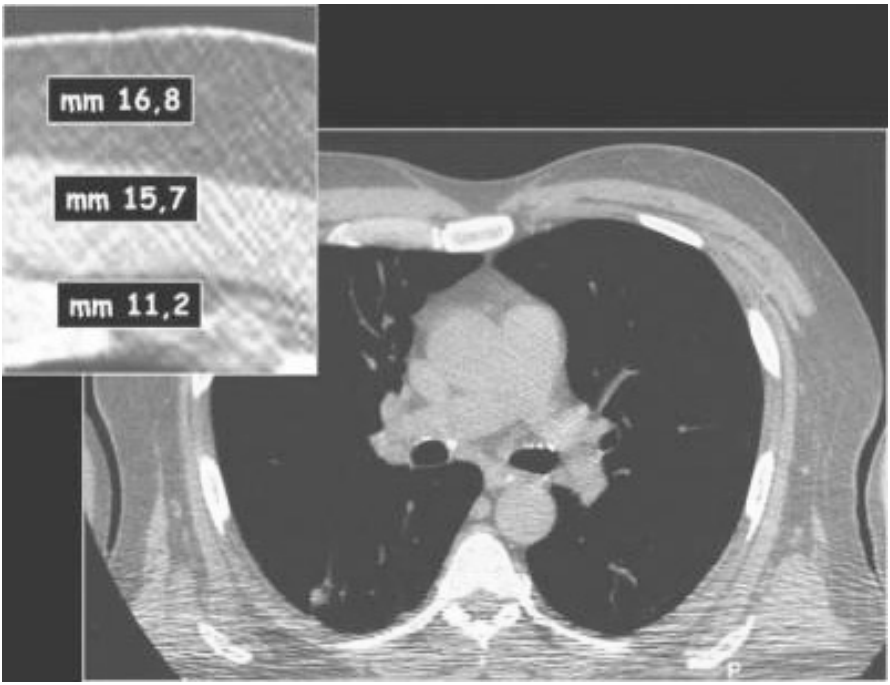

Fig. 3. *Main panel* Chest CT of a normal subject. The scan was taken at the 2nd intercostal space, with the arms along the body. *Inset* Thickness of the chest wall. Using a normal needle, in case of pneumothorax, an exploratory puncture of the pleural space would have given a false negative result

costophrenic sinus, increased hyperlucency of the lung parenchyma and a sharper-than-normal contrast of the cardiac profile [11]. However, based on the increased sensitivity and specificity of CT scan in the detection of PNX, both in adult and paediatric patients, its use has been advocated instead of CX as a primary tool of investigation in trauma patients. Recently, our group carried out a study involving 39 severely injured patients (Injury Severity Score (ISS) = 15), CX was obtained from all patients in the emergency department (ED) using a portable radiologic apparatus and identified six PNX out of 20 and two hemothoraces (HT) out of 17. The sensitivity for PNX was 30.0% with negative predictive value of 57.6%, and the sensitivity for HT was 11.8% with a negative predictive value of 44.4% [12].

Treatment

As stated above, treatment of PNX and HT associated with both blunt and penetrating injuries has evolved [4], basically due to assessment of the risk-benefit ratio of the proposed procedures. However, when assessing the different approaches, one must take into consideration that in patients with blunt injuries: (a) the

diagnosis of PNX very often cannot be made with certainty on the scene; (b) the related symptoms are far from being specific; and (c) initially stable patients can decompensate in a short time, possibly during transport, when life-saving procedures can be hard to perform. As a consequence, especially in the out-of-hospital setting and in mechanically ventilated patients, the treatment of PNX is warranted on the basis of a clinical suspicion only, considering the possibility of thereby avoiding a possible catastrophic derangement. This is particularly true when long transport time is preventable and/or the patient is transported via helicopter, as the reduction of atmospheric pressure favours an increase in the volume of air trapped in the pleural space [5]. At the present time, different approaches are available, each one with its pros and cons.

The exploratory puncture (see above) represents, at the same time, both a diagnostic and a therapeutic procedure, as air can escape from the pleura via either the indwelling canula or a smaller-bore catheter advanced in the pleural space. Alternatively, a small-bore catheter can be introduced via a needle and connected to a Heimlich valve or to a suction apparatus (NA). While this approach is simple to perform, relatively non-traumatic and can be useful to decompress a tensive PNX, thus gaining time for the implementation of other therapeutic measures, it has some significant limitations. First, as stated above, a false-negative can result. Second, clots and debris can occlude both the canula and the drainage tubes. Third, the catheter can be displaced or removed during transport, thus allowing the PNX to reoccur. According to procedures recommended by the ATLS, a second approach consists of direct placement of a chest tube through a small thoracostomy (TT) performed by blunt dissection of the fourth or fifth intercostal space anterior to the midaxillary line [16]. In a prospective study, Shmidt et al. [17] demonstrated that this procedure, performed in blunt trauma patients on the basis of physical signs such as crepitus and decreased breath sounds, was associated with a success rate of 98%. Interestingly, only 1% of patients managed with this "high suspicion strategy" required PNX decompression in the ED. Moreover, no patients developed procedure-related complications, such as new-onset HT or empyema. This technique is reltatively easy to perform, but is relatively time-consuming and carries the risk of tube displacement. Simple thoracostomy (ST) without tube placement represents an interesting alternative, is quicker and also easy to perform. The pleural space is penetrated through a 4- to 5-cm-long incision in the sixth intercostal space; a blunt dissection is performed through the chest wall and the pleura is pierced with blunt-tipped forceps; Thereafter, a gloved finger is inserted through the thoracostomy and swept around the pleura in order to free possible adhesions. As the negative pressure generated by spontaneously breathing patients would suck air into the chest, this procedure can be performed only in intubated and mechanically ventilated patients. A sterile gauze is dressed over the wound and taped on three sides, allowing air to escape from the fourth side during positive pressure inspirations and preventing its penetration during exhalation [18]. In a group of 45 patients, Deakin et al [18] demonstrated that: (a) ST, performed in the presence of abnormalities of chest wall excursions and of decreased breath sounds, was followed by an immediate resolution of the clinical picture; and (b) only minor

residual PNX, if ever, was demonstrable on the CX obtained in the ED and was easily managed by chest-tube insertion; and (c) no patient developed procedure-related infections. In our experience, ST prompted by the above-listed symptoms was associated with a high rate of success and the restoration of safe levels of SpAO2 (Fig. 4) in the absence of any early or late complication.

Even if the advantages and the limitations of each technique are taken into account, it is still difficult to demonstrate the superiority of one procedure over the others. This issue is further complicated by the paucity of comparative studies published so far. In other words, evidenced-based medicine (EBM) criteria still do not apply to a life-saving procedure. In a study of a group of patients treated by an aeromedical team, Barton et al. [19] demonstrated that improvement of the clinical condition were obtained with both techniques, but NA was associated with a substantial rate of failure to enter the pleural space. Although fewer patients treated by TT were pronounced "dead on arrival" in the ER as compared with NA (7% vs 19% respectively, *p*.05), the overall hospital mortality was comparable. Thus it is probably wiser to recognise that different clinical settings may require different approaches. As an example, in cases of multiple casualties such as occurring following terrorist bombing attacks [20], NA can be a reasonable option while waiting for more definitive treatments. Conversely, TT or ST are more convenient when only a few victims need to be treated. The choice between these two techniques is basically dependent on the skill and experience of the surgeon.

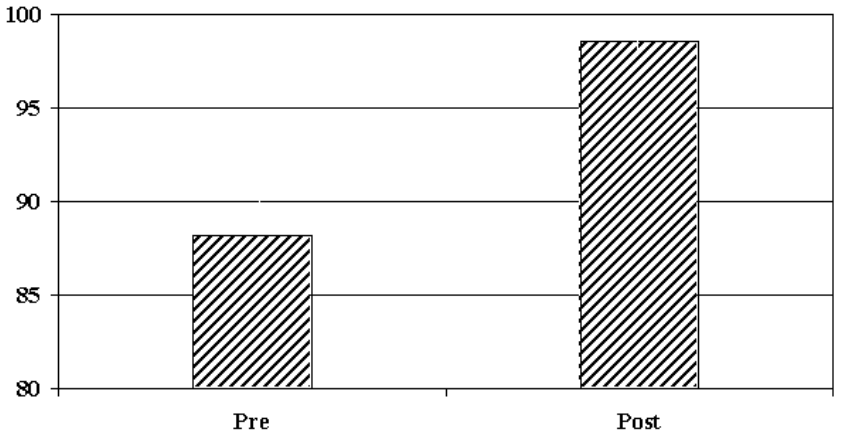

Fig. 4. Changes is SpAO2 following a thoracostomy in patients with blunt chest injury (n=31; p.005).

Conclusions

PNX represents both a common occurrence in trauma patients and a potentially avoidable cause of death. The PNX-related cardiorespiratory alterations are particularly rapid and severe in mechanically ventilated patients. Therefore, PNX should be suspected even in the absence of signs, such as subcutaneous emphysema, clearly indicating an air leak. Reduced breath sounds, crepitus and asymmetric expansion of the chest are appropriate triggers for a TT or ST in the out-of-hospital setting. The choice of technique depends more on the experience and training of the surgeon than on EBM criteria.

References

1. Di Bartolomeo S, Sanson G, Nardi G et al (2001) A population-based study on pneumothorax in severely traumatized patients. J Trauma, Inj, Infect & Crit Care 51:377-682
2. Clemmer T, Fairfax WR (1986) Critical care management of chest injury. Crit Care Clin 2:759-773
3. Baumann MH, Strange C, Heffner JE et al (2001) Management of spontaneous pneumothorax-An American College of Chest Physician Delphi Consensus Conference. Chest 119:590-602
4. Molnar TF, Hasse J, Jesansingham K, Rendeki S (2004) Changing dogmas: history of development in treatment modalities of traumatic pneumothorax, hemothorax and postraumatic empyema thoracis. Ann Thorac Surg 77:372-378
5. Rankin JM, Thomas AN, Fluechter D (2000) Diagnosis of pneumothorax in critically ill adults. Postgrad Med J 76:399-404
6. Wintermark M, Schnyder P (2001) The Macklin effect:a frequent etiology for pneumomediastinum in severe blunt chest trauma. Chest 120:543-547
7. Berlot G, Nicolazzi G, Maffessanti M (1997) Non-traumatic pneumopericardium in the adult. Int J Intens Care 4:105-107
8. Ravussin P, Bracco D, Moeschler O (1999) Prevention and treatment of secondary brain injury. Curr Opin Crit Care 5:511-516
9. Janssens U, Koch KC, Graf J, Hanrath P (2000) Severe transmyocardial ischemia in a patients with tension pneumothorax. Crit Care Med 1638-1641
10. Collins JA, Samra GS (1998) Failure of chest x-rays to diagnose pneumothoraces after blunt trauma. Anaesthesia 53:74-78
11. Maffessanti M, Berlot G, Bortolotto P (1998) Chest roentgenology in the intensive care unit:an overview. Eur Radiol 8:69-78
12. Holmes JF, Brant WE, Bogren HG et al (2001) Prevalence and importance of pneumothoraces visualized on abdominal computed tomographic scan in children with blunt trauma. J Trauma 50:516-520
13. Neff MA, Monk GS Jr, Peters K, Nikhilesh A (2000) Detection of occult pneumothoraces on abdominal computed tomographic scans in trauma patients. J Trauma 49:281-285
14. Rieger M, Sparr H, Esterhammer R, Fink C, Bale R, Czermak B, Jaschke W (2002) Moderne CT-diagnostik des akuten thorax-und abdominaltraumas. Radiologe 42:556-563
15. Massarutti D, Berlot G, Saltarini M (2004) Abdominal Ultrasonography and Chest Radiography are of Limited Value in the Emergency Room Diagnostic Work-up of Severe Trauma Patients with Hypotension on the Scene of Accident. Rad Med (in press)

16. American College of Surgeons (1989) Advanced Trauma Life Support Student Manual. Chicago, American College of Surgeons
17. Shmidt U, Stalp M, Gerich T et al (1998) Chest tube decompression of blunt chest injuries by physician in the filed, J Trauma 44:98-100
18. Deakin CD, Davies G, Wilson A (1995) Simple thoracostomy avoids chest drain insertion in prehospital trauma. J Trauma 39:373-374
19. Barton ED, Epperson M, Hoyt DB et al (1995) Prehospital needle aspiration and tube thoracostomy in trauma victims:a 6-year experience with aeromedicla crews:J Emerg Med 13:155-163
20. Peleg K, Ahronson-Daniel L, Stein M et al (2004) Gunshot and explosion injuries-Characteristics, outcomes and implications for care of terror-related injuries in Israel. Ann Surg 239:311-318

CLINICAL STUDY DESIGN

Chapter 62

Critical appraisal skills

S.B. Martins, A. Zin, W. Zin

Interpretation of scientific studies can be a daunting task, because many professionals receive little training in this area. A common tendency is to read the conclusion of a research paper and then apply the information as presented. This is an inadequate approach, because the conclusion generally represents the author's subjective opinion. The professional needs to learn how to identify information that does, or does not, validate the results and conclusions stated in the research article. With this information in hand the reader is empowered to make a judgment of the strengths and limitations affecting the results and the stated conclusions of the research paper. Critical appraisal skills provide a method to identify and interpret the strengths and weaknesses of a research report and their impact on the results.

The Evidence-Based Medicine Working Group has developed a manageable and user-friendly approach to critical appraisal. This approach greatly improves one's ability to discuss and understand research papers and consequently to apply the information to clinical care and/or research [1–29]. The papers just cited describe a systematic method of identifying components that support the interpretation of a variety of study designs, from clinical trials through economic analysis to qualitative research. Worksheets with questions for guidance through the critical appraisal are available on the web (http://www.cche.net/usersguides/main.asp). Guyatt and Rennie's book, "*Users' Guides to the Medical Literature*" is an excellent resource to expand your knowledge on interpretation of the medical literature and evidence-based clinical practice [30]. These and many other resources are available on the *Gruppo Italiano per la Medicina Basata sulle Evidenza* (GIMBE) website (http://www.gimbe.org/Home.htm) [31].

In critical appraisal of a paper the main areas of enquiry include the presence or otherwise of a focused research question, the type of study design used to answer the research question, the adequacy of the study sample, the completeness of the study, the quality and adequacy of outcome measurements, the analysis procedures and the presence of distorting factors.

Based on the work developed by the Evidence-Based Medicine Working Group, general questions are used to elicit information about the validity and results of research papers. There are two basic categories of questions: (1) screening for validity and (2) interpretation and applicability of results.

Initial screening of scientific studies

As a general rule, do not assume that any aspect of research is sound, even if it is published in traditional journals. Screening questions [5] can help you to assess rapidly whether it is worth investing more time in analysing a research paper. Screening questions help to identify quality markers in the paper. The presence of these quality markers strengthens the validity of the results of the paper. If the validity is compromised in a serious way then it is best to devote the time to looking for research of a better quality. In general, these questions should screen for the presence of: (1) a clear research question; (2) appropriate study design; (3) blinding and randomisation procedures; (4) quality of subject follow-up; and (5) standardisation of outcome measures. The questions used when screening for validity varies according to the research study design used (Table 1).

Table 1. Screening questions

Case control study design	Cohort study design	Clinical trial
Is research question clear about population, exposure variable and outcome variable?	Is research question clear about population, exposure variable and outcome variable?	Is research question clear about population, intervention, comparison group and outcome variable?
Was the study design appropriate to answer the research question?	Was the study design appropriate to answer the research question?	Was the study design appropriate to answer the research question?
Was blinding possible? Was blinding employed in the methodology?	Was blinding possible? Was blinding employed in the methodology?	Was blinding employed in the methodology? Were subjects randomised? If yes, which method was employed? Was there concealment of allocation?
How complete was follow-up of subjects?	How complete was follow-up of subjects?	How complete was follow-up of subjects?
Was outcome measured in same way for all subjects?	Was outcome measured in same way for all subjects?	Was outcome measured in same way for all subjects?

The first element to look for in a paper is the description of the research question. A research question contains three basic components: the population, the intervention or exposure of interest and the outcomes considered. In a controlled trial, a fourth component is the presence of a comparison group. The research question should be described in a clear and focused way. If you are not sure what research question the research report is addressing how can you evaluate the methodology used? Examples are given in Table 2.

Table 2. Examples of research questions as published

Study design	Research question in report	Population	Exposure or intervention	Outcome	Comments
Case control	"We investigated whether trauma is associated with increased risk of zoster using a case--control design." [32]	Undefined in question	Trauma	Zoster	Need to read the article to figure out that study was conducted in community-based patients with absence of immuno--deficiency
Cohort	"In this study we have examined the association between pertussis vaccination in infancy and asthma or atopy by age 7.5 years in a large, population based birth cohort." [33]	Population-based birth cohort	Pertussis vaccination in infancy	Asthma or atopy by age 7.5 years	Clearly defined
Rando--mised control--led trial	"To assess the efficacy of three days versus five days of treatment with oral amoxicillin for curing non--severe pneumonia in children" [34]	Children with nonsevere pneumonia	3-Day treatment with oral amoxicillin ***Comparison:*** 5-day treatment with oral amoxicillin	Cure of non severe pneumonia	Clearly defined

The study design that will produce the most valid results will depend on the type of research question. For questions related to therapy, aetiology or prevention the gold standard is the randomised controlled trial design. For questions related to prognosis or diagnosis the gold standard is the prospective cohort design. The Centre for Evidence-Based Medicine describes the level of evidence, i.e. which study designs produce the most valid results, for different types of research questions [35].

In randomised trials, procedures can be put in place to ensure that subjects, caregivers and outcome evaluators are unaware of the intervention each individual subject receives. Blinding enhances the validity of the study results and prevents investigator bias when they are interpreted. In cohort and case-control studies, interview bias can be avoided by making interviewers unaware of the study's real objective. Questionnaires can be designed to include questions on different topics

to detract focus from the study objective. Studies can also report on the effectiveness of the blinding procedures by surveying participants and investigators to find which intervention they believed was received. Fergusson conducted a review of 191 randomised placebo-controlled trials published between 1998 and 2001, evaluating reporting on success of blinding and found that 15 (8%) trials reported on success of blinding, 9 of which (60%) were imperfect [36].

In all study designs, it is important to look for completeness of follow-up. Completeness of follow-up refers to knowing what happened to all subjects who entered the study. Compare the number of subjects included in the study with the numbers used in the analysis. A drop-out rate of up to 10–15% is usually acceptable unless there is something striking about those who dropped out. Some journals require authors to be explicit about drop-outs or loss to follow-up and to use an algorithm for this purpose. If there is a large number of overall drop-outs, or if patients are selectively excluded from analysis, this can seriously compromise the validity of the results.

Were outcomes measured in the same way? Determine whether consistent procedural methods and comparable measurement tools were used for all subjects during collection of outcome data. Next, evaluate both the precision and the accuracy of the measurements. Weight, height and blood pressure are examples of measurements that require standardisation of defined procedures and calibrated instruments. When outcome data are derived from interviews or questionnaires, consider whether the study controlled for recall bias when asking subjects about events in the past. For example, patients with leukaemia might be more aware of the fact that they have lived near power plants than patients who do not have leukaemia. Ideally there should be different sources for such information that would remove the bias, such as using municipal data to confirm that the addresses of subjects were near power plants. To reduce recall bias in studies collecting drug use data, a recommended strategy to improve accuracy of drug use measurement is to utilise prescription databases rather than depending on the patient's memory about use of a specific drug [37].

When evaluating a paper that describes a controlled clinical trial review the methodology section for the presence of a randomisation procedure and concealment of allocation [38]. The randomisation procedure describes how the subjects were allocated to control or experimental intervention. Some methods are not truly random, e.g. when the decision on which intervention the subject is assigned to is based on alternation, record number or birth date. Lack of randomisation seriously compromises the validity of the results. Concealment of allocation refers to the process used to prevent foreknowledge of the assignment group in a randomised control trial: the commonly used method is opaque sealed envelopes containing the subject's assignment, none of which is opened until a subject enters the study.

Critical appraisal of methodology and results

Once the research report has been screened, if it is considered worthy of further assessment the next step is to examine the methodological details and the results.

Appraisal questions in the *Users' Guide* [30] are specific to the type of study design and help you focus on key aspects of the research design that could weaken or strengthen the validity of the results.

The first step in evaluating the methods is the assessment of the adequacy of the study sample, both in terms of it being a representative sample and in terms of numbers required to answer the research question. A representative sample should include the section of the population you are interested in. Let us take the example of a study with the following research question: "Does use of thiazide diuretics as a first line anti hypertensive drug in patients with primary hypertension lower the incidence of stroke?" The recruitment method, for example whether subjects are recruited from hypertension clinics rather than primary care clinics, will affect the generalisability of the results. A hypertension clinic will have a selected sample of hypertensive patients that is very different from those in primary care clinics, and therefore would answer a very different question. Common characteristics to look for in sample representation are age, sex, race, ethnicity, stage of disease, presence of co-morbidities and origin of subject (hospital based or community based).

The second element to be assessed in terms of sample adequacy is sample size. If the sample is too small to measure the effect you expect a negative result is not meaningful. The scientific term used to express the probability of the study to achieve a true positive conclusion is *power* [39]. Power is usually reported clearly in the methods section. For example a study that has a 90% power means that there is a 90% chance of detecting a 'true' difference between study groups. Conversely, you accept a 10% chance of not finding such a result even if it is true (false negative). In general, 80% is usually an acceptable power.

In case control, cohort and clinical trials it is important to ascertain the presence of blinding. If blinding was in place, who was blinded: subjects and/or study personnel? Sometimes it is not feasible, but blinding helps to strengthen the validity of the results. In surveys, if the interviewers know the objectives of the questionnaire they may ask the questions differently (interviewer bias). If subjects know whether they are receiving placebo or active drug they tend to change their behaviour in accordance with their beliefs about the effects of therapy. Researchers have used sham surgical procedures to study the benefits of certain procedures, e.g. arthroscopic surgery for osteoarthritis [40]. Also, if the professional measuring the outcome knows which intervention the subject has received he/she may evaluate the outcome differently. It is extremely important that at least subjects and personnel evaluating the outcomes be blind to the intervention given. Many study reports refer to a survey in which subjects and outcome evaluators are asked to guess which intervention has been given to confirm the success of the blinding procedure.

When evaluating the results of a research report, look for tables of baseline characteristics of the subjects studied to check for possible differences that could affect outcomes. In controlled trials and case control studies you should compare the study groups to detect differences that may not validate the results. In cohort studies you should check whether the study group is representative. For example, the incidence of recurrence of febrile seizures will vary depending on whether the

subject pool is community or hospital based. Another characteristic it is important to assess in the study sample is whether the subjects are at a similar point or stage of the disease being studied. If you observe differences in factors relating to outcomes of interest, validity may be seriously compromised.

Studies are usually designed around one primary outcome measurement. Always analyse the results for the stated primary outcome first, ignoring the other results. Secondary outcomes are other outcomes of interest that the study was not designed to answer. Validity of the results pertaining to secondary outcomes is limited and is hypothesis generating only. A new trial is necessary for specific evaluation of the research questions related to the secondary outcomes. As a general rule, look at the results of secondary outcomes as intriguing but far from definite.

When evaluating the primary outcome of a research report, we have assumed that the sample was representative, follow-up of subjects that entered the study was adequate and that the data collection process was reliable and accurate.

The selection, definition and relevance of the outcome measurements are the next step in evaluating the methods and results. Do the outcomes adequately reflect the outcomes of interest for that patient group? For example, high-frequency oscillatory ventilation improves oxygenation levels in neonates with respiratory distress syndrome; the outcome measured, oxygenation level, is an important outcome in the initial development of new technology. In clinical care, though, relevant outcomes for the patient group would be mortality, morbidity and/or lung damage. The relevance of the outcomes depends upon the research question you have in mind.

Accuracy of the primary outcome measurements requires close evaluation. A good example is measurement of blood pressure (BP), which is subject to wide variability depending on the method of measurement. Some factors that affect BP measurement can be controlled, for example by training the health professionals measuring the BP, establishing a protocol for the measurement of BP to standardise the method, using high-quality instruments that are frequently calibrated, etc. A description of the effort invested to achieve a proper BP measurement strengthens the validity of the results using BP as a primary outcome. Evaluate the methods used to improve the accuracy and precision of the outcome variables. If these are flawed the validity of the results is greatly compromised.

It is extremely important to assess the presence of alternative explanations for the results of the primary outcome(s). Look for the presence of confounding variables when reviewing a research paper. A confounding variable is a factor that is associated with the primary outcome and with the exposure studied. For example, in a study of the association between drinking and lung cancer, smoking is a confounder. People who drink frequently smoke, and smoking is strongly associated with lung cancer; thus, smoking is associated with both drinking and lung cancer. Unknown confounders are a challenge when study results are analysed. This is why the randomised controlled trial is the gold standard in study design, as it controls for the presence of unknown confounders [41].

How precise was the estimation of the effect? Confidence intervals allow you to

see the precision of the treatment effect. The width of the confidence interval determines how precise the results are: the wider the confidence interval the less precise the results. Usually the confidence interval narrows with increasing sample size. In therapeutic trials, if the confidence interval crosses "number one", e.g. 0.95–3.4, this can be interpreted as an indication that it is possible the treatment did not have the predicted effect.

In a clinical trial, there are different ways to express the differences between the study groups. One simple way of evaluating this difference is to look at the proportion of subjects that develop the outcome of interest in the experimental group (experimental event rate) and the control group (control event rate). The remainder obtained by the simple subtraction of the control event rate from the experimental event rate is defined as the Absolute Risk Reduction (ARR) (Fig. 1).

Absolute Risk Reduction = Control Event Rate–Experimental Event Rate

Fig. 1. Equation for calculation of absolute risk reduction

Relative Risk Reduction (Fig. 2) is obtained by dividing the ARR by the control event rate and denotes the percentage relative difference between the two groups. The relative risk reduction helps discern the clinical significance. Relative risk reductions above 50%, and frequently 25%, are clinically meaningful.

Relative Risk Reduction = Absolute Risk Reduction/Control Event Rate

Fig. 2. Equation for calculation of relative risk reduction

Using the ARR we can calculate the Number Needed to Treat (NNT), which gives us a more practical measure of how many people would have to undergo the intervention being studied to prevent one outcome event. For example, if a drug has an NNT of 10, it means you will need to treat ten people to prevent one additional bad outcome. It is useful when comparing treatments, as it takes into consideration the baseline risk of developing outcome (Fig. 3).

Number Needed to Treat (NNT) = 1/Absolute Risk Reduction

Fig. 3. Calculation of the number needed to treat

As an example, we will use data from Schulman's clinical trial, "A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism. Duration of Anticoagulation Trial Study Group." The

outcome studied was recurrence of venous thromboembolism in patients that had a first episode of deep venous thrombosis or pulmonary embolism. Data are shown in Table 3, and follow-up was for 2 years [42]. Other important issues when treatments are compared are the rate and severity of adverse effects and cost.

Table 3. Results from a published clinical trial [39] and calculated reference data for interpretation (*CI* confidence interval, *CER* control event rate, *EER* experimental event rate)

			Relative Risk Reduction (95% CI*)	**Absolute Riskto Reduction**	**Number Needed Treat (95% CI*)**
Outcome	Control event rate (CER)	Experimental event rate (EER)	(CER – EER) CER	CER – EER	1/ARR
Recurrence of venous thrombo--embolism	18.1%	9.5%	48% (23-63%)	8.6%	12 (8-24)

Making a judgement

The perfect study is very hard to come by, and there are always issues to debate. The answers to most of the questions that need to be asked when you check for the validity of study results are probably not distinct (a clear and unambiguous yes or no), but rather are nuances of maybe/probably/not sure. The research report may not give enough information for the reader to make an evaluation. The quality of the reporting may be poor. If this is the case, the reader has no other choice but to disregard the research report, because no judgement can be made about the validity of the results.

Once the reader has accepted the results as valid, or as probably valid, other considerations are then made about their applicability of the results. In clinical care, you would like to know whether the results could be applied locally. Is the study population sufficiently similar to the population you care for? Were all the relevant outcomes considered? Do the benefits outweigh the harms? What are the costs? [6].

This method of systematically evaluating research reports increases your understanding of the strengths and limitations of studies and empowers you to discuss the evidence with colleagues. It also helps you be more selective in your reading and dismiss poor-quality papers.

Poor reporting compromises the ability of the scientific community to evaluate the results of even the best studies. An international group of clinical trialists, epidemiologists, statisticians and biomedical editors developed the "Consolidated Standards of Reporting Trials (CONSORT)" to improve the reporting of clinical trials [40–42]. Moher states, "… [I]nadequate reporting borders on unethical practice when biased results receive false credibility" [43-45].

Busy professionals have little time to search for papers and review them. To facilitate this process printed journals and websites have developed critically appraised summaries of published studies that extract the important elements

necessary for the evaluation of the study quality and results. This process is explicit, and the reader can evaluate for him- or herself the strengths and limitations of the results. ACP Journal Club© and Evidence Based Medicine© are two examples of journals that produce one-page summaries of critically appraised research reports previously published.

References

1. Oxman AD, Sackett DL, Guyatt GH (1993) Users' guides to the medical literature. I. How to get started. The Evidence-Based Medicine Working Group. JAMA 270:2598-2601
2. Jaeschke R, Guyatt GH, Sackett DL (1994) Users' guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? The Evidence-Based Medicine Working Group. JAMA 271:1615-1619
3. Jaeschke R, Guyatt G, Sackett DL (1994) Users' guides to the medical literature. III. How to use an article about a diagnostic test. A. Are the results of the study valid? Evidence-Based Medicine Working Group. JAMA 271:703-707
4. Levine M, Walter S, Lee H et al (1994) Users' guides to the medical literature. IV. How to use an article about harm. Evidence-Based Medicine Working Group. JAMA 272:234-237
5. Guyatt GH, Sackett DL, Cook DJ (1994) Users' guides to the medical literature. II. How to use an article about therapy or prevention. A. Are the results of the study valid? Evidence-Based Medicine Working Group. JAMA 271:59-63
6. Guyatt GH, Sackett DL, Cook DJ (1994) Users' guides to the medical literature. II. How to use an article about therapy or prevention. B. What were the results and will they help me in caring for my patients? Evidence-Based Medicine Working Group. JAMA 271:389-391
7. Laupacis A, Wells G, Richardson WS et al (1994) Users' guides to the medical literature. V. How to use an article about prognosis. Evidence-Based Medicine Working Group. JAMA 272:234-237
8. Wilson MC, Hayward RS, Tunis SR et al (1995) Users' guides to the Medical Literature. VIII. How to use clinical practice guidelines. B. what are the recommendations and will they help you in caring for your patients? The Evidence-Based Medicine Working Group. JAMA 274:1800-1804
9. Richardson WS, Detsky AS (1995) Users' guides to the medical literature. VII. How to use a clinical decision analysis. A. Are the results of the study valid? Evidence-Based Medicine Working Group. JAMA 273:1610-1613
10. Hayward RS, Wilson MC, Tunis SR et al (1995) Users' guides to the medical literature. VIII. How to use clinical practice guidelines. A. Are the recommendations valid? The Evidence-Based Medicine Working Group. JAMA 274:1630-1632
11. Oxman AD, Cook DJ, Guyatt GH (1995) Users' guides to the medical literature. VI. How to use an overview. Evidence-Based Medicine Working Group (see comments). Can J Psychiatry 40:97-101.
12. Naylor CD, Guyatt GH (1996) Users' guides to the medical literature. XI. How to use an article about a clinical utilization review. Evidence-Based Medicine Working Group. CMAJ 155:1263-1268
13. Naylor CD, Guyatt GH (1996) Users' guides to the medical literature. X. How to use an article reporting variations in the outcomes of health services. The Evidence-Based Medicine Working Group. JAMA 275:1435-1439

14. Guyatt GH, Sackett DL, Sinclair JC et al (1996) Users' guides to the medical literature. IX. A method for grading health care recommendations. Evidence-Based Medicine Working Group (published erratum in JAMA 1996: 275:1232). JAMA 275:554-558
15. Guyatt GH, Naylor CD, Juniper E et al (1997) Users' guides to the medical literature. XII. How to use articles about health-related quality of life. Evidence-Based Medicine Working Group. Nurs Stand 11/30:32-33
16. Dans AL, Dans LF, Guyatt GH et al (1997) Users' guides to the medical literature: XIV. How to decide on the applicability of clinical trial results to your patient. Evidence-Based Medicine Working Group (see comments). Ned Tijdschr Geneeskd 141:1804-1806
17. Drummond MF, Richardson WS, O'Brien BJ et al (1997) Users' guides to the medical literature. XIII. How to use an article on economic analysis of clinical practice. A. Are the results of the study valid? Evidence-Based Medicine Working Group. JAMA 277:1802-1806
18. O'Brien BJ, Heyland D, Richardson WS et al (1997) Users' guides to the medical literature. XIII. How to use an article on economic analysis of clinical practice. B. What are the results and will they help me in caring for my patients? Evidence-Based Medicine Working Group (published erratum appears in JAMA 1997: 278(13):1064) JAMA 278:144-1451
19. Bucher HC, Guyatt GH, Cook DJ et al (1999) Users' guides to the medical literature. XIX. Applying clinical trial results. A. How to use an article measuring the effect of an intervention on surrogate end points. Evidence-Based Medicine Working Group. JAMA 282:771-778
20. Barratt A, Irwig L, Glasziou P et al (1999) Users' guides to the medical literature: XVII. How to use guidelines and recommendations about screening. Evidence-Based Medicine Working Group. JAMA 281:2029-2034
21. Richardson WS, Wilson MC, Guyatt GH et al (1999) Users' guides to the medical literature: XV. How to use an article about disease probability for differential diagnosis. Evidence-Based Medicine Working Group. JAMA 281:1214-1219
22. Guyatt GH, Sinclair J, Cook DJ et al (1999) Users' guides to the medical literature: XVI. How to use a treatment recommendation. Evidence-Based Medicine Working Group and the Cochrane Applicability Methods Working Group. JAMA 281:1836-1843
23. Guyatt GH, Haynes RB, Jaeschke RZ et al (2000) Users' Guides to the Medical Literature: XXV. Evidence-based medicine: principles for applying the Users' Guides to patient care. Evidence-Based Medicine Working Group. JAMA 284:1290-1296
24. McAlister FA, Straus SE, Guyatt GH et al (2000) Users' guides to the medical literature. XX. Integrating research evidence with the care of the individual patient. Evidence-Based Medicine Working Group. JAMA 283:2829-2836
25. McGinn TG, Guyatt GH, Wyer PC et al (2000) Users' guides to the medical literature: XXII: how to use articles about clinical decision rules. Evidence-Based Medicine Working Group. JAMA 284:79-84
26. Hunt DL, Jaeschke R, McKibbon KA (2000) Users' guides to the medical literature: XXI. Using electronic health information resources in evidence-based practice. Evidence-Based Medicine Working Group. JAMA 283:1875-1879
27. Giacomini MK, Cook DJ (2000) Users' guides to the medical literature: XXIII. Qualitative research in health care. A. Are the results of the study valid? Evidence-Based Medicine Working Group. JAMA 284:357-362
28. Richardson WS, Wilson MC, Williams JW Jr et al (2000) Users' guides to the medical literature. XXIV. How to use an article on the clinical manifestations of disease. Evidence-Based Medicine Working Group. JAMA 284:869-875

29. Giacomini MK, Cook DJ (2000) Users' guides to the medical literature: XXIII. Qualitative research in health care. B. What are the results and how do they help me care for my patients? Evidence-Based Medicine Working Group. JAMA 284:478-482
30. Guyatt G, Rennie D (eds) (2000) Users' Guide to the Medical Literature: American Medical Association, Chicago
31. Cartabellotta DA (1998) Gruppo Italiano per la Medicina Basata sulla Evidenza
32. Thomas SL, Wheeler JG, Hall AJ (2004) Case-control study of the effect of mechanical trauma on the risk of herpes zoster. BMJ 328:439-440
33. Maitra A, Sherriff A, Griffiths M et al (2004) Pertussis vaccination in infancy and asthma or allergy in later childhood: birth cohort study. BMJ 328:925-926
34. Editorial (2004) Three day versus five day treatment with amoxicillin for non-severe pneumonia in young children: a multicentre randomised controlled trial. BMJ 328:791-800.
35. Center for Evidence Based Medicine: Levels of evidence and grades of recommendation. http://www.cebm.net/levels_of_evidence.asp#levels
36. Fergusson D, Glass KC, Waring D et al (2004) Turning a blind eye: the success of blinding reported in a random sample of randomised, placebo controlled trials. BMJ 328:432-440
37. Bennett CL, Connors JM, Carwile JM et al (2000) Thrombotic thrombocytopenic purpura associated with clopidogrel. N Engl J Med 342:1773-1777
38. Sackett DL, Straus SE, Richardson WS et al (2000). Evidence based medicine. How to practice and teach EBM. Churchill Livingstone, Edinburgh
39. Kirkwood BR (1988) Essentials of medical statistics, 1st edn. Blackwell Scientific Publications, Oxford
40. Moseley JB, O'Malley K, Petersen NJ et al (2002) A controlled trial of arthroscopic surgery for osteoarthritis of the knee. N Engl J Med 347:81-88
41. Pocock S (1983) Clinical trials: a practical approach. Wiley, Chichester
39. Schulman S, Rhedin AS, Lindmarker P et al (1995) A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism. Duration of Anticoagulation Trial Study Group. N Engl J Med 332:1661-1665
42. Moher D, Schulz KF, Altman DG (2001) The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet 357:1191-1194
43. Moher D, Schulz KF, Altman D (2001) The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA 285:1987-1991
44. Altman DG, Schulz KF, Moher D (2001) Egger M, Davidoff F, Elbourne D, Gotzsche PC, Lang T (2001) The revised CONSORT statement for reporting randomized trials: explanation and elaboration. Ann Intern Med 134:663-694

Chapter 63

Literature search

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When developing a protocol for a research project you require information relevant to the research question and study design. A review of current research evidence will provide you with detailed knowledge on the topic of interest and support the argument for the need for the study to funding agencies. The review does not have to be extensive, but it does need to highlight the current issues that are relevant the specific research question.

The research question will guide the search in the literature. By increasing your knowledge on the topic you will be able to further develop and focus your research question and underlying hypothesis. Initially review papers are a good starting point to expand your comprehension on a given subject, but you do need to be aware of the potential for bias in narrative reviews.

Traditional reviews often do not include a clear statement of the question that elicited the review, how the selection of primary studies was achieved or how the author went about including and excluding studies. This makes it difficult for readers to evaluate how comprehensive the author was in his/her search for primary studies, the quality of included and excluded studies and, consequently, the conclusions reached. These reviews have been criticised as unsystematic and biased, as they express the subjective impressions of the individual reviewer [1].

Systematic reviews, in contrast, are explicit about both the research question and the methodology used. The author describes the process of selection of primary studies, the evaluation for quality markers and the statistical methods used to combine results. The quantitative combination of the results of different studies addressing the same question is called meta-analysis. The unique advantages of meta-analyses are the increased power and precision in estimating effects and risks. Qualitative and quantitative systematic reviews, with their explicit methods, may limit bias and improve the reliability and accuracy of recommendations [1]. "Researchers use the systematic review to identify, justify, and refine hypotheses; recognise and avoid pitfalls of previous work; estimate sample sizes; and delineate important ancillary or adverse effects and covariates that warrant consideration in future studies" [2].

Currently, the search for papers has become an easier task because of the Internet. Electronic access to databases and journals on the Internet is increasing every year. Much of this information is free, as is the case with the PubMed database and the journals *BMJ* and *The Canadian Medical Journal*. Some information is available through university connections, and some only by subscription. Compu-

ter skills are required, but the development of user-friendly software is making the procedures less 'technical' and more accessible.

The decision on which databases will be searched to look for the papers depends on the topic of interest. Studies done on search strategies in diverse topics have shown that there is much to be gained from searching various databases. Databases contain different journals, and the indexing terms and quality vary [3–7]. Talk to your librarian and other researchers in the field to find out about the databases available. Language can be a constraint, so evaluate the benefit of looking for primary studies in other languages, for example LILACS (Latin American and Caribbean Health Science Information Database).

The quality of indexing in bibliographic databases will affect the success of your search strategy. The National Library of Medicine together with the Cochrane Collaboration is updating the indexing of clinical trials to improve researcher's access to them. The Cochrane Collaboration's database of clinical trials is regularly updated and aims to contain all clinical trials published. The content is not limited by journal of publication.

Efficient literature searching is a skill that is acquired through both experience and learning about use of effective search strategies. Information is published in a range of sources, including journals, books and research reports. MEDLINE holds over 12 million references, and in 2002 502,000 citations were added (http://wwwns.nlm.nih.gov/). The quantity of materials may seem overwhelming, but there are four sources of evidence that can help make your search for clinical information more efficient:

1. Specialist organisations that are dedicated to summarising research findings and creating databases to aid dissemination.

A. The Cochrane Collaboration - An international organisation that aims to help people make well-informed decisions about health care by preparing, maintaining and ensuring the accessibility of systematic reviews of the effects of health care interventions: Italian Cochrane Center—http://www.areas.it/index.asp?IDL=ITA; UK Cochrane Center—http://www.cochrane.co.uk
B. NHS Centre for Reviews and Disseminations (University of York)—Established in January 1994 to provide the National Health Service (United Kingdom) with important information on the effectiveness of treatments and the delivery and organisation of health care. It is a good resource for systematic reviews: http://www.york.ac.uk/inst/crd/

2. Specialist journals that provide systematic reviews or review high-quality primary searches:

A. *ACP Journal*—bimonthly publication of structured abstracts of selected studies published in over 50 journals related to internal medicine that have met explicit criteria of scientific merit and clinical importance. A commentary from experts in the subject area of each is included. Published since 1991; http://www.acpjc.org/.
B. *Evidence-Based Medicine*—articles in the area of internal medicine, general and family practice, surgery, psychiatry, paediatrics, and gynaecology and obste-

trics are summarised in value-added abstracts and commented on by clinical experts if studies meet explicit criteria of scientific merit and clinical importance. Published since 1995; http://ebm.bmjjournals.com/

C. *The Cochrane Library*—an electronic publication designed to supply high-quality evidence about health-care-related issues and containing the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effectiveness and the Cochrane Controlled Trials Register. http://www.update-software.com/cochrane/

3.General and specialised databases that you can search using specific techniques to find relevant articles:

A. MEDLINE—National Library of Medicine (USA) bibliographic database of indexed biomedical journals. Free internet access through PubMed: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi.
B. PubMed Central—a new service provided by the National Library of Medicine with the objective of preserving and maintaining open access to electronic literature. There is free access to the full text of articles from the available journals. The list of available journals is growing rapidly. http://www.PubMedcentral.nih.gov/.
C. EMBASE—published by Elsevier Science, this is a comprehensive pharmacological and biomedical database.
D. Cancer-CD—a compilation by Silver Platter of CANCERLIT and EMBASE of cancer-related records from 1984.
E. PSYCHLIT—produced by the American Psychological Association, this database covers the areas of psychology, psychiatry and related subjects. Journals from 1974 and books from 1987 are included.
F. LILACS—Latin American and Caribbean Health Science Information Database, published since 1982. The database indexes 670 journals in the region, with abstracts in English, Portuguese or Spanish. Only 41 journals overlap with MEDLINE or EMBASE.

4.The Internet offers direct links to organisations that may hold the information you need.

A. Medical associations
B. Government organisations
C. Pharmaceutical industry

The search strategy

A structured question will help you focus your search, and determine which sources and search strategies to use. When deciding on a search strategy it is recommended that you start with a broader search approach. Although this may generate a lot of irrelevant material, limiting the search too early may cause you to overlook a vital piece of information that is pertinent to answering your question.

Deciding on the best words with which to begin a search is critical to identifying

key references. You can start by using 'natural language', e.g. terms such as *renal* or *renal disease*. These are known as a 'text words'. These text words can be used to search the database directly or to identify keywords by which related articles are indexed. The search engine will search for the specific term in the title or the abstract.

However, most databases have their own indexing terms based on a controlled vocabulary. For example, PubMed uses a controlled vocabulary called Medical Subject Headings (MeSH). In MeSH, a deliberate choice of the terms that describe the content of the study is made. Synonyms and spelling differences can be grouped under an indexing term to improve retrieval of relevant papers. Identify the indexed vocabulary of the database that best describes your keywords and include them in your strategy. For example, in MEDLINE a search for 'blood pressure' as a text word would retrieve only articles in which this exact term appears in the title or the abstract. If used as a MeSH term, articles that have 'systolic blood pressure', 'diastolic blood pressure' and 'pulse pressure' indexed would also be retrieved.

Search strategies have been developed to enhance the ability to retrieve relevant articles in PubMed. On the left-hand side menu of PubMed there is an option called 'Clinical Queries'. These enable the user to apply automated research methodology filters developed for different clinical queries, such as *therapy, prognosis, (a)etiology or prognosis*. There are options making it possible to focus on specificity or sensitivity. Specificity refers to a more focused retrieval, so that if you use this option you may miss some relevant papers. Sensitivity refers to a broader retrieval, and if you use this option you retrieve some irrelevant papers. The next step is to add a subject term to the search (Fig. 1).

You can develop your own search strategy, rather than applying automatic queries. You can improve the specificity of your search by using the 'single-term strategies' approach [8-9]. For example, if searching for studies on the aetiology of hypertension, using the text word 'risk' and the MeSH term 'hypertension' impro-

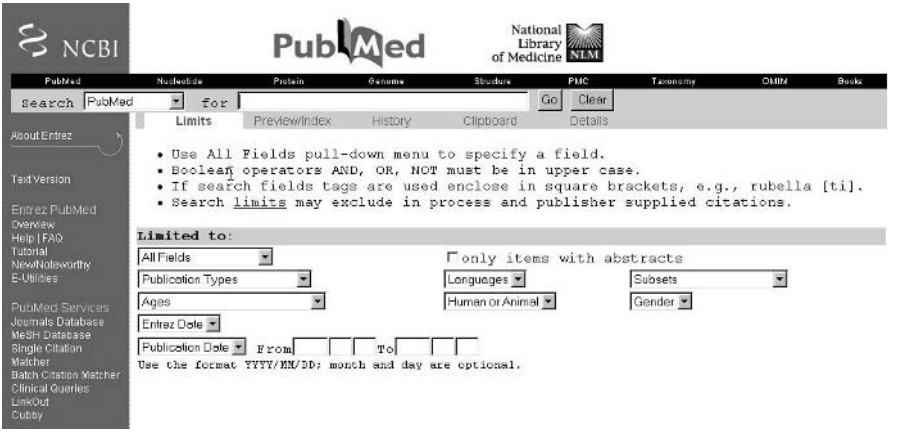

Fig. 1. 'Clinical Queries' web page in PubMed

ves your retrieval of studies about the aetiology of hypertension. Table 1 describes single-term strategies that provide the best specificity [8].

Table 1. Single-term search strategies with high specificity in MEDLINE [8]

Area of interest	Best single-term search	MEDLINE
Studies of therapy or prevention	Clinical trial	Field: publication type
Studies of aetiology	Risk	Textword
Studies of diagnosis	Sensitivity	Textword

Search strategies are regularly being improved and updated. Recently a search query has been added to PubMed specifically for systematic reviews [10]. Robinson and Dickersin report a highly sensitive search strategy for controlled trials [11].

No one strategy will pick up 100% of the articles relevant to your question. Checking the references of the papers, asking experts in the area, and using different databases are ways of expanding your bibliography and making sure you are not missing an important piece of work.

Levels of evidence

The research question determines the type of study design in which the best evidence can be found. For example, for evaluation of therapy efficacy a double-blind randomised controlled design is the gold standard, and for evaluation of prognosis the gold standard is a prospective cohort study design. The level of the evidence of a result in a research paper is determined by the fulfilment of quality indicators in the research design and implementation.

The highest level of evidence is usually found in reviews of primary research conducted in a scientific manner, i.e. the systematic review. A systematic review will explicitly answer a focused question, clearly defining the search criteria for the selection of primary papers (published and unpublished) and evaluating these for quality markers, extract the data systematically and analyse the data using a validated method. Homogeneity (the direction and degree of the results of the primary studies) is evaluated to further strengthen the validity of the results.

Meta-analysis is the technique through which data from primary studies are pooled and re-analysed. The data can be abstracted from the primary research reports or from the original patient data requested from the authors. Unpublished data can also be collected for the meta-analysis. This technique allows for an increase in power by enlarging the 'sample size', i.e. adding several study samples.

Level of evidence is used to define the grade of a recommendation for clinical practice. Clinical practice guidelines are increasingly defining the *grade of recommendation* for each recommendation developed [12–14]. Individual clinical practice guidelines generally state their definition of level of evidence and grade of recommendation. Table 2 is a summary of the grades of recommendations for therapy as displayed by the Centre for Evidence-Based Medicine [15].

Table 2. Grades of recommendations and levels of evidence, and evidence for therapy and prevention at http://www.cebm.net/levels_of_evidence.asp [15]

Grade of recommendation	Level of evidence	Therapy/prevention
A	1a	Systematic review (with homogeneity)
	1b	Individual RCT (with narrow confidence interval)
B	2a	Systematic review of cohort studies
	2b	Individual cohort study (including low quality RCT; e.g., 80% follow-up)
	3a	Systematic review (with homogeneity*) of case-control studies
	3b	Individual case-control study
C	4	Case-series
D	5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'

Databases

Electronic databases are very important tools for finding information about healthcare for research or clinical issues. Finding the best electronic databases for your area of interest requires some research; ask your librarian and colleagues in research, and explore the Internet. We will describe PubMed, EMBASE and The Cochrane Library.

PubMed

PubMed is the National Library of Medicine (NLM) search service: it provides access to over 12 million citations in MEDLINE, PreMEDLINE and other related databases, with links to participating online journals, through the Internet—http://www.ncbi.nlm.nih.gov/PubMed (Fig. 2). PubMed Central provides access to full-text articles from a growing number of journals.

MEDLINE is the National Library of Medicine premier bibliographic database covering the fields of medicine, nursing, dentistry, veterinary medicine, the healthcare system, and the preclinical sciences. MEDLINE contains bibliographic citations and author abstracts from more than 4,600 biomedical journals published in the United States and 70 other countries. The file contains over 12 million citations dating back to 1966. Coverage is worldwide, but most records are from English-language sources or have English abstracts.

Searching PubMed

The opening screen of PubMed is quite user friendly. The horizontal menu includes links that will help you develop and focus your search strategy. This menu includes 'Limits', 'Preview/index', 'History', 'Clipboard' and 'Details'.

Limits

The Limits option can be activated with a check mark (Fig. 2). The Limits window displays field tags that are available to focus your search. There is an 'All fields' option where the choices you can select from include: Author Name, Issue, Journal Name, Language, MeSH Major Topic, MeSH term, Publication type, Text Word and Title Word.

Additional fields exist to further support the focusing of your search: publication type, age group, publication date, languages, human or animal, database subset and gender. Examples of details of choices for different fields are described in Table 3.

Table 3. Description of options within 'Field Tags' in the 'Limits' section of PubMed

Field: publication type	Field: ages	Field: languages
Clinical trial	Newborn: birth to 1 month	English
Editorial	Infant: 1–23 months	French
Letter	Preschool child: 2–5 years	German
Meta-analysis	Child: 6–12 years	Italian
Randomised controlled trial	Adolescent: 13–18 years	Japanese
Practice guideline	Adult: 19–44 years	Russian
Review	Middle aged: 45–64 years	Spanish
	Aged 65+: 65+ years	
	Aged 80 and over: 80+ years	

Fig. 2. PubMed: Initial Screen

Preview/Index

In this window you can preview the number of articles retrieved when searching (Fig. 3). This feature helps you decide on the need to improve your search strategy before displaying the abstracts.

Boolean logic operators allow you to combine search results. The most commonly used operators are 'AND', 'OR' and 'NOT'. Using 'AND' will narrow your results to articles that include search criteria of different search sets, while 'OR' will combine all the articles found in different search sets, broadening the results. 'NOT' will exclude from the search articles with a given characteristic.

Using the index option you can search for terms indexed for a particular field (journal, MeSH) to see what is available. You can then choose to add the term to the search by clicking on Preview (Fig. 4).

History

A complete history of your search strategy is displayed. From this window you can increment search strategies by using the numbers of the previous searches rather than having to type out the whole strategy.

Clipboard

Clipboard is a place you can save the relevant citations while you are doing a search. In the field 'Send to' select Clipboard. Records can be added, the only limits on this being a time interval (60 min of inactivity) and a total number of 500. You can display the records at any time in the available formats (citation, MEDLINE, etc.).

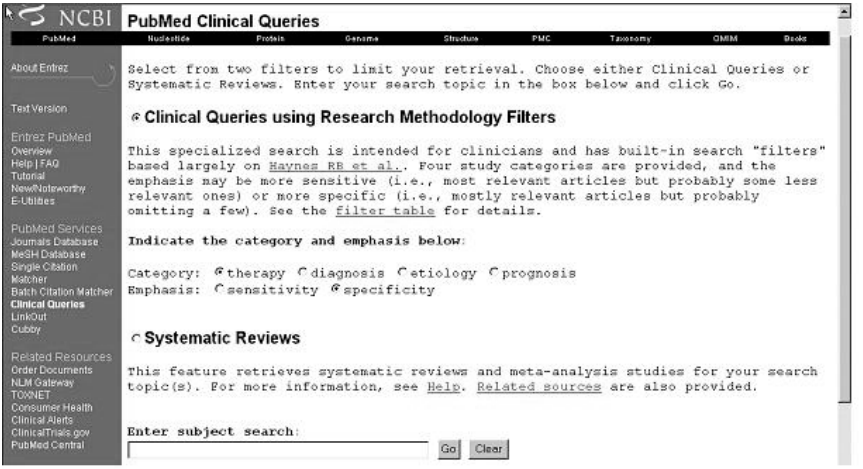

Fig. 3. 'Limits' screen in PubMed: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=Limits&DB=PubMed

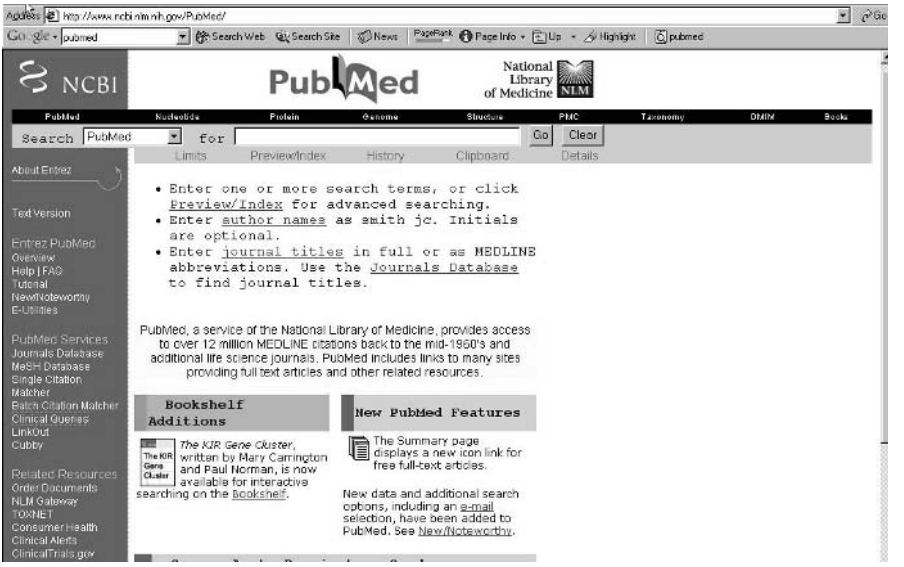

Fig. 4. 'review/Index' window in PubMed: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=Index&DB=PubMed

Details

Clicking on Details displays information about your search strategy. If you would like to save the search strategy for future use you can copy and paste the text string in a word document (Fig. 5).

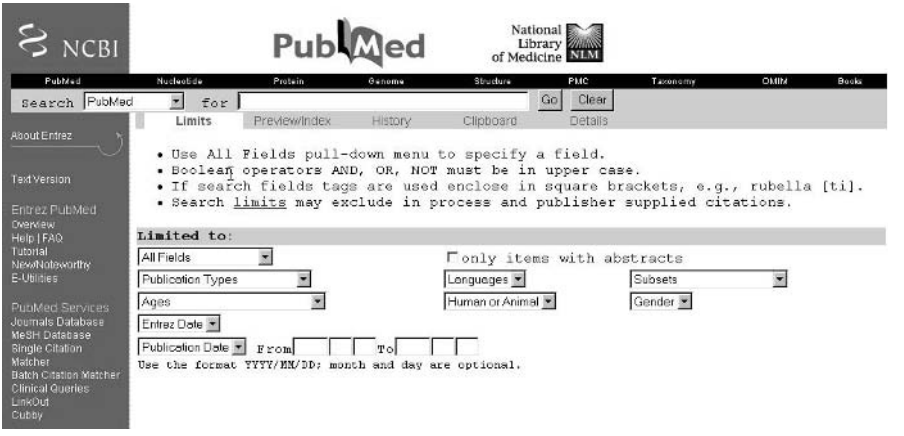

Fig. 5. 'Details' screen in PubMed: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=Details&DB=PubMed

MeSH

MeSH is the National Library of Medicine's controlled vocabulary used for indexing articles in PubMed. MeSH terminology provides a consistent way to retrieve information that may use different terms for the same concepts.

The hyperlink MeSH Database (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=mesh) on the left-hand-side menu of PubMed can be used to find descriptors of interest and see the relationship to other descriptors. MeSH organises its descriptors in a hierarchical structure.

Related articles

One useful feature is the 'See related articles' tag that appears after the citation you retrieve. If your search yields an article that meets your needs and you would like to see more papers on the same topic, clicking on this link retrieves additional related articles.

EMBASE

EMBASE, from Elsevier Science, is a comprehensive biomedical and pharmacological database (biology, medicine, psychiatry and drugs) renowned for extensive indexing of drug information from 4,000 journals published in 70 countries. EMBASE is available only by subscription. Updates of the database appear less than a month after publication of the journal. The database contains over 9 million records from 1974 to the present. Around 450,000 new records are added annually. Each record contains the full bibliographic citation, indexing terms and codes. The database includes EMTREE, a hierarchically ordered controlled thesaurus, which contains 45,000 preferred terms and more than 190,000 synonyms.

The Cochrane Library

The Cochrane Library is an electronic publication designed to supply high-quality evidence about healthcare-related issues. It is published quarterly on CD-ROM and the Internet (http://www.update-software.com/cochrane/http://www.cochrane.org/cochrane/revabstr/ccsales.htm). The Cochrane Library includes three databases plus other resources:

(1) Cochrane Database of Systematic Reviews (CDSR)—A rapidly growing collection of regularly updated, systematic reviews of the effects of healthcare. The systematic reviews are maintained by contributors to the Cochrane Collaboration who are committed to 'preparing, maintaining and disseminating systematic reviews of the effects of healthcare'. New systematic reviews are added with each issue of The Cochrane Library. The Cochrane reviews deal mainly with randomised controlled trials.
(2) Database of Abstracts of Reviews of Effectiveness (DARE)—Includes structu-

red abstracts of systematic reviews from around the world, which have been critically appraised by reviewers at the NHS Centre for Reviews and Dissemination at the University of York, England.

(3) Cochrane Controlled Trials Register (CCTR)—is a bibliography of controlled trials identified by contributors to the Cochrane Collaboration and others. This is an international effort with collaborators hand searching the world's journals to create an unbiased source of data for systematic reviews. CCTR includes reports published in conference proceedings and in many other sources not currently listed in MEDLINE or other bibliographic databases.

Managing your references

The development of software to manage references has greatly facilitated the organisation of references and writing up of manuscripts. Personal bibliographic software is designed to handle bibliographic information (journal articles, books, book chapters, conference proceedings, magazine articles, audiovisual material, patents, figures, images or even your own reference type) in a user-friendly way.

Within the software you can organise your references by subject area or by project. The software has a gateway to several databases on the Internet and allows you to download directly. You can opt to save your references in a specified format from a database and then import them. Of course, you also have the option of typing in the individual references.

When writing a manuscript, you can automatically insert citations into your manuscript. You have your bibliography software open and when you select the reference(s) you insert them in the specific point in your manuscript. A powerful search capability helps you find the references you need within the bibliography database. Search your reference database as you do your online databases by using Boolean criteria. Once you have located the reference(s) of interest you can insert them in the manuscript.

After inserting your references the software will generate a bibliography and update citations in the manuscript in the style you have defined. This can be done repeatedly, allowing you to change the text and to add or delete citations, and with a single click these updates are reflected in the manuscript and the bibliography. The software has predefined output formats for writing citations (e.g. Harvard or Vancouver style), or you can define your own. Some examples of personal bibliographic software are:

ENDNOTE– http://www.endnote.com/
PROCITE– http://www.procite.com/
REFERENCE MANAGER– http://www.refman.com/

References

1. Mulrow C (1987) The medical review article: state of the science. Ann Intern Med 106:485-488
2. Mulrow CD (1994) Systematic Reviews: Rationale for systematic reviews. BMJ 309:597-599
3. Kleijnen J, Knipschild P. (1992) The comprehensiveness of Medline and Embase computer searches. Searches for controlled trials of homoeopathy, ascorbic acid for common cold and ginkgo biloba for cerebral insufficiency and intermittent claudication. Pharm Weekbl Sci 14(5):316-320
4. Woods D, Trewheellar K (1998) Medline and Embase complement each other in literature searches [letter; comment]. Bmj 316(7138):1166
5. Topfer LA, Parada A, Menon D et al (1999) Comparison of literature searches on quality and costs for health technology assessment using the MEDLINE and EMBASE databases. Int J Technol Assess Health Care 15(2):297-303
6. Watson RJ, Richardson PH (1999) Identifying randomized controlled trials of cognitive therapy for depression: comparing the efficiency of Embase, Medline and PsycINFO bibliographic databases. Br J Med Psychol 72(Pt 4):535-542
7. Minozzi S, Pistotti V, Forni M (2000) Searching for rehabilitation articles on MEDLINE and EMBASE. An example with cross-over design. Arch Phys Med Rehabil 81(6):720-722
8. Haynes RB, Wilczynski N, McKibbon KA (1994) Developing optimal search strategies for detecting clinically sound studies in MEDLINE. J Am Med Inform Assoc 1(6):447-458
9. Shojania KG, Bero LA. (2001) Taking advantage of the explosion of systematic reviews: an efficient MEDLINE search strategy. Eff Clin Pract 4(4):157-162
10. Robinson KA, Dickersin K (2002) Development of a highly sensitive search strategy for the retrieval of reports of controlled trials using PubMed. Int J Epidemiol 31(1):150-153
11. Jacobi J, Fraser GL, Coursin DB et al (2002) Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Crit Care Med 30(1):119-141
12. MacIntyre NR, Cook DJ, Ely EW Jr et al (2001) Evidence-based guidelines for weaning and discontinuing ventilatory support: a collective task force facilitated by the American College of Chest Physicians; the American Association for Respiratory Care; and the American College of Critical Care Medicine. Chest 120(6):S375S-S395
13. Hirsh J, Warkentin TE, Shaughnessy SG et al (2001) Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. Chest 2001;119(1):S64S-S94S
14. Phillips B, Ball C, Sackett D (Oxford Centre for Evidence-based Medicine Levels of Evidence. In http://web.cebm.net/levels_of_evidence.asp#levels
15. McKibbon K, Walker-Dilks C (1994) Beyond ACP Journal Club: How to Harness Medline for Diagnostic Problems. ACP Journal Club September/October:A10-A12

Chapter 64

Study design

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Research Methodology

Scientific methodology comprises a set of rules and procedures to investigate the phenomena of interest. These rules and procedures are not set in stone, but actually being developed continuously and incorporated into the current standards. Similar standards apply to both to basic science research and clinical research. In this chapter we will focus on research methodology involving human subjects.

Research should abide by ethical principles, be feasible and produce valid answers. It is a waste of time, effort and money if you are unable to complete the study or have valid results. Key aspects of the scientific methodology include study design, selection of subjects, definition of study variables, specification of the intervention, data collection procedures, data analysis and interpretation of the results. We will also cover good clinical practice procedures and ethical considerations in research involving human subjects.

The research question guides the choice of the best study design to obtain a valid answer. The research question is refined in an iterative process, supported by an analysis of the current literature and conversations with experts. It is then refined into a hypothesis, which should be clear, observable and measurable.

Initially when investigating new phenomena observational study designs are used (Fig. 1). The investigator is observing the phenomena of interest. Descriptive study designs are used to gather general information such as age, habits, diseases, symptoms, etc. Analysis of the results of descriptive studies serve as a basis for the

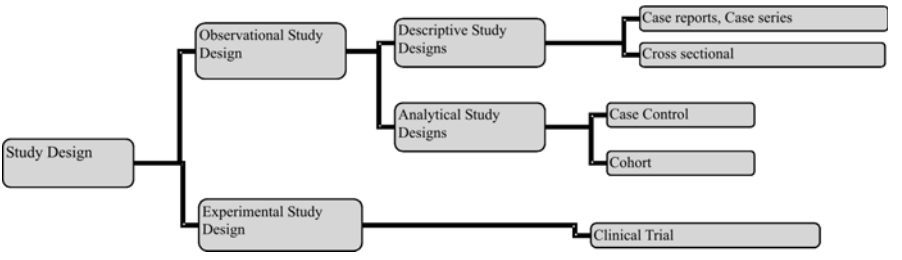


Fig. 1. Study designs

development of new research questions and hypothesis which can be tested using analytical designs such as cross sectional or cohort studies. Here measures of association between characteristics of interest are determined, for example: as smoking and lung cancer. To firmly establish a relationship of cause and effect, the investigator is no longer just an observer but plans an experiment (Fig. 1) such as therapeutic trials. The gold standard of study designs for establishing a cause/effect is an intervention study, for example clinical trials.

One should describe the study in one sentence that includes the type of study design, population, intervention (if existent), primary outcomes and length of follow up. Study design description may include the terms prospective or retrospective. Although sometimes confusing, the terms usually refers to the time of the events being studied. If they happened in the past and you are reviewing medical charts or medical databases, then the study is retrospective. If data about the events of interest are collected as they happen, for example patients with SARS, the term prospective is applied. Prospective studies are sturdier designs, as the investigator can eliminate errors related to coding of diseases, incomplete information and apply strict criteria for defining conditions across different study sites.

The choice of design is influenced not only by the research question but by feasibility factors as well. The main feasibility factors are the time frame you have to conduct the study, the level of funding, the type of data required and the resources available. Prospective studies like cohorts and clinical trials are more time consuming and expensive. Multi site studies add another level of complexity for implementation. We will describe the main types of study design.

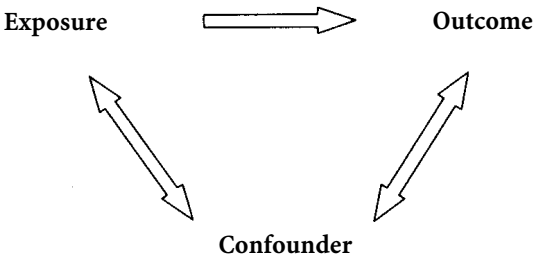
Most clinical studies involve comparison of groups and can be broadly divided into two categories: observational and experimental.

Before considering the study designs, some concepts regarding what is being studied have to be established: the outcome, the primary exposure or risk factor of interest (the one which is included in the hypothesis) and other exposures that may influence the outcome (confounders).

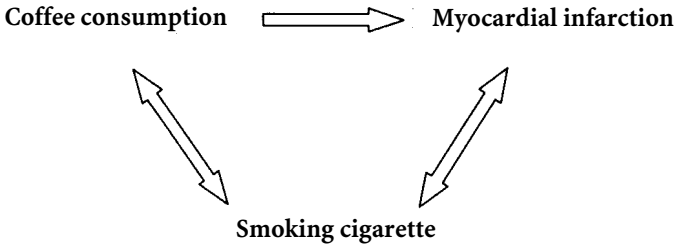
Outcome is a broad term. It can be a defined as a disease, death or a state of health.

The primary exposure of interest is the one which is included in the hypothesis.

A confounder is an alternative explanation for the outcome. In order to be a confounder, a factor has to be: associated with the exposure being investigated and independently associated with the risk of developing the outcome of interest.



For example, the association of drinking coffee (exposure) and increased risk for myocardial infarction (outcome) could be in part due to the habit of smoking cigarette (confounder), since coffee consumption is associated with smoking and smoking is independently associated with the risk of myocardial infarction.



A factor can be an outcome in one study and an exposure in another.

The first step in a research study is to define the hypothesis that will be tested. This should be done in a way that makes clear what are the primary outcome(s), exposure(s), and potential confounders. Then, the most appropriate design will be chosen. In designing a study to determine if there is an association between exposure (risk factor) and an outcome (a disease), one should anticipate the potential alternative explanations that might be responsible for such an association.

Awareness of the existence of a confounding factor is essential in clinical studies and many study designs are built around the control of confounding.

Observational studies

Observational studies collect information on events that are happening or have happened, over which we have no control. Data can be collected from populations or from individuals. There are some observational studies where the outcome of interest is described with no reference to exposure (descriptive studies), while others consider a possible association of outcome of interest and exposure (analytic studies).

The basic strategy designs used in clinical research can be broadly categorized according to whether these investigations focus on describing the distributions of disease or elucidating its determinants. Descriptive studies are concerned with the distribution of disease, what populations are affected, in what geographic location and how the frequency of occurrence varies over time. Such information can provide clues leading to the formulation of a hypothesis that is consistent with existing knowledge of disease occurrence. Analytic studies focus on the determinants of a disease by testing the hypothesis formulated from descriptive studies.

Descriptive studies

A descriptive study describes the general characteristics of the distribution of a disease, mainly related to person, place and time. Information such as age, sex, race, marital status, occupation, medication use, consumption of foods, geographic distribution of a disease, seasonal patterns in disease onset are example of the kind of data that can be collected. They can be done quickly and easily as such information is usually available. Descriptive studies have usually provided reliable information about the possible determinants of a disease. However, due to limitations of design, this kind of study is useful to formulate hypothesis that can be tested later using an analytic design.

There are three main types of descriptive studies: case reports or case series and cross-sectional studies.

Case Reports and Case Series

The case report is the most basic type of descriptive study of individuals. They are usually used to describe a new or unusual condition or circumstance and are often the first reported indications of a problem. Case series are collections of individual case reports in a short period of time. Usually indicate the beginning or presence of an epidemic. For example, Acquired Immunodeficiency Syndrome, Crohn's disease and many other conditions were originally reported as a case series. One important limitation of case reports is that it is based on the experience of one person. Case reports and case series are limited to carefully describing a problem and suggesting potential hypotheses to be tested in future studies.

Case reports are among the most common types of studies published in medical journals. Case reports document unusual medical occurrences and may represent the first clues in the identification of a new disease or adverse effect of exposures.

Cross-Sectional Surveys

In cross-sectional studies exposure and disease status are assessed at the same time in a defined population. The presence or absence of both the exposure and the disease are determined at the same time point. For example, a cross-sectional survey might determine whether subjects were current smokers (exposure) and whether they had evidence of emphysema (disease). Because both exposure and disease are determined at the same time, it is impossible to determine, in most cases, which came first. Therefore, cross-sectional studies can suggest associations between an exposure and a disease but cannot prove causality. Cross-sectional studies are relatively simple to conduct, cheap and take a short time. For these reasons, they are frequently used for planning purposes. In general, they are used to estimate the prevalence of common conditions of reasonably long duration or to determine the distribution of continuous variables within a population.

Hypothesis formulation from descriptive studies

The first step in the search of the solution of a problem is to formulate a testable hypothesis. Descriptive data addresses some questions:

1) "Who is getting the disease?"
2) "Where are the rates of disease highest and lowest?"
3) "When does the disease occur commonly or rarely?" and "Is the frequency of disease at present different from the corresponding frequency in the past?"

Analytic studies

Analytic study designs are used for testing the hypotheses formulated by descriptive studies. These studies enable comparison among groups, determining whether or not the risk of disease is greater in individuals exposed or not exposed to a known risk factor.

In an observational analytic study, the researcher does not interfere with the natural course of events. In intervention studies, the researcher allocates the exposure at random in a sample of sufficiently large size, following the groups for the development or not of the outcome of interest.

There are two main types of observational analytic studies: case-control and cohort.

Case-Control Study

A case-control study is designed to help determine if an exposure is associated with the outcome of interest. The first step is to identify a group of cases, i.e. individuals with the outcome of interest (a disease) and a group of controls (individuals without the illness). The proportion exposed to a suspected risk factor is then measured in the two groups and compared. If the proportion of exposed to the factor is higher in the case group than in controls, then the exposure might be a risk factor for the disease. If it is lower, it might be a protective factor.

A case-control study can be used to investigate the relationship between exposure and outcome. If there is a strong association and it meets temporal requirements, i.e., the exposure occurs before the outcome, then causation can be hypothesized. The relationship between lung cancer and smoking [2] is a historical example. Further research is required to support the theory of causation. Case-control studies are also useful to identify adverse effects of treatment.

For diseases that are rare, a case-control design become the only useful alternative.

Study Question

The first step in designing a case control study is to clearly establish the study question.

Definition and Selection of Cases

The association measured in the study will be between the suspected risk factor and the outcome in the case definition, so the definition of a case is essential. Diagnostic criteria should be explicit and clear in order to select cases that represent a homogenous entity.

It is also important to consider if the cases chosen are representative of all cases fulfilling the case definition: consider the access to health services, patient survival, referrals to specialist hospitals and refusals.

An important decision is whether to include prevalent as well as incident cases. Prevalent cases include patients who may have had the disease for some time and may exclude those who died soon after the diagnosis. If the risk factor is related to early mortality, then the effect will be diluted. These patients are still alive, still ill and may have changed their habits because of the disease. Prevalent cases reflect determinants of duration as well as the development of the disease. The interpretation of such a study may be complicated. Incident cases include newly diagnosed patients. Whenever possible, it would be better to limit the cases to those newly diagnosed within a determined period.

Once definitions of disease and diagnostic criteria have been clearly established, the individuals can be selected from different sources.

The study might be hospital-based, which include identifying patients with the disease who have been treated at a particular hospital, during a specified period of time. This is more common because it is relatively inexpensive and easy to conduct.

Alternatively, the study might be population-based, which involve locating and obtaining data from all affected individuals from a defined population over a period of time. The advantage is that it avoids bias arising from selection factors. In general, these studies are easier to interpret, but a lot difficult to conduct.

Selection of Controls

The selection of the control group is a very difficult task when designing a case-control study. The controls must be representative of the population that originated the case; otherwise selection bias will be introduced. Thus, the definition of the source population determines the population from which controls are sampled. Someone is eligible to be a control if that person would have been selected to the study as a case if he/she developed the disease or outcome of interest.

If the number of cases is limited, two or more controls can be taken for each case. More than four controls per case is not worthwhile.

Source of controls. The question to have in mind when selecting controls is "what is the population that originated the cases?" Care should be taken when choosing hospital controls in order to avoid selection bias. Hospitalised people usually tend to have higher prevalence of adverse exposures than the general population. Also, patients with diseases known to be associated with the exposure of interest should be excluded from the control series. The best argument for using hospital controls

is costs and logistics. The use of general population controls assures the great level of comparability. Identifying controls from general population is usually more costly and time-consuming than from hospitals.

Sample size

When planning any investigation, a common problem is to determine what sample size is required. Usually, the sample size is calculated by a statistician according to the type of study design, type of data (categorical, continuous) and previous estimates of the frequency of the outcome. The chances of obtaining a statiscally significant result are dependent on the real difference between the groups and sample size. If the sample size is too small, a non significant result may be obtained.

Usually, a significance level of 5% is acceptable, i.e. the investigator accepts a 5% chance that he/she might reject the null hypothesis and conclude that a real difference exist when there is no difference (type I error). To calculate the sample size, the power of the study must be determined, which means the chances of detecting a real difference if it exists. Generally a power of 80-90% is accepted. This means that there is a 10-20% chance that the real difference could be missed although it may in reality exist (Type II error).

Measurement of exposure

Data on exposure can be gathered in many ways – by examining medical occupational records, taking biological samples or by personal, postal or telephone interview. It is important that the information is not influenced by the fact that he/she is a case or a control. Case-control studies are vulnerable to information bias as the individuals are recruited on the basis of their disease status. If the information is based on recall, this is a particular problem. Response bias refers to the situation whereby the information given by study subjects differs in controls and cases. Recall bias is an example: the fact of having a disease may influence the recall of exposure. Responder bias may be minimised by keeping the interviewed individuals blind to the study as well as ensure that both cases and controls have similar incentives to remember the events. The interviewer should be blind to the hypothesis under study, to who is a case or a control in order to avoid observer bias. This is very difficult to achieve, so the investigator or interviewer should be trained in the unbiased collection of data, avoiding probing cases longer than controls regarding exposure. Information should be collected using the same questionnaires and forms for cases and controls.

Matching. The effect of confounders can be adjusted for in the design of the study. Matching is the procedure whereby controls are chosen to have the same distribution as cases in terms of confounders. Common matching variables are age, sex, place of residence or socio-economic status. Care should be taken for not matching too many variables, which could lead to difficulties. There are other ways to control potential confounding in case-control studies: restriction, stratification,

logistic regression, etc. Matching should not take place on variables related to the risk factor only, since this will result in equal distribution of risk factors in cases and controls and therefore, no result. Cases could be individually matched to one or more controls or frequency matched to controls (equal number of cases and controls in each level of matching variable). Matching design requires matched analysis.

Analysis

Case-control studies estimate the strength of the association between the exposure and outcome of interest. It cannot estimate directly disease, unless all cases in a defined population are available. To calculate the relative risk it is necessary to know the population at risk and this information is not available in a case-control study. The only measure of association that makes sense in a case-control study is the odds ratio. The odds of an event are defined as the number of occurrences by the number of non-occurrences.

$$\text{Odds of disease} = \frac{\text{No of subjects who develop disease during follow-up}}{\text{No of subjects who do not develop disease during follow-up}}$$

The odds of disease and risk of disease are 2 different measures of the same process. If risk is low, both numbers are very similar. Odds tend to be expressed as a proportion.

The odds of disease and risk of disease are 2 different measures of the same process. If risk is low, both numbers are very similar. Odds tend to be expressed as a proportion.

Odds = Risk/ (1-Risk)

Odds ratio is the comparison of two odds.

$$\text{OR} = \frac{\text{Odds of disease in exposed subjects}}{\text{Odds of disease in non-exposed subjects}}$$

or

$$\text{OR} = \frac{\text{Odds of exposure in those with disease}}{\text{Odds of exposure in those without disease}}$$

Case-control studies can estimate the ratio of the odds of exposure, which can be a valid estimate of the odds of disease. Since case-control studies deals with rare diseases, the odds ratio is an acceptable approximation of the relative risk.

Unmatched case-control studies. Data from exposed and unexposed cases and controls can be arranged in a 2x2 table as follows:

	Cases	Controls
Exposed	a	b
Unexposed	c	d
Total	a+c	b+d

The odds ratio is obtained dividing the odds of exposure in cases (a/c) by the odds of exposure in controls (b/d):

$$OR = \frac{a/c}{b/d} = ad/bc$$

Confidence intervals can be calculated.

Individually matched case-control studies. If the study is matched, then a more complex matched analysis is necessary. Matched pairs are analysed if they are concordant or discordant in relation to their exposure. There are corresponding tables for matched sets (more than one control per case, variable number of cases and controls in each set, etc).

	Control exposed	Control unexposed
Case exposed	a	b
Case unexposed	c	d

The odds ratio is b/c. Confidence intervals can be calculated.

In case-control studies, confounding can be controlled for using restriction, stratification and logistic regression on unmatched and matched data. Adjusted odds ratio is used when controlling for confounders. Logistic regression and stratified analysis are used for unmatched data. Logistic regression is used for matched data. For frequency matched data, stratified analysis should be employed.

Interpretation of results

The odds ratio is the measure of strength of the association between the exposure and the outcome. An odds ration of 4 means that exposure to the factor is associated with an increase in 4 fold in the risk of disease. An odds ratio of 0.5 means that exposure was associated with halving the risk of disease and an odds ratio of 1 means that there was no association between exposure and outcome.

Quality indicators should be sought for when analyzing case-control studies. In a major review of case control studies 35 different sources of bias were identified [3]. The selection of subjects and measurement of outcomes of interest were the main problematic areas for introduction of bias. When appraising a case control study quality indicators include:

a) Do the selection criteria for control subjects match those of the case subjects in every respect except for the presence of disease or risk factor being studied?
b) Were the measurements on the control subjects free from bias?

If an association is found, one must consider if it was due to chance, selection bias in the choice of cases and controls, information bias in the gathering of exposure data or presence of confounding factors not considered or controlled for in the design of the study.

Advantages of case-control studies

1) Quick and cheap.
2) Only feasible method for very rare disorders or those with long time gap between exposure and outcome.
3) Can investigate a wide range of risk factors.
4) Fewer subjects needed than in cross-sectional studies.
5) Consistency of measurement techniques maintained.

Disadvantages of case-control studies

1) Bias in determining exposure (recall bias, interviewer bias, missing data, lack of standardization of pre-recorded data, measures affected by disease onset, use of non-newly diagnosed cases).
2) Bias in choosing controls (inappropriate source, over-matching).
3) Problems in sorting out sequence of events (because retrospective).
4) No estimate of absolute risk.
5) Only one end-point (disease).
6) Not suitable for investigating rare exposures (unless only cause of disease).
7) Cannot estimate disease incidence.

Cohort Studies

In a cohort or follow-up study a group of individuals is followed up over a period of time, looking at the development of some outcome. Therefore, an exposed and an unexposed group to a potential cause of disease are followed-up over time and the incidence of disease in one group is compared with the incidence in the other. The exposure can be a personal characteristic, behavior, exposure to anything, e.g. radiation. At the time exposure status is defined, all subjects must be free of disease under investigation. All participants are then followed up to assess the occurrence of the outcome.

Schematic representation of a cohort study

	Disease +	Disease -	Total
Exposed	a	b	a+b
Non-exposed	c	d	c+d

Cohort studies are useful to evaluate disease aetiology, prognosis (natural history of disease) and incidence of a disease, as all subjects in both groups (exposed and non-exposed) are free of disease at the beginning of the study. Incidence can be calculated as follows:

$$\text{Incidence rate} = \frac{\text{No of new cases of disease (in a time period)}}{\text{Population size}}$$

A cohort study design can be used to investigate research issues such as when it is not ethical to carry out a randomized controlled trial to determine the outcome of a treatment. The findings from this type of study enable the elaboration of quality indicators, for example, readmission rates to be based on evidence. Experiments in the organization and delivery of health services are also ideal for the cohort design; for example, the relationship between volumes of procedures carried out in a hospital and outcomes such as complication rates or mortality.

There are three study design features that are pivotal in the outcome of an appraisal of cohort studies. The first one is the recruitment of subjects, which has to be evaluated for its completeness. It can be useful to ask about the subjects not recruited. Also assess the possibility of a selection bias before entry point. For example the more severe cases may be referred elsewhere. Secondly, the criteria to evaluate outcomes of care must be valid or validated; for example, hospital mortality may vary due to variations in length of stay and therefore is not a valid measure. A validated measure would be 30-day mortality. Third, when analyzing the results make sure that some measure of control for co-morbidities is taken into account, as this can systematically bias the results.

Types of Cohort

Cohort studies may be prospective or retrospective. These terms refer to the temporal relationship between the initiation of the study and the occurrence of the disease outcomes being studied.

Prospective. The groups of exposed and unexposed individuals have been assembled but the disease has not occurred yet. The researcher must follow the patients up for a certain period to ascertain the outcome of interest.

Retrospective. The investigation begins at a point in time after both exposure and outcome have already occurred.

A cohort study is ambidirectional when data are collected both retrospectively and prospectively in the same cohort. This type is applicable for exposures having both short-term and long-term effects.

Retrospective studies can be conducted more quickly and cheaply than prospective studies. Hence, retrospective studies are more suitable in investigating diseases with long latency periods, which would require many years for significant results to be achieved. However, it depends on availability of previously recorded data on exposure. Sometimes this can result in incomplete and incomparable data for all study subjects such as information on possible confounders (i.e. smoke, diet, coffee intake) is not recorded.

In prospective studies the investigator can assess information on exposure and potential confounders directly from study subjects.

Study Hypothesis

Formulate a clear hypothesis. Usually the hypothesis has been already tested by other study designs (cheaper and quicker as case-control studies).

Selection of the exposed population

The group of subjects selected to represent the exposed group can originate from different sources. The choice of a particular group will depend on the frequency of exposures under study, the need of accurate and complete information on exposure, follow-up of all participants, and nature of the hypothesis of the study.

If the exposure of interest is a rare condition, or related to a particular occupation, it is more efficient to choose a special exposure population (such as workers on uranium mining, shipbuilding), which would allow a sufficient number of exposed individuals in a reasonable period of time.

If the exposure is a common condition, the exposure population can be chosen among members of certain groups (professions) such as doctors, nurses and workers, in which the collection of relevant information is easier.

Selection of the Control Group

As in case-control studies, the selection of the control group is an important step in designing a cohort study. Groups being compared should be as similar as possible with respect to all factors related to the disease, except the exposure under investigation. In addition, it is fundamental that the data obtained from the unexposed group be comparable to that of the exposed one.

In cohort studies, it is important to consider the potential confounders at the beginning of the study and measure them accurately later on, so they might be taken into account on analyses.

Sources of Data

Another crucial point in designing cohort studies is the availability of complete and reliable information of all cohort members concerning the exposure under investigation and/or development of any outcome of interest.

Information on exposure status can be obtained from pre-existing records (hospital, employer). This source has the advantage of information availability for almost all participants of the cohort and to provide unbiased information on exposure. However, information previously recorded is sometimes insufficient to address some specific questions of the research. Also, potential confounders may not have been considered. In this case information may be provided by the participants through questionnaires or interviews. Bias may be introduced when collecting data this way, as patients may have preconceived ideas on the exposure under investigation.

A cohort study offers the possibility of examining a range of outcomes, which will depend on the chosen method of measurement. Whatever the procedure, it is

crucial for the validity of the study that the method of ascertainment be identical for those exposed and those unexposed.

Follow-up

Failure in collecting information on every subject is a source of potential bias in a cohort study and would greatly affect the validity of the results. The longer the follow-up period, the more difficult it will be to achieve complete follow-up as more subjects are likely to move and change jobs. A drop out of 10-15% is usually acceptable.

Sample size

The assistance of a statistician is required to calculate the sample size. Once the appropriate sample size is determined, add an extra percentage to allow for dropouts. A loss of up to 10%- 15% of subjects is acceptable.

Usually, a significance level of 5% is acceptable, i.e. the investigator accepts a 5% chance that he/she might reject the null hypothesis and conclude that a real difference exist when there is no difference (type I error). To calculate the sample size, the power of the study must be determined, which means the chances of detecting a real difference if it exists. Generally a power of 80-90% is accepted. This means that there is a 10-20% chance that the real difference could be missed although it may in reality exist (Type II error).

Analyses

There are many ways of comparing the risks in exposed and non-exposed populations. A risk is the probability of occurrence of an event over a defined period of time. The rate is the amount of change per unit time. Risks are defined per persons alive at the start of the study. Rates are defined per person-year of follow-up (for instance, one person-year is one person followed for 1 year). The absolute risk and incidence rate of the end point in cohort studies are defined as follows:

$$\text{Absolute risk} = \frac{\text{No of subjects with disease during follow-up}}{\text{No of subjects disease free at start}}$$

$$\text{Incidence rate} = \frac{\text{No of subjects with disease during follow-up}}{\text{Average population during the period}}$$

The most commonly employed comparative measure of risk is the relative risk (RR), also called risk ratio. A relative risk greater than one, means that the risk in the exposed population is greater than in the non-exposed one. Relative risk less than one means the exposure is protective. If the relative risk equals one, there is no difference between groups. It is the best measure of strength of an association between exposure and outcome.

$$\text{Relative risk (RR)} = \frac{\text{Risk in exposed}}{\text{Risk in unexposed}}$$

Another comparative measurement is the risk difference (attributable risk or excess risk), which is the subtraction between risk in exposed and non-exposed. If there is no difference, there is no risk. This measure is a more direct and useful indicator of the impact of prevention.

$$\text{Risk difference} = \text{Risk in exposed} - \text{Risk in non-exposed}$$

For example: if risk in exposed is 7% and in non-exposed is 2%, there is an excess or attributable risk of 5% of developing the outcome under investigation in the exposed group compared to the unexposed group.

$$\text{AR\%} = \frac{\text{Risk difference}}{\text{Risk in exposed}}$$

The attributable risk per cent (AR%) is defined as the percentage of the absolute risk in the group exposed to the risk factor.

Although OR is not very used in the analyses of cohort studies, it is a good approximation to the relative risk in low risk situations.

$$\text{OR} = \frac{\text{Odds of disease in exposed}}{\text{Odds of disease in non-exposed}}$$

or

$$\text{OR} = \frac{\text{Odds of exposure in those with disease}}{\text{Odds of exposure in those without disease}}$$

Interpretation

It is important to consider the possibility of bias, chance and confounding as an alternative explanation for the results of a cohort study.

Misclassification of exposure and/or disease may increase the similarity between exposed and non-exposed groups. Hence, any possible association will be underestimated.

A major problem in cohort studies is the bias introduced by losses during follow-up. The only way of eliminating this effect is prevention to minimize losses.

Not all eligible subjects to participate on a study agree to do so. Non-participants may differ from participants in various ways, such as smoking habits, diet and health care. The results may be valid for the studied population but cannot be generalized.

Advantages of cohort studies

1) Ethically safe.
2) Subjects can be matched.
3) Timing and directionality of events can be established.
4) Rare exposures can be examined by appropriate selection of study cohorts.
5) Multiple outcomes can be studied for any one exposure.
6) Incidence of disease can be measured in the exposed and non-exposed groups.
7) If prospective, minimize bias in the ascertainment of exposure.
8) Eligibility criteria and outcome assessments can be standardized.
9) Easier and cheaper to manage than a randomized controlled trial.

Disadvantages of cohort studies

1) Controls may be difficult to identify
2) Exposure may be linked to a hidden confounder
3) Blinding is difficult
4) Randomization not present
5) For rare disease large sample sizes or long follow-up is necessary
6) Very expensive and time consuming particularly if follow-up is long and outcome is rare
7) If retrospective requires the availability of adequate records
8) Validity of results can be affected by losses to follow-up
9) Changes over time in exposure status and diagnostic criteria can affect the classification of individuals according to exposure and disease status.

Experimental studies

Clinical trials

In experimental research the researcher plans an intervention and observes the outcomes. The process of studying the effects of an intervention has evolved tremendously in the last century.

In medical research the clinical trial is the experimental study design of choice for studying the effects of therapies. The first description of a comparative clinical trial was made in the mid 1700's in Britain. In 1834 Louis, in France, established a scientific approach to clinical trials and epidemiology by discussing the importance of accurate observations of patient outcome, knowledge of the natural progress of untreated controls, precise definition of disease prior to treatment and careful observation of deviations from intended treatment. Random allocation of subjects to treatment and blinding were concepts introduced in the early 20th century. The first clinical trial to use a placebo control in a double blind manner was conducted in 1950[4].

A clinical trial is a carefully ethically planned experiment. Amongst clinical trials the most representative design is the double blind randomized controlled

trial (DB RCT), considered the gold standard in the scientific community for determining a causal effect. *Double blind* means researchers and subjects are not aware of which intervention the subjects received; *randomized* means the researchers have no influence in choosing which subjects received the experimental or control intervention and *controlled* means there is a control group. This design is used to assess the efficacy of an intervention. This intervention can be a drug therapy/device (risk of myocardial infarction associated with antihypertensive drug therapy), a method of clinical or surgical management (management of patients with venous leg ulcers) or an evaluation of health services organization (acute stroke intervention: special stroke unit v. general medical ward).

In drug development, once a drug is shown to be reasonably efficacious it is necessary to compare it with the current standard treatment(s) for the same condition in a larger study. Results from double blind randomized controlled trials are the standard required for approval of new drugs through government agencies like the Food and Drug Administration (USA) and the EMEA (European Medicines Agency). These are called Phase 3 trials of drug development.

The steps depicted in Fig. 2 are included in the study design to minimize the effects of unknown confounders and strengthen the validity of the results. We will detail characteristics of the clinical trial design that improve the validity of the results.

Comparison group. The comparison of the effects between equivalent experimental group (receiving the active intervention) and control group (receiving the placebo or standard care) is an essential element of study design towards making an assertion of cause and effect of an intervention.

The control group can receive different types of "control" intervention. For example when studying the effects of new drugs, the control intervention is usually a placebo. Placebo is defined as being very similar to the intervention except for the active ingredient, for example in appearance and taste. The control intervention may also be standard of care, for example when studying the effects of a new drug for diseases with established therapy.

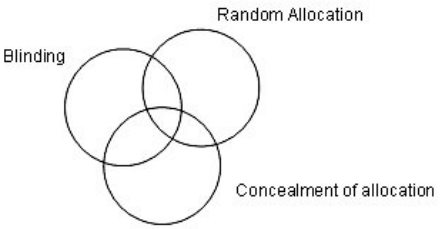


Fig. 2. The main steps introduced to minimize the effects of chance findings in experimental studies

It is vital in the study design that the control group be treated in the same way as the intervention group in every aspect related to their care. For example thought needs to be given to use of adjunct therapy, involvement of other healthcare providers such physiotherapists, number of tests, etc. Subjects can make changes in their life-style, unrelated to the intervention, in a manner that affects the outcome. This is described as the Hawthorne effect. If there are important differences between the control group characteristics and the intervention group characteristics, the validity of your results may be reduced.

Randomization Procedure. Randomization refers to the way you select from your study sample who will receive the active intervention and the control intervention. The goal of randomization is to maximize the probability that groups receiving different interventions will be comparable. When an adequate randomization procedure is used, the assignment of subjects to the intervention is determined by chance alone, i.e. the potential for bias in allocation to study groups is removed. Study groups tend to be comparable with respect to all known confounding variables as well as other unsuspected confounders. However there is no guarantee that differences will not arise by chance between the two groups. A larger sample size reduces the risk of differences between groups.

The randomization method should provide true random allocation. Computer generated random numbers and tables of random numbers are the most commonly used methods of randomization. Alternate allocation and allocation by birth date or medical record number are not true randomization procedures. Central randomization procedures are preferable to local randomization; i.e. randomization is carried out by a statistician or a researcher not involved in the recruitment and follow up of subjects.

When the researcher is unaware of which intervention group the subject will be allocated to there is *concealment of allocation*. This should remove any possibility of manipulation of subject allocation in the field. Concealment of allocation strengthens the randomization process. It is usually achieved by using sequentially numbered, sealed, opaque envelopes.

If there is a need to balance the number of subjects in different strata of subject characteristics a blocking procedure can be used when randomising the sample. Subjects are first classified with respect to variables that will affect the outcome (e.g. age, sex, severity of disease) and then randomized. The two most important elements in eliminating bias in clinical trials are randomization and blinding.

Blinding. Blinding refers to defining who does NOT have knowledge of which intervention subjects are receiving. In a clinical trial subjects, investigators and statisticians can be blinded to the intervention received by each study group. When subjects and investigators know the intervention being given the trial is referred to as having an open label design. The aim of blinding is to avoid bias both in the study execution and in the interpretation of the results.

Investigators, clinicians, and subjects are prone to change their behaviour if they know who is receiving which treatment. Blinding avoids the effect of this

change of behaviour in the results. Blinding is especially important when knowledge of the treatment received may influence the outcomes. Subjective outcomes, for example pain, are especially prone to be influenced by the knowledge of the treatment received. Hard outcomes like death or recurrence of a disease are not affected as much.

Ethical and practicability issues need to be taken into consideration when deciding the level of blinding in a clinical trial. Increasing the level of blindness brings higher costs, increased complexities and longer timelines for trials. Blinding can be described as single, double or triple depending on who is unaware of the intervention given (Table 1). Double blind is the most common type of blinding used in clinical trials.

Table 1. Types of Blinding

Single blind	Subjects are unaware of the treatment they are receiving but the researcher evaluating the outcome is informed.
Double blind	Health professionals providing care and subjects are not aware of the intervention received. Health professionals assessing the outcome are not aware of the intervention received.
Triple blind	Health professionals, subjects, statisticians and research personnel are unaware of the intervention being given.

Advantages of the clinical trial design are that blinding and randomization allow for the unbiased distribution of unknown confounders between study groups and this strengthens the validity of the results. The disadvantages of the clinical trial design include the ethical constraints when designing the study, the high cost both in financial terms and in time and a risk of volunteer bias in selection of subjects.

Clinical trials can have many different design characteristics. A *cross-over* design occurs when subjects are exposed to both the experimental and the control intervention sequentially usually with a wash out period in between [5, 6]. A *run in* design relates to having all patients on placebo initially, and compliance is evaluated to select those more likely to be compliant. A *factorial* design refers to studying 2 interventions simultaneously; subjects are randomized to one intervention and then the other establishing a total of four study groups.

Selection of subjects

One key objective of research studies is to be able to make inferences from the results of a study to a more general population. Target population is defined as the group from which you will be selecting your study sample. The characteristics of the target population for the study determine the extent to which the study conclusions can be generalized to a wider population. Clearly define subject eligibility criteria by establishing inclusion and exclusion criteria. Characteristics frequently taken into consideration include: age, sex, function of major body systems, mental status, previous health conditions and/or previous drug treat-

ment. The inclusion and exclusion criteria may affect the generalizability of the results.

The broader the inclusion criteria the easier it is to find study subjects and the results can be generalized to a wider population. Exclude subjects unlikely to comply with study procedures and have a higher risk for adverse drug reactions. For example, patients with mental illness may have more difficulty in complying with study procedures, so unless your research question is geared to this population you may want to exclude them.

Clearly define the condition of interest to select your target population. For example, when defining diabetes are you going to use results from laboratory tests such as HbA1c, glucose tolerance tests, presence of current prescriptions for hypoglycaemic drugs and/or presence of an ICD9 code for diabetes in the medical record? Review the literature to see what definitions were used in previous studies. Are there validated definitions? Are there issues relating to staging the severity of illness that need to be clearly described? When the clinical course of a disease is extremely variable, assessing treatment effects by clinical observation can be extremely unreliable. For example, patients with systemic lupus erythematosus have a variable clinical progression. Take into consideration the natural history of the condition of interest and the existence of validated prognostic markers to support the effect of intervention on the outcome variables.

Once you have determined your target population, you will need to think of ways to screen and recruit patients. Establish the screening procedure to select potential subjects. Where will you obtain the information about potential subjects? Will clinicians be screening during clinic or will there be chart reviews? What information will be collected?

The recruitment procedure is decided with two goals in mind. The first is to recruit a sample that adequately represents your target population. If you are recruiting from a hospital-based population, this limits the generalizability of your results. You may not be able to expand the results to community based patients. The second is to recruit enough subjects to meet the sample size required. The inability to enrol sufficient subjects is a frequent problem in clinical research. The accessible population, from which you recruit your study sample, should have a greater number of probable subjects than you require in your study sample. There is always a tendency for investigators to overestimate the number of subjects meeting the study criteria that will agree to participate. Develop contingency plans if recruitment efforts fail in the initial effort [5].

Patients who refuse to participate can be systematically different (by social class, severity of disease or other factors) from those who agree to enter the study. Keep an account of subject refusals so a comparison can be made between those who consented and those who did not. A low response rate of recruited subjects' influences the ability to generalize the results to a wider population.

Ethical and privacy considerations are taken into account when determining the screening and recruitment methods and these must be must be approved by the Institutional Review Board. Subjects will be more motivated to participate in a study design that avoids invasive and uncomfortable tests. Language barriers can be overcome by using bilingual staff [5].

Sample size

Sample size is generally determined by a statistician rather than relying on judgment or guesswork. Important considerations when calculating sample size include whether the outcome measures are continuous (example- height) or categorical variables (example-death), the estimated effect size of your intervention and the incidence of the outcome in the control group. Data from previous studies or from a pilot study can provide preliminary data on estimates of effect size. If an outcome is rare you usually require a larger sample size and a longer follow up to observe a difference between groups.

Once you determine the appropriate sample size, add an extra percentage to allow for dropouts or withdrawals. It is almost inevitable that some subjects will drop out, will not comply to study protocol, or will be lost to follow up. As a general rule, a loss of up to 10%- 15% of subjects is acceptable and should not bias the result unless there is a strong confounder present.

Statistical power of the study defines how certain one is of detecting a statistically significant result. Generally a power of 80-90% is regarded as adequate. This means the investigator accepts having a 10-20% chance of not detecting a significant difference between interventions although it may in reality exist (Type II error). To start a study knowing you will not be able to recruit the necessary sample is unethical and a waste of time.

Definition of study variables

You will be collecting many data points to fully explore the results of your study. Efforts should be focused on collecting valid data related to the research question and the primary outcomes. In the primary outcome you have the predictor and outcome variables defined. Predictor variables are variables that will be used to compare groups. For example, in clinical trials it will be the study group assignment, which relates to the intervention received. In cohort studies it will be the exposure of interest, so you will compare the outcome in the group that was exposed to the unexposed. Outcome variables are the relevant clinical endpoints to the condition of interest and should be clinically relevant to the treatment of future patients[4].

The measurement of the study variables should be clearly defined. For example if stroke is the outcome of interest, a clear definition of your measurement should include the signs, symptoms, results of diagnostic procedures and other reliable indicators. Review the literature to find validated measures or use similar methods to previous studies. If the important parameters cannot be reliably measured, it may not be ethically justifiable to conduct a trial.

Accuracy and precision are measurement characteristics. Precision relates to the method obtaining the same or very similar results after repeated measures. Precision is affected by observer variability (example: skill in using an instrument when measuring blood pressure), subject variability (example: mood when responding a questionnaire) and instrument variability (example: hearing screening tests

affected by background noise). Actions to enhance precision includes standardizing the measurement methods, training the observers, refining instruments, automating the instruments and repeating the measurements [5]. Accuracy is defined by how close the measurement is to the "true" value. Systematic error is reflected by less accuracy, for example when a scale that is not calibrated. Assess accuracy of instrument by using a "gold standard" or by comparing it with a technique that has had it's accuracy accepted. Strategies for enhancing accuracy include standardizing the measurements methods, training the observers, refining the instruments, automating the instruments, developing measures that subjects are not aware of, blinding and calibrating the instrument [5].

Give preference to measures that have been validated in the literature. Continuous variables are those that can be ranked on a spectrum of quantifiable intervals, for example: body weight and blood pressure. Categorical variables are those derived from characteristics that can be grouped, for example sex and blood type. Continuous variables can provide more informative statistics (mean and standard deviation) than categorical variables (rates, counts and proportions) and add power to the study by reducing the required sample size [5].

Specification of the Intervention

A detailed description of the intervention includes the randomization procedure, intervention assignment strategy, schedule and duration of study intervention. If the intervention is drug therapy, include details about dispensation, supplies (e.g. bottles with capsules) and labelling. Include a clear account of the management of forecasted situations such as handling dose reduction in drug therapy trials, changes allowed in background therapy (e.g. use of other agents), use of different health care services (physiotherapy, behavioural therapy, etc.) and temporary study discontinuation.

Several types of control interventions can be used in clinical trials, which include: placebo, active drug, different dose of the same drug or use of standard care. Placebo refers to trials where the control group receives the same "intervention" except for the active ingredient. It is important for the interventions to be similar in every way perceivable by the subjects: size, colour, taste, etc. Compliance bias occurs when there are dissimilarities in the interventions being compared. These generate differences in patient adherence to treatment (ex: one group receives a pill with a sour taste and the other with a sweet taste). In surgical trials, placebo interventions are mock surgeries are performed where patients undergo anaesthesia and have cuts similar to the intervention group [7].

Active drug refers to a trial that compares the effects of 2 drugs, for example in hypertension therapy. The control group can also use a different dose of the same drug. In health services research it is common to compare with standard of care, for example use of stroke units versus wards for rehabilitation of patients with stroke [8]. Historical controls refer to data from subjects collected before the intervention or to data from similar subjects from other studies that received standard of care or no therapy.

Data collection

Case report forms are created to permit accurate and systematic collection of individual subject data. The design of the case report forms is extremely important because it facilitates recording of data to meet study objectives and promotes investigators adherence to protocol. The case report form for should allow for a rapid and effective review of subject data and facilitate the database generation.

The purpose of a baseline evaluation is to define and describe the characteristics of the study population at the start of the study. This allows the researcher to assess if the characteristics in intervention and control groups are similar before the intervention. It is important to measure demographic characteristics, disease states, socio-economic aspects and/or predictors of outcome, such as risk factors or existing conditions that can influence the outcome. In the case of a chance misdistribution between study groups, the researcher can make statistical adjustments in the analysis phase. This adjustment reduces the impact of a sampling misdistribution on the results, for example having an age misdistribution.

The follow up period should be long enough to detect enough occurrences of the outcomes of interest. One common mistake investigators make is to not allow a follow up period that is long enough, and consequently the investigator misses the effect of the intervention.

Frequency of follow up contacts varies depending on your requirement for data and the need to keep informed about the subject's status. In your protocol describe the strategies used to minimize the incidence of subject dropouts and withdrawals. Phone calls and house visits are methods employed to follow up on subjects who are not complying with the study procedures. Record the reasons why the subject withdrew from the study.

One should always actively ask subjects about use of other therapies. Many times subjects use concurrent interventions inadvertently and this can go unrecognized by study personnel. In the protocol describe what kind of concurrent therapy (medications, physiotherapy) will be accepted and which shall be motive for excluding a subject. This can happen before as well as during the study, so it is important to elicit such information throughout the study period.

If loss of subjects in the follow up period is related to the intervention it will affect the outcome. One illustration is when an intervention causes discomfort to the subjects and this leads to an increased drop out rate in the experimental group. As a consequence there is an under- or over-estimation of effects of the intervention. The potential bias resulting from dropouts or withdrawals should be carefully considered. A loss to follow up in excess of 20% causes serious concern about the validity of the trial data. Intention to treat analysis is a strategy used in analysis of clinical trial data to control for loss to follow up. The procedure for handling withdrawals and replacements and other forecasted problems should be established in the protocol.

Thought should be given on how to deal with complications arising from the disease or the intervention and how to respond to new problems. If adverse events arise will the intervention be discontinued temporarily or permanently? Will the

dose be decreased? Which other actions should be taken? For clinical trials studying new interventions, proactive safety procedures are determined in the protocol. There are standards for adverse event reporting, which include the steps to taken if an adverse event occurs.

Define the procedures for data collection and protection of subject confidentiality. Detail back up methods, storage procedures and security measures to avoid access by non-research personnel to sensitive health information of subjects.

Data Analysis

Planning the Analysis

A statement about the sample size, the power of the study and the significance level (p value) to test the primary outcome(s) is included in the study protocol. The analysis strategy to evaluate primary and secondary outcome variables is defined in the study protocol. Describe the types of variables collected for outcomes and statistical tests planned. For clinical trials define if the analysis is "intention-to-treat" or "as treated". The handling of specific situations should be described in advance. For example, will there be a subgroup analysis? [9].

An interim analysis is a planned analysis conducted at a pre-determined time in the study. The strategy used for this analysis is defined in the protocol. In clinical trials an interim analysis is conducted to (1) assess trends in incidence of adverse events and (2) assess efficacy results. If a new intervention is found to be particularly successful or obviously harmful at the interim analysis then an early termination of the trial and publication of the results is mandatory. Ethical issues and cost are the main justifications for planning interim analyses. In drug development trials an independent monitoring group separate from the investigators conducts the interim analysis.

Conducting the Analysis

Statistical analysis of the data collected provides information about the strength of the association between predictor variables and outcome variables. It supports the answer to the primary outcomes.

Descriptive statistical analyses are used to summarize the data using non-comparative techniques such as frequency distributions (proportions), description of averages (mean, mode and/or median) and description of the spread of the values (standard deviation and standard error). Assess assumption for statistical tests, i.e., if the data has a normal distribution or not. Compare baseline characteristics searching for differences that may impact the outcome, like demographic characteristics and prognostic factors.

Analytic statistical analyses are used to test your primary outcomes (hypotheses) and secondary outcomes. Variables are compared to evaluate the pattern and strength of relationships. The adequate statistical test depends on a variety of factors (example: presence of normal distribution, between/within subjects varia-

tion, repeated measures, etc.) and circumstances (example: time line) surrounding your data. Consult a statistician to plan the appropriate analysis methodology in advance, including subgroup analysis. The analysis plan is dynamic and additional analysis may be planned before looking at the data.

Hypotheses can be proven wrong, but they can never be proven correct because the investigator cannot test all the existing subjects with the condition of interest. Consider all the specific factors that may have influenced or biased the data and/or the interpretation reached [10].

Intention-to-treat analysis has as a principle the inclusion of all randomized patients in the analysis, independent of which intervention the subject received in the study. The outcome is analysed by the intervention originally assigned to the subject and includes dropouts. It is the preferred approach for pragmatic studies. If one starts excluding patients from the analysis for a variety of apparently "justifiable" reasons (subjects later not found to have met criteria, non compliers, missed study visits, moved, had other illnesses or dropped out of the trial before completion), a large percent of patients may be excluded from analysis thus compromising the validity of the results. The intention to treat analyses eliminates the risk of creating a bias due to these exclusions. When planning to do an intention to treat analysis, differences between treatments can be obscured and sample size needs to be increased.

As-Treated analyses strategy uses an algorithm based on the degree to which the patient "complied" with the protocol. This determines which subjects are included in the analysis. For example, subjects would be included only if they took all the study medications as defined in the protocol. The sample size used in this analysis is reduced because not all subjects meet compliance criteria. The power of the study is thus compromised. Bias can be created, as the subjects that did not comply (example: suffered adverse effects) may be different from subjects that did comply. The validity of the statistical testing is undercut, and an imbalance may result. It is advisable to perform an intention-to-treat analysis as well, so both types of analysis support the results.

Data may also be evaluated using subgroup analyses. The subgroups are decided in advance in the study protocol with a hypothesis on how different subgroups might react differently. Subject characteristics are frequently used for subgroup analyses such as: age, sex, race, severity of disease at baseline or duration of therapy. Within a subgroup, study data can be further divided into strata, for example: females A years of age versus 65 or older. The more strata used, the fewer the subjects in each stratum, resulting in less power to detect differences. If a decision to do subgroups analysis is made after the data is collected this is denominated post hoc analysis and can be helpful only for generating hypothesis for future studies [11].

Interpretation of Study Results: Drawing Conclusions

Interpretation begins after the trial is completed, the data is collected, edited, and entered into a database, appropriate statistical tests have been performed to analyze the data, and the statistical report providing a permanent and detailed record of

the study is compiled. This report allows other investigators to repeat the study using identical design and audit of the results.

Analyses of data are primarily statistical exercises, whereas interpretation of data is an exercise in discerning the clinical meaning of the data evaluated. The researcher is primarily concerned with drawing conclusions to report in publications. The goals of interpreting research data include establishing meaning of the data collected with an emphasis on clinical significance, reporting the results of the original objectives of the study while comparing with results from previous studies, developing hypothesis for future studies, and gaining insight into interpretations of the condition of interest.

When interpreting the analyses results one should look for factors that may bias the data or affect their interpretation. These include characteristics of the study design, subject enrolled, the condition being evaluated, the study intervention, the investigator and staff, and the trial environment. Other factors that can be responsible for bias are the conduct of the clinical trial, the characteristics of the tests and measures used, statistical factors, characteristics of the data report and possibly errors of deceit committed accidentally or wilfully before, during or after the trial [10].

Statistical significance, on its own, does not provide information about whether a result is clinically important. When considering clinical significance evaluate the relevance of chosen outcomes, the size of the effect observed, the risk/benefit and also cost/benefit [12].

Good Clinical Practice: conduct of a trial

In 1990 government agencies and pharmaceutical companies from the USA, Japan and Europe joined forces to create an international standard, both ethical and of scientific quality, for designing, conducting, recording, and reporting clinical trials that involve human subjects. This group known as the *International Conference on Harmonization* released the Good Clinical Practice (GCP) guideline in 1996. Compliance with GCP assures (1) trial subjects rights, safety, and well being are protected and (2) credibility of the clinical trial data. This guidance facilitates the mutual acceptance of clinical data by the regulatory authorities in the USA, Japan and Europe [8].

The Medical Research Council describes the principles of the Good Clinical Practice guidelines [9]:

1) Clinical trials must be conducted in accordance with ethical principles originating from the Declaration of Helsinki and be currently consistent with GCP and applicable regulatory requirements;
2) A clinical trial should be initiated and continued only if anticipated benefits outweigh foreseeable risks for the individual participant;
3) Rights, safety, and the well being of the individual participants should prevail over the interest of science or society;
4) The intervention proposed in the clinical trial should have adequate information, clinical or non clinical, supporting the trial design;
5) The design of the clinical trial should be scientifically sound and clearly described in the study protocol;

6) The clinical trial should be conducted in compliance with the protocol approved by the Institutional Review Board;
7) Qualified health professionals should provide care to participants;
8) All individuals involved in conducting the clinical trial should be adequately qualified by training, education or experience to perform their roles;
9) Freely given consent should be obtained for every participant prior to participation;
10) All clinical trial information should be recorded, handled and stored in a way that allows accurate reporting, interpretation and verification;
11) Confidentiality of records that could identify participants should be protected, respecting privacy and confidentiality rules in accordance with applicable regulatory requirements;
12) Investigational products should be manufactured, handled and stored in accordance with Good Manufacturing Practice and used in accordance with the protocol approved by the Institutional Review Board; and,
13) Systems with procedures that ensure the quality of every aspect of the trial should be implemented.

Ethical Considerations

The basic ethical principles of autonomy (respect for human subjects), non-maleficence (do no harm), beneficence (do good) and justice (exclusion) underlie the ethical considerations in medical research. Ethical considerations are important in all aspects of a study, from the development of the research question, decision on the study design, implementation of study protocol through to analysis, interpretation and publication of the results. There are also concerns relating to individual study subjects and to scientific novelty and integrity. Ethical questions are not merely present or absent, but range from those which are obvious to those that can be strongly debated.

The ethical principle of autonomy incorporates two separate moral requirements: (1) to acknowledge autonomy and (2) treat individuals as autonomous agents and to protect those individuals with reduced autonomy. In most cases of research involving autonomous human subjects, the principle of autonomy requires that subjects enter into the research voluntarily and with adequate information about the study. In some cases, individuals are not capable of deciding in their best interest, either because of maturity (children), illness (coma), mental disability (Alzheimer's) or other circumstances (prison). Subjects that are not autonomous will require varying degrees of protection if they are to be included as human subjects in research.

The ethical principles of beneficence and maleficence involve an obligation to secure the well being of human subjects, by maximizing benefits and minimizing or entirely avoiding harm. The critical decision is if the risk of harm justifies the possible benefits. Ethical issues in research studies concern *individuals* rather than society at large. The objective is that no individual should be exposed to unreasonable risk for the sake of the community.

The third ethical principle, that of justice, refers to the selection of human subjects and who derives the benefits of the research results. In the early 20th century poor people treated in public hospitals served as subjects for studies but they did not derive the benefits of the results. Private patients of the same physicians were the ones who benefited. An example of flagrant injustice was the use of unwilling concentration camp prisoners as study subjects during World War II. Selection of human subjects should be based upon reasons directly related to the study question, not upon easy access, convenience and/or availability.

Ethical concerns when developing and implementing a research protocol must also be taken into consideration with relation to scientific validity, recruitment procedure, participation procedures, potential harms and benefits and informed consent.

The ethical basis for the research question first needs to be established. Has the research question already been answered by good quality studies? If this is the case, is it reasonable to deprive subjects of a therapy that has been proven to be effective? Has your research question been answered? Are there benefits that would justify the risk of harm? The next step is to support these assertions in your protocol.

Once a research question has been established and a study protocol developed, a requirement for meeting these ethical considerations is to have the research protocol reviewed by an independent committee to assess if any ethical principles have been violated, the Institutional Review Board. The Institutional Review Board is a multidisciplinary committee that has as objectives to protect patients' rights and to assure that ethical standards are met by the study protocol. They review the protocol and any subsequent amendments, providing their approval and recommendations. They do not however inspect to see if the study procedures described are being adequately followed. It is the responsibility of the sponsor and the researcher to conduct research in accordance with the guidelines recommended.

The Institutional Review Board's are established in hospitals and educational institutions carrying out medical research, with an aim to protect human subjects. National policy provides the guidelines for the Institutional Review Board. For a multi site studies, the study protocol has to be approved at each site. The Institutional Review Board also serves as a resource for the investigator developing a protocol. The knowledge of the Institutional Review Board requirements for protocol approval helps the investigator include all the necessary information in the first version of the protocol avoiding multiple corrections and delay of the study.

The Institutional Review Board determines if there is a need for an *Informed Consent Form* (ICF) and will approve the content. Informed consent should be obtained from all subjects entering the study and should be retained for future audit. The ICF is written in non-technical language to facilitate the subject's understanding of the potential risks and benefits of entering the study. Some of the elements that should be included in the ICF are listed below:

1) An explicit statement that the project involves research, a description of the purposes of the research, and the procedures for the selection of subjects;
2) A clear identification of the researchers and sponsors;
3) A description of the time and type of commitment required from the subjects;

4) An explanation of the concept of randomization and blinding and the assignment of experimental and control intervention;
5) An explanation about the probability and magnitude of benefits and harms, mentioning procedures used to maximize benefits and minimize harms;
6) A description of alternative treatments if they are available outside the scope of the study;
7) Information about potential costs and the possibility of disclosure of the results;
8) A statement about procedures to maintain confidentiality;
9) Assurance that participation is voluntary and that declining from participating or withdrawing at any time during the study will not incur penalties;
10) An explicit offer to answer questions or provide further information;
11) Clear information about whom to contact for further information, the rights of study subjects, and any adversities related to the study stated.

The Informed Consent Form provides a process for certifying that the researcher has established the subject's autonomy, provided appropriate and adequate information on the study protocol, benefits and risk of harm, clarified that the subject is able to withdraw from the study at any time without suffering consequences, and explained the protection of confidentiality so the individual can decide whether or not to participate in the study.

Other issues that require clarification in the protocol are the protection of subject confidentiality and compensation. All study information regarding the subject's state of health must be confidential. If disclosure to a third party is required, specific consent from the subjects must be obtained beforehand. The staff involved in carrying out the study procedure has to insure subject confidentiality and comply strictly with protocol procedures. Study records should have an identifier, usually a subject number, which cannot be traced to the subject. Transmission of data over the Internet should meet strict standards to assure that confidentiality is not broken.

Compensation of subjects requires Institutional Review Board's approval. Study subjects are usually not paid, unless it can be demonstrated that this is not an inducement. Only out- of-pocket expenses may be reimbursed. The sponsors, however, must provide compensation, regardless of legal liability, if the subject suffers deterioration in health or well being that is caused by participation in the study.

Once the Institutional Review Board approves the study protocol and the Informed Consent Form, the research study can be initiated, not before. Ethical considerations are relevant to all individuals and groups connected with the study, the investigator research team, and the sponsor.

In certain circumstances early study discontinuation is ethically required. For example, when research staff fails to comply with study procedures or an interim analysis of a clinical trial may indicate an increase of harmful effects in the group receiving an experimental intervention. In the ALLHAT trial for hypertension management the study arm receiving an alpha-blocker was discontinued because in the interim analysis a doubling of risk for congestive heart failure occurred. In similar way if beneficial effects are determined in the interim analysis, ethical concerns are raised for patients not receiving this intervention.

References

1. Masur H, Michelis MA, Greene JB et al (1981) An outbreak of community-acquired Pneumocystis carinii pneumonia: initial manifestation of cellular immune dysfunction. N Engl J Med 305(24):1431-1438
2. Gottlieb MS, Schroff R, Schanker HM et al (1981) Pneumocystis carinii pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency. N Engl J Med 305(24):1425-1431
3. Durack DT (1981) Opportunistic infections and Kaposi's sarcoma in homosexual men. N Engl J Med 305(24):1465-1467
4. Pocock S (1983) Clinical Trials: A practical Approach. Chichester: John Wiley & Sons
5. Hulley S, Cummings S, Browner et al (2001) An Epidemiologic Approach. 2nd Edition, Lippincott Williams & Wilkins Publishers
6. Ebrahim G, Sullivan K (1995) Mother and Child Health Research Methods. 1st ed. London, Book-Aid
7. Moseley JB, O'Malley K, Petersen NJ et al (2002) A controlled trial of arthroscopic surgery for osteoarthritis of the knee. N Engl J Med 347(2):81-88
8. Jorgensen HS, Kammersgaard LP, Nakayama H et al (1999) Treatment and rehabilitation on a stroke unit improves 5-year survival. A community-based study. Stroke 30(5):930-933
9. Chambers G, Fairbarn M (1998) Clinical Trial Design: An Introduction to Good Clinical Trial Design and the Protection of Human Subjects. Applied Clinical Trials 7(9):60-66.
10. Spilker B (1996) Fundamental Principles, Considerations, and Techniques in the Interpretation of Clinical Data. In: Guide to Clinical Trials, Lippincott-Raven T, Philadelphia pp 505-558
11. Detsky A, Naglie I (1995) Subgroup analyses: primary and secondary. ACP Journal Club May/June:A12-A14
12. Cook D, Sacket D (1992) On the Clinically Important Difference. ACP Journal Club September/October:A16-A17

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