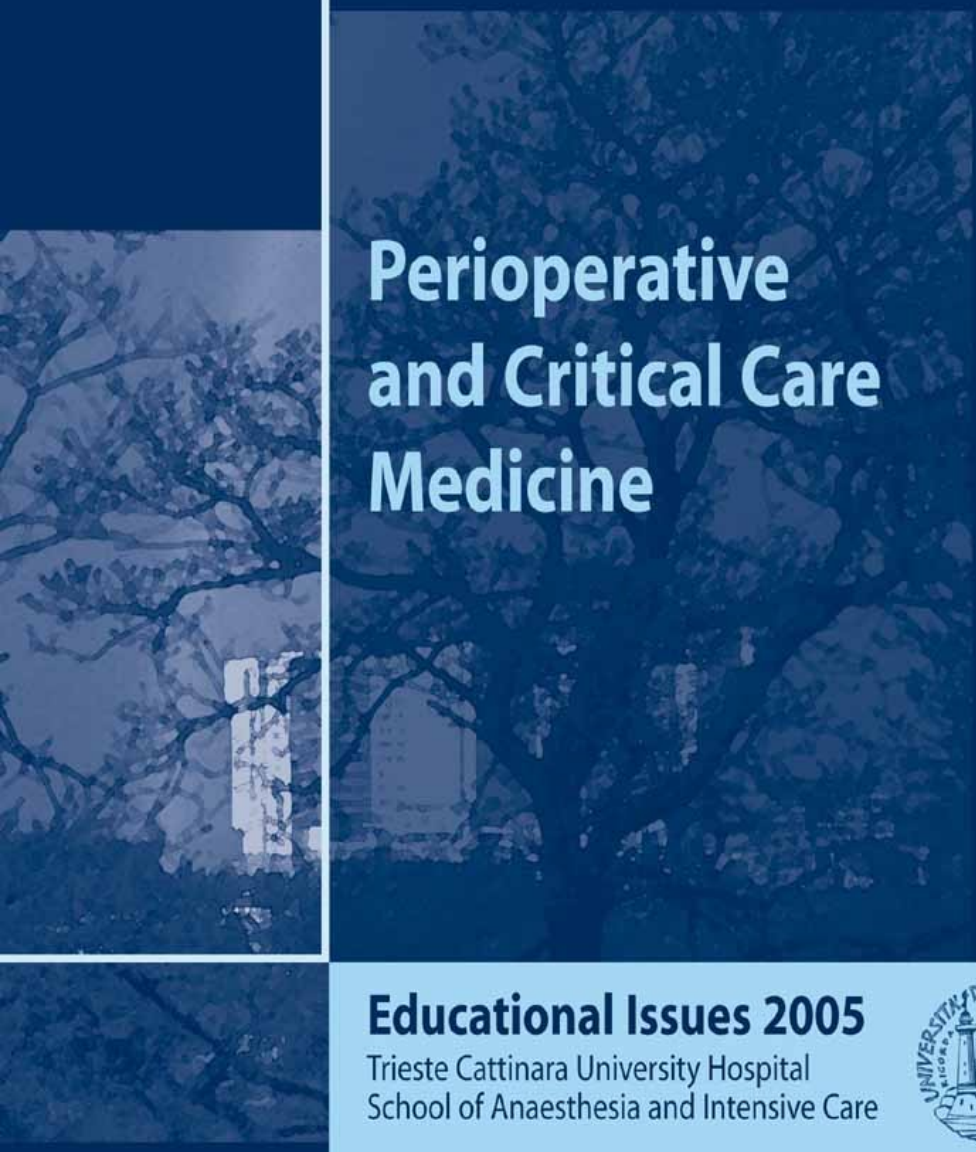
A. Gullo • G. Berlot (Eds.)

Perioperative and Critical Care Medicine



Educational Issues 2005

Trieste Cattinara University Hospital
School of Anaesthesia and Intensive Care

Springer

Perioperative and Critical Care Medicine

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University of Trieste
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Preface

Teaching is an ancient activity; it requires a predisposition and ability to transmit one's own knowledge to others. It is also an innate quality that tends to strengthen over time, due to the interaction between teacher and pupil that develops and intensifies during their association, and to the ready availability of constantly improving teaching methods. Teaching is a predisposition to communication. It is a constant commitment that becomes a way of life and offers the capacity for self-renewal. In the clinical context, this desire to transfer and receive information, together with the ability to summarise and authoritatively reach decisions take on both professional and ethical significance.

Training provides an opportunity to deepen one's foundation of knowledge and to stimulate the development of a reasoned clinical approach that allows significant elements to be emphasised, with a view to improving one's ability to correctly recognise and evaluate important clinical indications, both in routine and in emergency situations. Clinical evaluation marks a key moment in the training process, and knowing how to take note of all the relevant elements, including paucisymptomatic ones, forms an integral part of a long process that, though fully attainable, demands methodological meticulousness and the use of specialised forms of teaching. These include teaching in small groups, establishing a one-to-one relationship between teacher and pupil, taking advantage of computer systems (micro-teaching), and a willingness of the teaching team to share ideas while employing a practical, personalised approach. Finally, also required is a close empathy between teachers and pupils, who must share the aim of gaining excellence (mastery learning); this is best supported through multidisciplinary collaboration. For example, if a diagnosis cannot be confirmed by standard investigations, the doctor must call into play all available resources, so that the clinical approach is newly focused and geared towards improving the patients' quality of life.

This type of situation underlines the importance of continuous improvement of those methods associated with the most delicate phase of the long medical teaching process. Training in medicine is a critical element; it requires a series of educational instruments and methods able to optimise the various curricula.

This is especially true if we take into account the fact that the theoretical aspect and the professional training elements are closely linked.

In 2004, the Board of the School of Anaesthesia and Intensive Care of Trieste considered that the time had come to offer pupils a collection of selected lessons offered by members of the teaching staff of the School, and by internationally renowned researchers and clinicians.

The first volume stimulated considerable interest and encouraged us to continue with the initiative. The main goal is to offer pupils a useful guide to explore the key components of the training process for future specialisation. With this in mind, the aims of the course of 2005 have been confirmed due to the keen participation of the teachers of the School, its staff, and those who have edited the present volume. The lessons and seminars contained within this volume are dedicated to the pupils and to all those who have an interest in supporting a continuous educational process in the field of anaesthesiology and intensive therapy.

Trieste *Antonino Gullo*
November 18th, 2005 *Giorgio Berlot*

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Abbreviations

ACC	American College of Cardiology
AHA	American Heart Association
AHCPR	Agency for Health Care Policy and Research
AHI	Apnoea/Hypopnoea Index
ALI	Acute Lung Injury
ANH	Acute Normovolaemic Haemodilution
APS	Acute Pain Service
ARDS	Acute Respiratory Distress Syndrome
ATLS	Advanced Trauma Life Support
BALF	Bronchoalveolar Lavage Fluid
CHEOPS	Children's Hospital of Eastern Ontario Postoperative Scale
COP	Colloid Osmotic Pressure
CPAP	Continuous Positive Airway Pressure
CPP	Coronary Perfusion Pression
CT	Computed Tomography
CVA	Cerebrovascular Accident
DAD	Diffuse Alveolar Damage
DH	Dynamic Hyperinflation
DNR	Do Not Resuscitate
EBM	Evidence Based Medicine
ECM	Extracellular Matrix
ECT	Electroconvulsive Treatment
EELV	End-Expiratory Lung Volume
EFL	Expiratory Flow Limitation
EGF	Epithelial Growth Factor
ESWL	Extracorporeal Shock Wave Lithotripsy
$EtCO_2$	End-Tidal Carbon Dioxide Tension
ETI	Endotracheal Intubation
FEV_1	Forced Expiratory Volume in the First Second
FGF	Fibroblast Growth Factor
FRC	Functional Residual Capacity

FVC	Forced Vital Capacity
GA	General Anaesthesia
GAG	Glycosaminoglycans
GCS	Glasgow Coma Score
HES	Hydroxyethyl Starch
HGF	Hepatocyte Growth Factor
HPV	Hypoxic Pulmonary Vasoconstriction
HS	Hypertonic Saline
ICP	Intracranial Pressure
ICU	Intensive Care Unit
IL	Interleukin
IRB	Institutional Review Board
KGF	Keratinocyte Growth Factor
LR	Lactated Ringer's
MAC	Monitored Anaesthesia Care
MEFV	Maximal Expiratory Flow-Volume
MMP	Metalloproteinases
MODS	Multiple Organ Dysfunction Syndrome
MOF	Multiple Organ Failure
MRI	Magnetic Resonance Imaging
MTOS	Major Trauma Outcome Study
MW	Molecular Weight
NB	Neuraxial Blockade
NEP	Negative Expiratory Pressure
NFL	Non-Flow Limited
NIV	Non-Invasive Ventilation
NO	Nitric Oxide
NRS	Numerical Rating Scale
NSAID	Non-Steroidal Anti-Inflammatory Drug
OPS	Orthogonal Polarisation Spectral
OR	Operating Room
OSAHS	Obstructive Sleep Apnoea Hypopnoea Syndrome
P_A	Alveolar Pressure
Pbs	Body Surface Pressure
PCA	Patient Controlled Anaesthesia
PCO_2	Carbon Dioxide Tension
PDGF	Platelet Derived Growth Factor
PEEP	Positive End-Expiratory Pressure
PG	Proteoglycans
PONV	Postoperative Nausea and Vomiting
PRC	Packed Red Cells

RCT	Randomised Controlled Trial
ROSC	Return of Spontaneous Circulation
SNP	Single Nucleotide Polymorphism
STAR	Sepsis Treatment and Response Registry
TEE	Transoesophageal Echocardiography
TGB	Transforming Growth Factor
TIA	Transitory Ischaemic Attack
TIMP	Tissue Inhibitors of Metalloproteinases
TNF	Tumour Necrosis Factor
TR	Trauma Registry
VAS	Visual Analogue Scale
VD	Volume of Distribution
VEGF	Vascular Endothelial Growth Factor
VF	Ventricular Fibrillation
VILI	Ventilator-Induced Lung Injury
V–P	Volume–Pressure
Vr	Relaxation Volume
VRS	Verbal Rating Scale
V_T	Tidal Volume

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Professionalism, Ethics and Curricula for the Renewal of the Health System

A. Gullo

Introduction

There is an ongoing heated debate concerning the best possible model for a healthcare system able to respond to public expectations. Society wants changes – radical changes – that place the organisational apparatus of the current healthcare system in a critical position. Public opinion, as well as the opinion of the medical profession, reflects doubts concerning the ability of physicians to preserve their current role in serving patients.

Control over people's health in terms of prevention, as well as care, has rendered the management of the healthcare system more and more complex. The budget is so conspicuous that it has an important role in the economies of even the most industrially advanced countries. In such a context, it is difficult to know with absolute certainty whether future physicians will have professional autonomy and the ability to excel in their role as healthcare providers, or whether their role, of necessity, will be submerged in, and secondary to, bureaucratic and administrative considerations. This second possibility is a cause of great concern among physicians, who are conscious of their changing role in society and the progressive decrease in personal prestige. The reality of the situation is reflected in the increasing tendency of the relationship between physician and patient to become impersonal.

The insufficient quality of healthcare that professionals are able to provide as a result of this situation raises doubts concerning the endurance of the public healthcare system. It is not difficult to imagine what could result from the opposition between commercial interests and healthcare standards based on quality and professional ethics (Table 1), particularly if the medical profession is unable to reverse the current trend [1].

The term professionalism occurs frequently in the medical literature, as well as in debates on clinical and healthcare-related subjects. Although there is no consensus on the best definition of 'professionalism,' the term is closely related with the moral principles and standards, handed down from genera-

Table 1. Main qualities of a physician

– Belief in the importance of the medical profession
– Transmission of medical knowledge to others
– Having good relations with the patients and the public
– Being humanitarian and altruistic
– Being honest and upright
– Belief in the medical team
– Standards of excellence
– Being at the patient's and society's service
– Being brave and heroic if necessary
– Being a model for teaching professionalism

tion to generation, that make up the foundations of the medical profession. As John D. Lubahan expressed it, the term 'professionalism' is 'the image of the ethical and moral conduct of those who practice the medical profession' [2].

It is therefore important to analyse the components that comprise the meaning of the concept, professionalism. First of all, it is necessary to consider the time-honoured principles and methods for training physicians, and the importance of planning a curriculum of excellence. At the same time, one must not lose track of the new and emerging models concerning the role of today's physicians (this will be discussed at greater length later). Lastly, it is important to understand the role of the scientific community in determining the correct guidelines for spreading the philosophy of professionalism as a quality label that will accompany the physician throughout his or her career. Part of this philosophy entails the ability of physicians to subordinate their personal interests to the interests of their patients. As a result, the ethical and moral conduct of physicians must be exemplary. Physicians must possess the qualities of humanity, honesty, integrity, compassion, altruism, empathy, confidence in truth and respect towards others. Furthermore, they must be ready to respond to the needs of patients according to the mandate given by the community. Medical practitioners, teachers and students all have the responsibility of ensuring that the principles set forth in the charter, 'Medical Professionalism in the New Millennium,' are honoured [3, 4]. In summary, there are several points pertaining to the concept of professionalism that are very closely connected. The term is primarily identified with the ethical and moral principles constituting the basis of the medical profession, and the solid integration of these principles in medical practice requires the availability of rigorous training programs and continuous medical education.

Professionalism and Ethical Principles

The word 'profession' originates from the Latin verb *professare*, 'to declare.' In the past, this term was used to confer a set of privileges on the person practicing a profession, and this was deemed a fair exchange for the benefits conferred on society. In other words, the term profession indicates a specific occupation through which a person carries out activities beneficial to society from an economic, political and social point of view [5].

Every profession of necessity results in a sort of monopoly and, thus, provides a certain degree of autonomy in relation to the mandates of the profession and its relationship with external institutions. This autonomy is dependent on the ability of the profession to fulfil the expectations of society. Ethics is of fundamental importance; inherent in the concept of professionalism is the superiority of activity linked to helping others, versus promoting personal gain. Consequently, professional activity in the medical arena is regulated by well-defined, universal principles, such as the welfare of the patient, autonomy and social justice, for which it is important to give brief comment.

Welfare of the patient – this principle is based on a dedication to safeguarding the interests of the patient. Altruism contributes to the trust that is central to the relationship between the physician and patient. Commercial interests, pressures exerted by society and administrative needs must not be allowed to jeopardise this trust.

Patient's autonomy – physicians must respect the autonomy of their patients and empower them to make informed decisions about their treatment. The wishes of the patient concerning his/her care must be given priority; patients must be supported in a practical way and within the boundaries of ethical principles, with the objective of avoiding requests for inappropriate care.

Social justice – the medical profession must promote social justice. This represents one of the most important principles in the healthcare system, and it includes the fair distribution of healthcare resources. Physicians must strive actively to eliminate discrimination, whether based on race, gender, socioeconomic status, ethnicity, religion, or any other social category.

It is important to keep in mind that every medical intervention is worth much more than any economic benefit [6]. It is essential to ensure a balance between personal benefits, even if legitimate, that may be derived and the public perception that the profession must guarantee a fair distribution of resources in terms of healthcare.

Historically, the legitimisation, authority and legal privileges that society afforded to most professions considered prestigious originated in the demands of the various guilds and their commitment to safeguarding the appropriate recognition of professional activity. At the heart of these demands was a strong civil commitment and a distinct interest in helping the

community [7, 8]. This commitment had its origin in social values that are still present in the medical profession, much more so than in other occupations [9].

Steven Britts maintains that, without a strong sense of interest for the defence of the public and social life, professional activities risk losing their distinctive voice in the public debate [10]. Webster's English dictionary defines professionalism as, 'the conduct, aims or qualities that characterise or mark a profession or a professional person' [11]. The term 'professionalism' as it applies to the medical field, confirms a contract between medicine and society. This contract entails placing the patient's interests above the physician's interests; and it also entails that the physician be available and able to inspire confidence in terms of his/her skills, moral integrity and commitment to guaranteeing the patient's welfare. To better understand the meaning of the term professionalism it is necessary to examine the nature of the profession and the essence of the physician's activity.

The term professionalism implies 'good medical practice,' which derives from the long and demanding training process that the profession requires. The demand for a better definition of professionalism is a result of significant changes within society and a growing need to guarantee improved quality in community healthcare services [12]. In other words, increasingly, the term professionalism is being identified as the essence of competence and specialisation [2].

Medical Profession

Understanding the changes taking place in society help elucidate the need for adapting the clinical management of the healthcare system to the new needs of the community. In the United States, during the first half of the last century, the medical profession achieved a role of undisputed autonomy and dominion on the same level as a powerful lobby. Suffice it to say that in this historical period the medical profession was able to control associations, work places, finance and even relations with the state [13]. This trend rapidly spread throughout the world, particularly in the wealthier and more technologically advanced nations. As unrestrained growth continued, however, a subtle change began to occur and quickly gain momentum. The acquisition of new knowledge and the availability of new technologies began to favour situations that were not easily controllable, and that were to the advantage of only a minority. This resulted in increased complexity and chaos that lead to an inexorable decline of the universal principle of the humanisation of medicine. The situation also worsened as a result of the rise of costs with respect to the resources available, which were no longer unlimited.

This progressive institutional degradation resulted in the community taking action to ensure more rigorous control of the functioning of the healthcare system. Radical changes in the management of public health ensued, and these changes led to a limitation in the autonomy of physicians and a reduction in their acquired privileges. The progressive weakening of the image of physicians and the decrease in their power resulted in the inability of physicians to participate actively in the clinical management of the healthcare system. As a consequence, doubts concerning the professional role of physicians began to emerge. All of these elements were to the advantage of the widespread, growing and dominant industrial alternative in the management of healthcare [14]. Powerful lobbies in the pharmaceutical, biomedical and financial sectors served to tighten the hold of these interests on the healthcare system, a situations that was, and continues to be, facilitated by the limited political and economic strength of those in the medical profession.

The competition between the medical sector and capitalism was able to maintain a degree of balance and equilibrium until the end of the last century. Afterward, however, the inability of the medical profession to preserve its autonomy began to become increasingly obvious. Soon physicians were not even consulted in, or considered integral to, the decision-making process pertaining to important changes in healthcare policy. The effect of these developments on the professional sovereignty and autonomy of physicians is obvious and runs the risk of confining them to a subordinate position, leading to potentially catastrophic consequences [15]. The progressive decline in the role of physicians also has made possible a definitive shift in the management of the healthcare system to the state and various corporations (Table 2).

Table 2. Characteristics of the corporation in the medical field

– Centralisation of leadership
– Organisation and infrastructures
– Human resources
– Capital
– Financial management
– Strategic planning
– Strategic alliances
– Legal support
– Support for all patients and the community
– Quality, safety and effectiveness of care
– Control and prevention of medical errors
– Control of cost–effectiveness of care

Among the negative elements of a system controlled by corporate interests is the reduced safety for patients. This has led to an alarming increase in the number of lawsuits for medical malpractice, which, in turn, has led to drastic social inequalities, with the number of people lacking health insurance, even in countries with high incomes, reaching startling levels. In this context, it is easy to see the degree to which we have diverged from the system apparent in previous generations, where respect for the physician's professionalism guaranteed certain universal principles. Foremost among those principles was the availability of healthcare for everyone. The urgency of the current situation has motivated professional associations, government bodies and trade unions – to name only a few interested parties – to recognise the need for safeguarding the medical profession and to give reform through administrative and legal measures an important priority.

To better understand the reasons why the physician's professional responsibility is essential to quality healthcare, it is important understand the elements that are inseparable from the concept of professionalism (Table 3).

Professional competence – In order to maintain the highest possible level of professionalism, physicians must be committed to their own continuing education as a means of increasing both their knowledge base and their manual skills. Equally important for achieving the best results possible is their willingness and ability to collaborate with others on the team.

Honesty towards the patient – Physicians must make sure that patients are completely and honestly informed, both before consenting to a treatment and after the treatment. This does not mean that patients require constant updates during medical treatment, but it does mean that they are in a position and have the knowledge necessary beforehand to grant authorisation to the physician for making decisions during their therapy.

Table 3. Professional responsibility of the physician

– Professional competence
– Honesty with the patient
– Confidentiality concerning the patient's personal data
– Relationship with the patient
– Quality of care
– Access to care
– Distribution of resources
– Use of scientific knowledge
– Maintaining trust by managing conflicts of interest
– Professional responsibilities

Physician must also be able to acknowledge during this initial stage the possibility of medical errors that could injure the patient. In the event that a patient is injured as a result of medical care, the physician must inform the patient promptly. This is necessary from an ethical point of view and in order to maintain the patient's trust. Reporting and analysing medical errors creates the basis for appropriate preventative and improvement strategies, and for appropriate compensation to the injured party.

Confidentiality concerning the patient's personal data – The patient's trust requires the confidential use of information. Confidentiality must also be extended to the people acting on the patient's behalf when the patient cannot be informed and, therefore, cannot give his/her consent. It is important to stress that the confidentiality of personal data is especially critical today, given the widespread use of electronic information systems.

Relationship with the patient – Given the unique vulnerability and psychological dependency of the patient, it is important to avoid certain relationships between physicians and patients. Physicians must never exploit patients for sexual advantage, personal financial gain or other private purpose.

Quality of medical care – Physicians must do their utmost to improve the quality of healthcare. This commitment implies the need to maintain and continuously update their skills through ongoing education, and it also implies the need to work in collaboration with other professionals.

The main goals are to reduce medical errors, increase patient safety, avoid the unnecessary use of available resources and improve the outcome for patients.

It is the physician's duty to participate actively in improving the quality of medical services; this includes working collaboratively with the institutions and organisations in charge of delivering healthcare resources to everyone in the community. Physicians, both personally and by means of their professional associations, must take responsibility for improving the elements necessary for optimising the quality of services and the efficiency of medical care.

Access to care – In order to create a more equitable system, physicians must be committed, personally and collectively, to reducing or abolishing any barriers that exist to the access to medical care. Physicians must be aware of situations that can lead to unequal care as a result of education, laws, finances, ethnic origin and social discrimination. The healthcare system must be organised in such a manner as to ensure the health of the entire community through preventive medicine. Furthermore, physicians must act as guardians of the weak and not be influenced by personal interests.

Distribution of resources – Physicians must understand the patient's needs and be able to provide care that takes into account the availability of limited

resources. The collaboration among physicians, the functional connections between hospitals, and the role of those who finance the system are all important strategic elements in providing cost-effective care. The professional responsibility of physicians entails the control and appropriate use of the resources available, avoiding, for example, the use of procedures and clinical tests that seem superfluous. Requiring unnecessary exams and therapies not only diminishes the resources available for other patients, it can also expose the patient to potential risks of personal harm or serious injury.

Use of scientific knowledge – Medicine's contract with the community is based on integrity and the use of evidence-based scientific knowledge and technology. Physicians have the duty to improve organisational and clinical standards; it is also their duty to promote research, publicise new knowledge and guarantee its appropriate use.

The medical profession is based on intellectual work and specialised knowledge, and, within this framework, skill plays a substantial role in the quality of the outcome. The medical profession is responsible for the integrity of knowledge based on scientific evidence which, when associated with the physician's experience, must express standards of excellence.

Maintaining trust by managing conflicts of interest – Physicians and their organisations have many opportunities for personal gain that can lead to a compromise in terms of their professional responsibility. In the economic sector, the main objective is profit. Interactions with companies, such as medical equipment manufacturers, insurance companies and pharmaceutical industries, that might go beyond the usual limits can be dangerous. Physicians have an obligation to disclose to the general public their relationships with companies in which they have an interest, and the nature of that interest. This danger of this type of situation results from the fact it could influence the management of a study or scientific magazine, or favour interventions that interfere with the guidelines of a treatment.

Professional responsibilities – Physicians have the duty to work in close collaboration with each other in order to optimise the treatment of patients. It is therefore essential that they establish relationships of reciprocal respect, uphold professional rules, and take action when necessary to resolve dysfunctions created by colleagues who fail to meet professional standards. In order to promote the training of future generations, it is also important within the professional setting to clearly define organisational criteria for university education and specialisation. Finally, physicians have a personal, as well as a collective, duty to participate in and support the various components that comprise professional responsibility. Thus, evaluation within the system, and control outside of it, are essential components of professional responsibility.

Curricula

An indispensable ingredient for good medical preparation is the availability of a sufficient amount of time for the achievement of training objectives. The duration of studies depends on the time necessary for students to acquire the ability to understand and synthesise clinical data, to demonstrate familiarity with the various skills necessary for good medical practice and to acquire specialised training. Medical training involves the use of sophisticated procedures and technologies, and it is important that a sufficient period of time be allotted for the student to master these procedures and technologies. Students must also receive guidance on how to interact with patients. The Socratic method is the best approach for imparting this type of knowledge, even though it requires longer periods of time from the teacher and more intense participation on the part of both teacher and student [16]. Unfortunately, because many things have changed as a result of the transformation of the healthcare system, there is less time available for professors to dedicate themselves to teaching, or to research. Instead, often they are required to devote most of their time to treating patients.

Present healthcare policies tend to focus on the economic motives and encourage a greater turnover of patients, a situation that creates severe discomfort among students, who, as a result, have little time to study and evaluate patients and to verify the efficacy of the care given. It is difficult to imagine how these changes in healthcare policies could possibly enhance the quality of the training process. Professionalism involves humanistic values, altruism, ethics and moral aspects that are associated with a continuous effort in the training process. Professionalism is an indispensable tool for the guidance of students, physicians and teachers who take specialised during the postgraduate period. But professional ability and the relationship between physicians and patients represent only some of the important elements [17–19]. Students must also acquire the necessary experience to be able to interact appropriately and effectively with patients, particularly during their daily practice [20].

Students often ask implicit as well as explicit questions and it is not uncommon for teachers to find themselves in a bind with respect to how much autonomy to give students. Clearly, physicians cannot make decisions and take responsibility without the freedom to decide autonomously (even in situations that can lead to erroneous results). Who can deny the importance of learning from possible errors? Teachers must therefore be able to provide guidance when appropriate, rather than simply give instructions or orders, and students who are training to be physicians must develop autonomy and accustom themselves to giving a score to their performance. It goes without

saying, of course, that they must also develop the necessary mastery and ability to make responsible and autonomous decisions.

Conclusions

In recent years, medical professionalism has been a topic of great interest, both in the medical sector, where, increasingly, it is the topic of discussion in scientific literature, as well as in the general media. There appears to be a widespread perception that the value of medical professionalism is undergoing a progressive decline due to the difficulty of medicine to provide satisfactory solutions to the requests of patients, and that, as a consequence, medical professionals are not in a position to fulfil the expectations of society. This progressive loss of confidence, and the reduced amount of time available for physicians to spend with patients, has taken its toll on the significance and the value of the term 'professionalism' as it pertains to the practice of medicine. It is obvious that, in the medical field, a radical transformation is underway (Table 4).

Table 4. Comparison between the old and new healthcare system (modified from [21])

Classical approach	New rules
Care based on the data from the visit of the patient	Care based on an improved collaboration between specialists
Professional management of care	Patient at the centre of the medical intervention
Registration of clinical data	Shared knowledge and rapid transmission of information
Clinical decisions on training and experience	Clinical decisions based on evidence
Individual responsibility of the damage	Safety in the care system
Priority on the confidentiality of clinical data	Indispensable transparency
System capable of responding to needs	Organisation capable of preventing needs
Hospitalisation, diagnosis and treatment	Early discharge, day-hospital, home care
First aid	Department of emergency medicine and trauma centre
Reduction of costs	Reduction in the waste of resources

The changes that have taken place in society have resulted in important alterations in the organisation and management of the healthcare system, and this is primarily evident in the most advanced countries. A question that naturally come to mind is, what exactly is changing in these capitalistic and corporate cultures? The so-called 'old professional authority' of the physician was, only a few decades ago, based on the physician's training, the achievement of the appropriate license for professional practice and the prospect of a good medical practice. In a relatively short period of time, society appears to have undergone a deep metamorphosis – one that, for the majority of the population in the most advanced countries, has unleashed an era of consumerism. In this environment, the emerging authority is based not so much on professional trust and respect as it is on individual performance. The use of the Internet has resulted in the demolition of boundaries and the chance to obtain online a list of the 'best doctors' and structures available for guaranteeing the highest quality of care.

The terms 'consumerism,' 'performance,' and 'marketing' have become a part of everyday language and represent important elements for understanding the future of our society. Some serious thought should be given to understanding the dimension and complexity of the problems resulting from the changes in technologically advanced countries; and it is particularly important to evaluate the effects of these changes with respect to the choice of objectives affecting the scientific community.

There is a widespread belief that the term 'mission' is inherent in the meaning of professionalism. The implementation of the quality of care [22–24] is a priority objective; clinical practice must be based on scientific evidence and the scrupulous, clear and sensible application of the best decisions and choices possible for the care of patients [25–27]; the improvement of the outcome in terms of morbidity, mortality and quality of life represents the underlying priority [28]; and the acquisition of improved scientific knowledge and a more functional use of technology represent new frontiers of medicine [29, 30].

It is important to be able to carry out a training project and to apply a research method based on solid scientific foundations, correct statistic analyses and respect for the principles of bioethics [31]. All these elements are indispensable in providing precise indications of the path to be taken. Changes require strong individual action and the availability of widespread communication for sharing principles, so that these elements, which are regulated, may be identified with the authority inherent in the term professionalism. This is the real challenge for the renewal of the medical profession, and it must be accomplished in accordance with the fulfilment of certain princi-

ples. The renewal of the medical profession thus entails improvements in the quality of professional attributes having to do with ethics and morality, clinical practice based on evidence, and standards for medical care and the use of new technologies. It also involves improvements in monitoring quality of the outcome, acquisitions of knowledge and the use of such knowledge through the observance of the Hippocratic oath. Along the same line, it involves improvements in monitoring clinical research conducted for the sole purpose of helping patients. The correct application of all these elements, and the presence of a solid and dynamic process of continuous medical education and specialisation, represent the true mission of the medical profession.

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Respiratory Mechanics in Health

E. D'Angelo, A. Lucangelo

Statics

The statics of the respiratory system and its component parts is studied by determining and analysing corresponding volume–pressure (V–P) relationships. These relationships are usually represented as single lines, in spite of the fact that static pressures differ depending on volume, as well as on timing. V-P relationships obtained in subsequent steps from minimal to maximal lung volume and back again appear as loops, referred to as 'hysteresis loops,' that are attributed to both viscoelasticity, i.e. a rate-dependent phenomenon, and plasticity, i.e. a rate-independent phenomenon. Indeed, only plasticity is responsible for static hysteresis. Although there is no information concerning pressure related to tissue plasticity in humans, it has been suggested that this pressure component should be very small in the tidal volume range [1]. Moreover, the static pressure across the lung and chest wall varies at different sites because of the effects of gravity and different shapes of these two structures [2], while the static pressure across the respiratory system may become non- uniform under conditions involving airway closure. Nevertheless, for analytical purposes, static V–P relationships will be considered as single functions.

Respiratory System

The net pressure developed by the respiratory system under static conditions (Pst,rs) results from the forces exerted by its elastic elements, and equals the difference between alveolar pressure (P_A) and body surface pressure (Pbs). Conversely, Pst,rs indicates the pressure that the respiratory muscles must exert to maintain that lung volume with open airways, provided the shape of the respiratory system is kept fixed. For a given volume, the elastic energy, and hence, the elastic pressure, is minimum for the configuration during paralysis, and is increased whenever that configuration is changed.

In anaesthetised, paralysed subjects, the V–P curve of the respiratory system has been assessed using various methods, resulting in different evaluations of the elastic properties. Because of the very low V_{CO_2}/V_{O_2}, lung volumes can be markedly overestimated when these curves are obtained in steps, particularly when the pauses between successive volume changes are numerous or long [3], leading to an overestimation of both compliance and hysteresis. An additional source of variability can be due to the anaesthetic agents, which have been shown to affect the V–P curve of excised dog lungs [4]. Moreover, in paralysed subjects, V–P curves have been obtained only for volumes above the resting volume (FRC) of the respiratory system, and have rarely been extended to Pst,rs > 30 cmH_2O.

Figure 1 shows the inflation V–P curve of the respiratory system and its component parts obtained during anaesthesia and paralysis in recumbent normal subjects ventilated on zero end-expiratory pressure. The V–P curve is slightly sigmoidal, and, as a result, the compliance of the respiratory system ($Crs = \Delta V/\Delta P$) is changing with the inflation volume. The initial inflection ('knee') in the inflation V–P curve occurs at a Pst,rs of 2–3 cmH_2O, but in certain subjects it occurs at a Pst,rs as high as 5 cmH_20, while in others it is essentially absent [5, 6]. The presence of the 'knee,' together with its variable position in the inflation V–P curve, makes Crs, assessed as the ratio of volume to pressure changes at a given pressure, questionable. In a substantial volume range above the initial 'knee,' the inflation V–P curve of the respiratory system, as well as its component parts, is almost linear, and the slope of the V–P curve in this volume range probably gives a true measure of compliance that can be used for comparison among subjects and conditions.

Table 1 summarises the reported average values of Crs, besides lung and chest wall compliance. As pointed out above, the largest part of the variability among the various studies is likely due to the different methods and anaesthetics employed, but a substantial fraction could also be due to different volume ranges and to the different ways in which the compliance was computed. On the other hand, it has been shown that Crs does not change progressively with time during anaesthesia, with repeated inflations to high distending pressures, with increasing depth of anaesthesia, or with muscle paralysis [6–10].

Lung and Chest Wall

Because the chest wall (w) and lung (L) are placed pneumatically in series, the volume changes in the chest wall (ΔVw) and the lung (ΔVL) should be the same, except for blood shifts, and they should equal the volume changes of the respiratory system (ΔVrs), whereas the algebraic sum of the pressure exerted by the lungs (PL) and chest wall (Pw) equals the pressure of the respiratory system. It follows that the reciprocal of Crs equals the sum of the

reciprocals of lung (CL) and chest wall compliance (Cw). The pressure exerted by the lung is the difference between alveolar and pleural surface pressure (Ppl); that exerted by the chest wall is the difference between Ppl and Pbs. Thus, the resting volume of the respiratory system is reached when the inward recoil of the lung is balanced by the outward recoil of the chest wall, i.e. PL + Pw = 0. In paralysed subjects, Pw = Ppl, the latter being obtained from oesophageal pressure measurements, the interpretation of which, however, requires some caution [15, 16].

The V–P relationship of the chest wall and lungs above FRC is curvilinear: that of the chest wall decreases its curvature with increasing lung volume, while that of the lung increases its curvature, except in the initial part, which is usually convex towards the pressure axis (Fig. 1). There is, however, a substantial range of volumes slightly above FRC, in which the V–P curve of both the lung and chest wall is nearly linear: in this volume range, Cw has been found to be larger than CL (Table 1).

Table 1. Quasi-static compliance of respiratory system (rs), lung (L) and chest wall (w) in anaesthetised paralysed normal subjects lying supine

N	Age yrs	Crs $cmH_2O \cdot L^{-1}$	CL $cmH_2O \cdot L^{-1}$	Cw $cmH_2O \cdot L^{-1}$	Ref.
15	40 (18–63)	0.064 ± 0.004	0.097 ± 0.007	0.204 ± 0.023	6
10	38 (21–49)	0.090 ± 0.010	0.171 ± 0.016	0.221 ± 0.047	11
22	47 (29–68)	0.113 ± 0.005	0.204 ± 0.018	0.305 ± 0.024	12
5	27 (24–29)	0.099 ± 0.011	0.140 ± 0.016	0.430 ± 0.118	10
5	26 (23–28)	0.087 ± 0.005	0.168 ± 0.012	0.212 ± 0.048	9
18	31 (17–42)	0.071 ± 0.006	0.112 ± 0.008	0.161 ± 0.010	13
17	43	0.081 ± 0.004	0.150 ± 0.013	0.203 ± 0.018	14
15	20 (14–28)	0.083 ± 0.007	0.141 ± 0.012	0.210 ± 0.021	5

Values are mean ± SE. *N*, number of subjects

While the fall in Crs at high lung volumes is entirely due to the decrease of CL, the low Crs at low inflation pressures is also due to the chest wall, though to a lesser extent than the lungs (Fig. 1). However, the inter-subject variability of the position of the initial 'knee' in the inflation V–P curve of the respiratory system should reflect that of the lung V–P curve only [5]. Moreover, the initial 'knee' is abolished when a positive end-expiratory pressure (PEEP) of 5 cmH_2O is applied [6, 17]. These observations suggest that the progressive increase in CL and Crs that occurs by increasing the lung volume above FRC

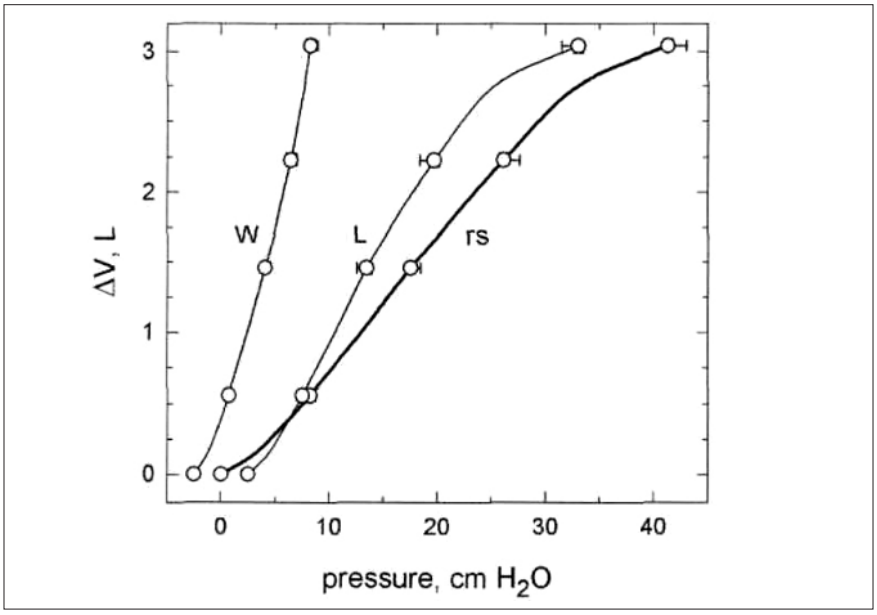

Fig. 1. Relationship between lung volume above functional residual capacity (FRC) and quasi-static pressure across the respiratory system (rs), lung (L) and chest wall (w) in 13 paralysed, anaesthetised normal subjects (modified from [5])

is due to reopening of small airways and recruitment of dependent lung units. Owing to the low values of FRC in recumbent, anaesthetised, normal subjects, and the presence of a vertical gradient of Ppl, it seems likely that small airways in the dependent part of the lung are exposed to either zero or positive pressure, and thus collapse. As a consequence, an inverse relationship should exist between normalised FRC and the position of the initial 'knee' along the pressure axis. Unfortunately, no pertinent data are available.

Lung volume changes occur both because of the displacement of the rib cage facing the lung (rc,L) and because of the diaphragm-abdomen (di-ab). From this viewpoint, these two structures may be considered to operate in parallel: hence, Pw = Prc,L = Pdi-ab, ΔVw = ΔVrc,L + ΔVdi-ab, and Cw = Crc,L + Cdi-ab. This model has been used by Wade [18] and Agostoni et al. [19] to construct the V–P curve of the pulmonary part of the rib cage and diaphragm-abdomen in normal subjects during voluntary relaxation. Partitioning of ΔVw has also been performed between two parallel pathways represented by the entire rib cage (rc) and the diaphragm-abdominal wall (di-ab,w), respectively; hence, ΔVw = ΔVrc + ΔVdi-ab,w, Pw = Prc = Pdi-ab,w, and Cw = Crc + Cdi-ab,w [8, 20]. The latter model has been used to assess the V–P curves of the chest wall and its component parts in supine, anaesthetised, paralysed normal

subjects [21]. In the volume range between FRC and FRC + 1.13 L, Crc was ~ 2.5 times greater than Cdi-ab,w, contributing 70–75% of Cw, and, hence, of ΔV. Lower values of Crc/Cdi-ab,w likely pertained to the subjects studied by Jones et al. [22] and Vellody et al. [23], as the contribution of rib cage displacement to ΔV was only 48% and 27%, respectively. In the mechanically ventilated subject, the ratio Crc/Cdi-ab,w should be relevant in determining the V_A/Q distribution and the efficiency of gas exchange.

Effects of Anaesthesia and Paralysis

The most frequently reported effect of general anaesthesia in normal supine subjects is a reduction of FRC. According to Rehder and Marsh [24], this decrease is given by ΔFRC = 10.18 - 0.23 age - 46.7 weight/height, where age, weight and height are years, kilograms and centimetres, respectively; and ΔFRC is expressed as a percent of FRC while awake. Such a decrease occurs also in the prone posture, but not in the sitting nor, most likely, lateral position [25, 26]. Although several mechanisms have been invoked to explain the reduction of FRC in recumbent, anaesthetised subjects, the marked intersubject variability of this reduction (Fig. 2) suggests that this decrease depends on several factors, none of which consistently prevails.

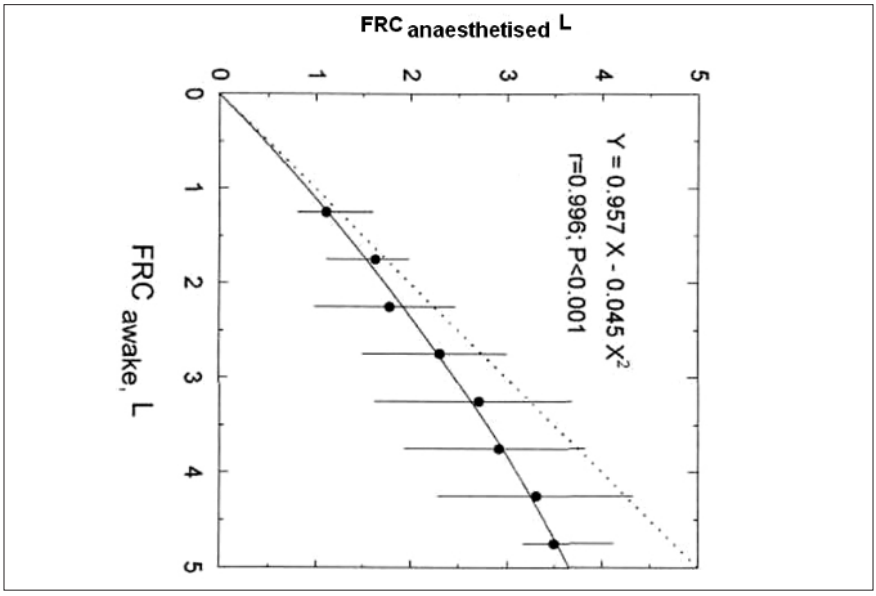

Fig. 2. Relationship between functional residual capacity (FRC) in the awake and anaesthetised states assessed in 128 subjects. Symbols are mean values falling within each subsequent 0.5 L interval, beginning from 1 L FRC awake. The continuous line represents best fit through mean values (data from [27])

It has been suggested that the tonic activity of both the inspiratory rib cage muscles and the diaphragm augment the chest wall recoil in awake subjects [8, 28, 29]. However, this tone is minimal in the supine position, when ΔFRC is large, and it is larger in the erect posture, when ΔFRC is absent [8, 28]. Perhaps tonic activity affects only the shape of the diaphragm, as these shape changes are not followed by any net cephalic displacement of the diaphragm with induction of anaesthesia and paralysis [8, 20, 30]. The shape of the chest wall also changes with anaesthesia: the anterior-posterior diameters of both the rib cage and abdomen decrease, while the transverse diameters increase [22]. It is unclear whether the volume of the thoracic cavity is effectively reduced because of these dimensional changes [7, 8, 31]. Finally, expiratory activity that appears in abdominal muscles with anaesthesia [32] does not seem a main factor in lowering FRC [10].

Increases in intrathoracic blood volume up to 0.3 L have been reported to occur with anaesthesia-paralysis [7, 8]. Although these changes can be large enough to account for the reported reductions in FRC, the lack of an established intrasubject relationship with the fall of FRC prevents any firm conclusion concerning the role of blood shifts.

As for FRC changes, those in the elastic recoil of the respiratory system present large intersubject variability, suggesting that the same factors could be responsible for both effects. In this connection, the entity of the resting volume with anaesthesia might be critical: indeed, no change in respiratory system compliance occurs in sitting subjects, either with anaesthesia (when FRC does not fall) or with submaximal muscular paralysis (when FRC decreases because of blood shift, but still remains larger than that of awake, supine subjects) [26, 33].

The fall of FRC with general anaesthesia in recumbent normal subjects reflects the fact that under this condition the balance between the outward recoil of the chest wall and the inward recoil of the lungs occurs at lower lung volume. The majority of evidence suggests that the decrease of Crs is mainly due to changes in lung mechanical properties [6, 9, 10, 34–36], although some authors have found no change [11, 12]. Several mechanisms can lower CL, such as increased smooth muscle tone or stimulation of other contractile elements in the airways or lung parenchyma, atelectasis, small airway closure, and changes in surfactant function. In supine anaesthetised, paralysed normal subjects, the atelectasis that eventually develops during ventilation on zero end-expiratory pressure is eliminated with inflations to $P_A > 30$ cmH_2O [37]. Such alveolar recruitment can quantitatively account for both the increase in CL and the leftward shift of the static V–P curve of the lung observed with PEEP ventilation in some anaesthetised, paralysed normal subjects [17]. However, similar changes in lung mechanics have also been observed in normal seated subjects after maintained hyperinflation, and they

have been attributed to changes in either pulmonary blood volume or airway muscle tone [38–40]. Finally, Westbrook et al. [10] have suggested that changes in C**L** are secondary to a rightward shift of the V–P curve of the chest wall, leading to volume reduction, in view of the fact that ventilation at low lung volumes in awake, normal subjects is eventually associated with increased lung recoil, probably due to higher surface tension [41]. This sequence of events, however, contrasts with the observation that, in supine, anaesthetised, paralysed subjects, C**L** remains substantially lower [17] than that reported by Agostoni and Hyatt [42] for awake, supine subjects at comparable lung volumes.

The V–P curve of the chest wall seems to undergo only relatively minor changes with anaesthesia and paralysis in the supine posture, in spite of substantial changes in configuration (see above). Quasi-static Cw (Table 1) is similar to that reported for awake supine subjects during relaxation [42], but the outward recoil could be reduced at low lung volumes [10]. Indeed, the increase in chest wall compliance with PEEP in anaesthetised, paralysed subjects is only one fourth of that occurring over the same range of lung volume during relaxation in awake, supine subjects [17].

Changes in the elastic properties of lung and chest wall with anaesthesia and paralysis, together with the dependent alterations in chest wall configuration, could likely influence the distribution of inspired gas during mechanical ventilation. Only some of the differences in the distribution of ventilation observed in most postures between awake, spontaneously breathing and anaesthetised, paralysed subjects can be attributed to differences in the distribution of forces applied by the respiratory muscles and ventilator [43]. Indeed, the direction of changes in regional ventilation with anaesthesia-paralysis in the various postures is not always consistent with the known pattern of respiratory muscle activation in awake subjects. More or less pronounced changes in the distribution of inspired gas occur in all but the prone posture [43]. Although several mechanisms, such as the mechanical interdependence of lung parenchyma, collateral ventilation and lobar sliding, may limit the modification of regional ventilation, the changes in chest wall shape occurring with anaesthesia should, as a result, influence regional lung expansion, and, hence, the distribution of regional lung compliance. Moreover, these changes, while implying relatively minor modifications in overall compliance, might reflect important changes in regional chest wall compliance, and, thus, further influence the distribution of ventilation.

Dynamics

The pressure that opposes the driving pressure arises from: *a)* elastic forces

within the lung and chest wall, including those required to compress or decompress the intrathoracic gases and to change the respiratory system from the relaxed configuration; *b)* viscous forces due to flow of gas along the airways and of lung and chest wall tissues; *c)* viscoelastic forces due to stress adaptation units within the tissues of lung and chest wall; *d)* plastoelastic forces, as reflected by differences in elastic recoil pressure of the lung or chest wall at iso-volume between inflation and deflation under true static conditions; and *e)* inertial forces of tissues and gas in the airways. Among these factors items *a)* through *c)* provide the relevant pressures that, under normal conditions, oppose the driving pressure developed by the respiratory muscles, or the ventilator, in spontaneously breathing or mechanically ventilated, anaesthetised subjects. The dynamic forces that more commonly develop in opposition to the driving pressure, as well as the dynamic performance of the components of the respiratory system are discussed below.

Viscous Forces

The pressure that causes the flow of gases along the airways is the difference between alveolar and airway opening pressure. On the basis of measurements of airway dimensions taken post mortem, Rohrer [44, 45] proposed the following relationships between gas flow ($\dot{V}$) and the pressure dissipated within the airways (Pres) or airway resistance (Raw):

$$\text{Pres} = K1 \cdot \dot{V} + K2 \cdot \dot{V} \quad (1)$$

$$\text{Raw} = K1 + K2 \cdot \dot{V} \quad (2)$$

where K1 and K2 are constants. Moreover, Raw has been shown to depend also on lung volume, according to Briscoe and DuBois [46].

$$\text{Gaw} = 1/\text{Raw} = a + b\,\dot{V} \quad (3)$$

where *a* and *b* are constants. Although the physical meaning originally assigned to K1 and K2 is no longer accepted, Rohrer's equations are still widely used, because they closely approximate experimental data [47]. On the other hand, the values of K1 and K2 reported in the literature vary substantially, mainly because of differences in the measurement techniques, as well as differences in experimental conditions. The average values of the constants in Eqs. 1–3 for the interrupter resistance of the respiratory system obtained in anaesthetised, paralysed normal supine subjects are shown in Table 2. In mechanically ventilated subjects, evaluation of K1 and, especially, K2 is difficult, due to the presence of the endotracheal tube (ETT); because the ETT

resistance in situ may differ from that in vitro [27], the use of the subtraction technique to correct for the ETT resistance may be inadequate (Table 2). The agents used during general anaesthesia are another source of variability, as they may have varying effects on bronchomotor tone [24, 48]. Of the two methods currently used to estimate airflow resistance, the body plethysmographic and the interrupter method, only the latter can be applied in anaesthetised subjects. This method allows the computation of viscous resistance as the ratio of the sudden pressure change that occurs with rapid airway occlusion to the flow existing immediately before the occlusion (Fig. 3). Depending on whether airway opening, oesophageal or transpulmonary pressure is being measured, this ratio gives the interrupter resistance of the respiratory system (Rint,rs), chest wall (Rint,w) or lung (Rint,L), respectively. In anaesthetised, paralysed subjects, airway opening pressure is usually measured at the proximal end of the ETT; therefore, Rint includes the ETT resistance, which is strongly flow-dependent. Because corrections of EET resistance are often problematic, especially when the ETT has been kept in place for some time, assessment of Rint,rs and Rint,L is best performed by measuring airway opening pressure in the trachea, a few centimetres away from the distal end of the ETT. Table 3 shows the mean values of Rint,rs, Rint,L and Rint,w obtained using this method in supine anaesthetised, paralysed normal subjects, while Fig. 4 illustrates the dependence of Rint,rs on flow and volume above FRC.

Assessment of Rint,w in human beings is problematic because rapid airway occlusions are rarely associated with evident sudden changes in oesophageal pressure in anaesthetised paralysed subjects, whether they are breathing spontaneously [49] or mechanically ventilated [13, 17, 50]. However, with the use of a rapid airway shutter and ensemble-averaging of

Table 2. Constants Kl and K2 in Eq. 2, and constants *a* and *b* in Eq. 3, obtained for the interrupter resistance of the respiratory system in anaesthetised, paralysed normal subjects lying supine

K1 $cmH_2O \cdot s \cdot L^{-1}$	K2 $cmH_2O \cdot s^2 \cdot L^{-2}$	a $L \cdot s^{-1} cmH_2O^{-1}$	b $s^{-1} \cdot cmH_2O^{-1}$	N	Ref.
1.47 ± 0.08	0.058 ± 0.028	0.64 ± 0.05	0.13 ± 0.02	28	5
1.87 ± 0.10	0.367 ± 0.027			26	13, 17

Values are mean ± SE. K1 and K2 were computed from measurements performed at volumes 0.41–0.76 L above functional residual capacity and flows 0.22–1.31 $L \cdot s^{-1}$, with [13,18] or without the need of correction for the endotracheal tube resistance (see text). Constants *a* and *b* were computed from measurements performed at volumes from 0.5 to 3.2 L above functional residual capacity and flows of 0.82-0.97 $L \cdot s^{-1}$. N, number of subjects

Table 3. Interrupter resistance (Rint) and quasi-static elastance (Est) of the respiratory system (rs), lung (L) and chest wall (w) in anaesthetised, paralysed normal subjects lying supine

Rint,rs $cmH_2O \cdot s \cdot L^{-1}$	Rint,L $cmH_2O \cdot s \cdot L^{-1}$	Rint,w $cmH_2O \cdot s \cdot L^{-1}$	Est,rs $cmH_2O \cdot L^{-1}$	Est,L $cmH_2O \cdot L^{-1}$	Est,w $cmH_2O \cdot L^{-1}$	N	Ref.
1.54 ± 0.13	1.13 ± 0.11	0.41 ± 0.03				12	49
1.48 ± 0.07 (1.12–1.65)			15.0 ± 0.7 (10.1–19.3)	9.3 ± 0.5	5.8 ± 0.4	28	5

Values are mean ± SE; range in parentheses. Values refer to measurements performed in the volume and flow range 0.41–0.76 L above functional residual capacity and 0.22–1.31 $L \cdot s^{-1}$, respectively. *N*, number of subjects

30–40 tests breaths to allow for cardiac artefacts (Fig. 3), Rint,w has been assessed in mechanically ventilated, anaesthetised, paralysed normal subjects. In the range 0.24–1.12 $L \cdot s^{-1}$, Rint,w was independent of flow, and amounted to ~0.25% Rint,rs [51]. As the measurements of Rint,rs in intubated subjects were based on tracheal pressure changes, upper airway resistance was obviously not included; therefore, in anaesthetised subjects ventilated through a mask, Rint,w should represent a substantially lower fraction of Rint,rs. This explains the results obtained by Liistro et al. [52], who found

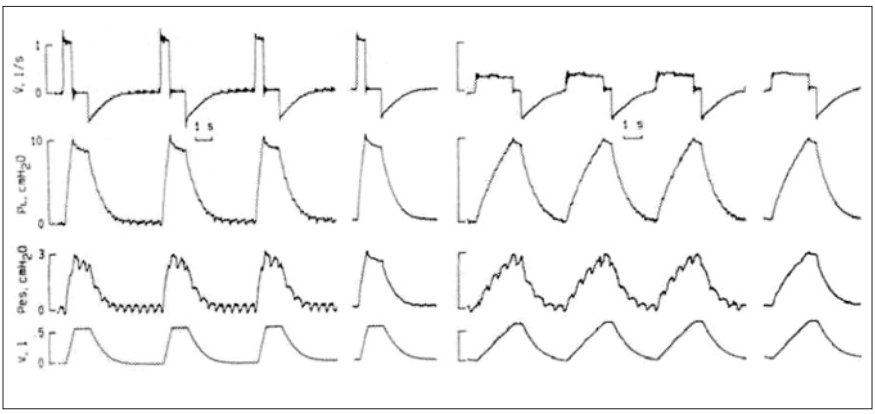

Fig. 3. Records of flow ($\dot{V}$), changes in transpulmonary (PL) and oesophageal pressure (Pes), and in lung volume (V) of three consecutive breaths and after ensemble average of 33–35 consecutive breaths pertaining to the same condition, obtained in a paralysed, anaesthetised normal subject during ventilation with high (*left*) and low (*right*) inflation flow (modified from [51])

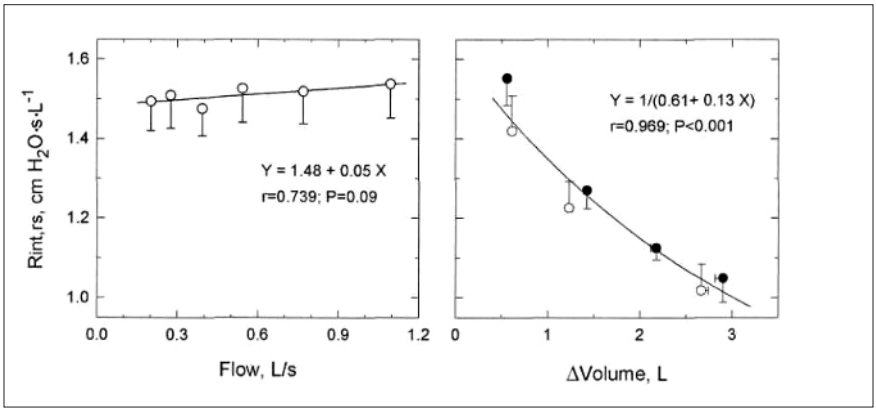

Fig. 4. *Left:* relationships between inflation flow and interrupter resistance of the respiratory system (Rint,rs) obtained in 30 paralysed, anaesthetised normal subjects (data from [5, 17]). *Right:* relationship between volume above functional residual capacity and Rint,rs in 13 and 15 paralysed, anaesthetised normal subjects (*closed and open symbols, respectively*) ventilated on zero end-expiratory pressure with different tidal volumes and fixed tidal volume (0.61 ± 0.05 L) on zero and positive end-expiratory pressure of 9 and 23 cmH_2O, respectively (data from [5])

Rint,rs close to Raw measured with the body plethysmographic method in awake, normal subjects. Moreover, Rint,w should become a negligible fraction of Rint,rs in patients with increased Raw. Indeed, in patients with adult respiratory distress syndrome, Rint,w was normal (0.3 ± 0.1 $cmH_2O\ s{\cdot}L^{-1}$), and it amounted to only ~6% Rint,rs [53].

While Rint,w reflects the viscous resistance of chest wall tissues, Rint,L should correspond to the sum of Raw and the viscous resistance of lung tissues. However, using the alveolar capsule technique in open-chest dogs [54] and rats [55], it has been shown that the pulmonary tissues do not contribute appreciably to Rint,L, whereby Rint,L ≈ Raw. In the normal tidal volume range, Rint,L should represent a constant fraction (~ 0.75) of Rint,rs, since both Rint,L and Rint,w are essentially independent of $\dot{V}$ [17]. Conversely, any dependence of Rint,rs on $\dot{V}$ and ΔV should reflect that of Rint,L, because Rint,w is independent of both $\dot{V}$ and ΔV.

The directly measured Rint,rs (no need to correct for ETT resistance) is flow-independent [1, 5, 51], at least in the range 0.2–1.3 $L{\cdot}s^{-1}$. In mechanically ventilated subjects, the effective resistance of the respiratory system becomes, however, markedly flow-dependent, owing to the presence of the ETT and, during expiration, the expiratory valve of the ventilator. Consequently, for a given tidal volume and breath timing, both the mean resistive pressure and the viscous work depend on the shape of the flow wave, the more so the larger the value of the constant K2 and the mean flow [56].

Viscoelastic Forces

The pressure developed by viscoelastic elements cannot be measured directly, but it can be assessed from the slow change of pressure that takes place when airflow is suddenly stopped and the volume is kept fixed until pressure becomes constant or nearly so. This phenomenon, usually referred to as *stress relaxation,* provides the basis of the rapid airway occlusion method that has been used in anaesthetised, paralysed humans and animals for determining the viscoelastic properties of lung and chest wall, in addition to their viscous resistance and quasi-static elastance. Figure 5 illustrates the rapid airway occlusion method, as applied during constant flow inflation in an anaesthetised, paralysed normal subject: *a)* the immediate drop in transpulmonary pressure (Pmax-P1) with airway occlusion divided by the flow preceding the occlusion ($\dot{V}$) results in Rint,L; *b)* the slow decay in transpulmonary and oesophageal pressure to a nearly constant value, achieved in 3–4 s, represents the viscoelastic pressure dissipation (Pvisc = P1 - Pst), which, divided by $\dot{V}$ or ΔV, results in additional resistance (ΔR = Pvisc/$\dot{V}$) or elastance (ΔE = Pvisc/ΔV), due to tissue viscoelasticity; and *c)* the apparent plateau of transpulmonary and oesophageal pressure (Pst) represents the quasi-static recoil pressure that, divided by the volume change, results in the quasi-static elastance (Est = Pst/ΔV) of the lung and chest wall.

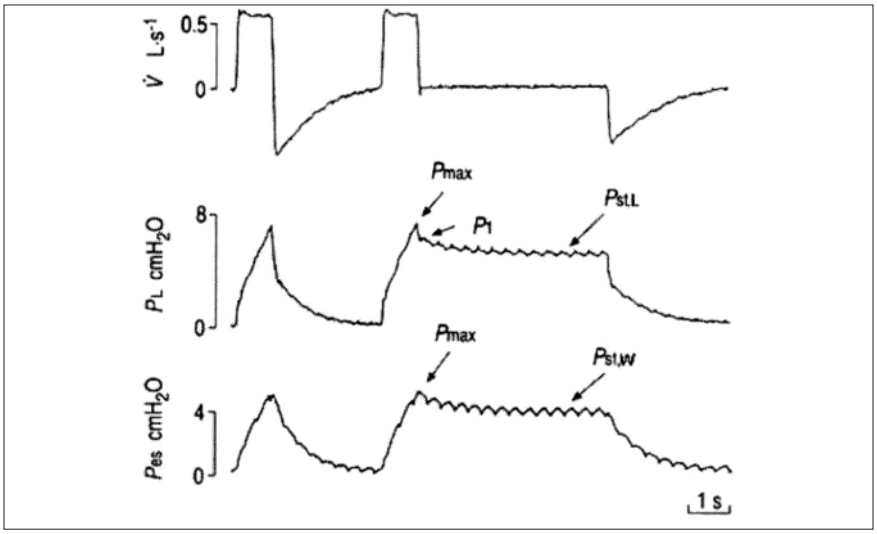

Fig. 5. Records of flow ($\dot{V}$) and changes in transpulmonary (P_L) and oesophageal pressure (Pes) in a paralysed, anaesthetised, normal subject in whom, during constant-flow inflation of 0.55 $L \cdot s^{-1}$, the airway was rapidly occluded at a lung volume of 0.6 L above functional residual capacity

In the presence of an end-inspiratory pause, attention must be paid to the possible effects on the expiratory phase, as complete lung emptying could be prevented by the resulting decrease in expiration time. On the other hand, an end-inspiratory pause allows for check of leaks, as no plateau pressure can be reached under this condition.

In normal subjects, the alveolar pressure at the end of a normal expiration is next to zero. Large expiratory time constants, expiratory flow limitation, or inadequate respiratory patterns (high tidal volume or high respiratory rate) result in intrinsic PEEP, which can be detected performing an end-expiratory occlusion manoeuvre.

Figure 6 depicts the simplest model, originally proposed by Mount [57], that satisfactorily reproduces the time course of oesophageal and transpulmonary pressure in experiments like those presented in Fig. 5. Note that both the lung and chest wall submodels comprise a dash-pot, $R_{int,L}$ (~Raw) and $R_{int,w}$, respectively, arranged in parallel with a Kelvin body, which consists of a spring representing the quasi-static elastance ($E_{st,L}$ and $E_{st,w}$) in parallel with the Maxwell body. The latter is made by a spring ($E_{visc,L}$ and $E_{visc,w}$) and dash-pot ($R_{visc,L}$ and $R_{visc,w}$) arranged serially, which, together with the corresponding time constant ($\tau_{visc,L} = R_{visc,L}/ E_{visc,L}$ and $\tau_{visc,w} = R_{visc,w}/E_{visc,w}$), accounts for the viscoelastic behaviour. This is because, with constant flow inflation

$$\Delta R = R_{visc} \cdot (1-e^{-T_I/\tau_{visc}}) \quad (4)$$

the viscoelastic parameters R_{visc}, τ_{visc}, and E_{visc} can be computed from ΔR values of test breaths with different durations of inflation (T_I).

The lungs and chest wall comprise a large number of elements that very likely possess different mechanical properties. Indeed, on the basis of stress–relaxation data obtained in excised cat lungs, Hildebrandt [58] has proposed a plastoelastic linear viscoelastic model in which the viscoelastic compartment consists of elements with a continuous spectrum of time constants, the mechanical analogue being represented by a number of Maxwell bodies arranged in parallel. Other models suggested so far [59–61] basically represent variations of Hildebrandt's model. On the other hand, it has been shown [5] that the performance of the Hildebrandt and simpler Mount model in fitting impedance data obtained in normal subjects with the forced oscillation technique over an extended frequency range is essentially the same (see below).

Viscoelastic constants assessed in normal anaesthetised, paralysed humans, using the 'rapid airway occlusion at end-inflation' technique, are independent of flow and volume up to 1.3 $L \cdot s^{-1}$ and FRC+3 L, respectively [5, 13, 17, 50]. Their average values are shown in Table 4, together with the average values of Est obtained in the normal tidal volume range. Conversely, Sharp et al. [62] found that stress adaptation in the respiratory system, lung and chest wall of anaesthetised, paralysed normal subjects became somewhat

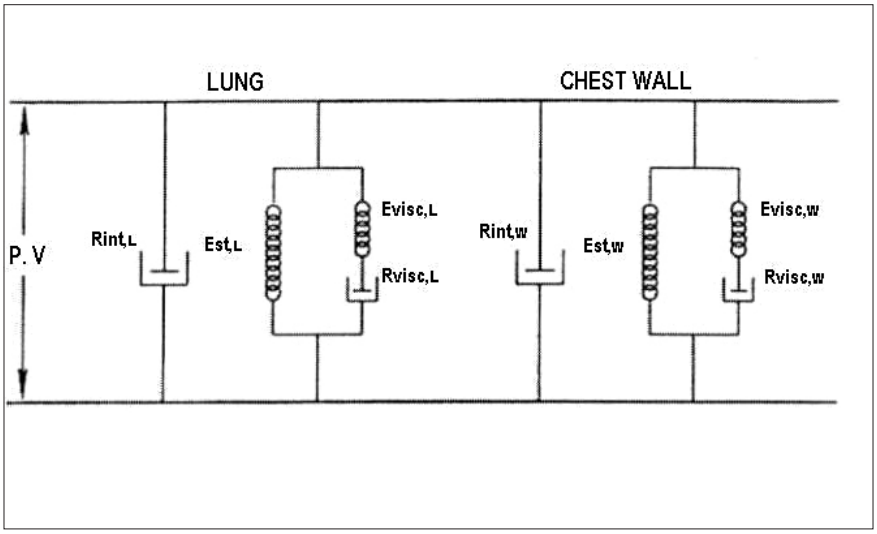

Fig. 6. A mechanical viscoelastic model for interpretation of respiratory mechanics. The respiratory system consists of two parallel units, i.e. lung (L) and chest wall (w), each made by a dash-pot (interrupter resistance: Rint,L ≈ airway resistance and Rint,w, respectively) in parallel with a Kelvin body, which in turn consists of a spring (static elastance: Est,L and Est,w, respectively) in parallel with a Maxwell body. The latter, with its spring (Evisc) and dash-pot (Rvisc) arranged serially, represents the viscoelastic (*stress adaptation*) units. The distance between the horizontal bars is analogous to lung volume (V), and force applied to the bars is analogous to pressure applied to the respiratory system (P)

larger at high lung volumes. Although this observation might indicate increased Rvisc and Evisc, since τvisc computed from the pressure decay during the end-inspiratory hold did not change with lung volume, more than likely it can be explained by the limitations of the procedure used [5]. Hence, lungs and chest wall appear to behave as an essentially linear viscoelastic system. It is important to keep in mind, however, that the evaluation of viscoelastic properties from single ΔR measures can be misleading; because of their time dependence (Eq. 4), comparison of ΔR values requires that the duration of inflation be kept the same.

In contrast with constant inflation flow ventilation, pressure-controlled ventilation (PCV) does not allow the analysis described above. Under this condition, the ventilator adjusts the flow in order to keep the inspiratory pressure constant: the inspiratory flow assumes the characteristic decelerated shape, becoming eventually zero as the duration of inflation is adequately prolonged (Fig. 7). In this case, an additional amount of volume is delivered and the alveolar pressure becomes equal to that set by the ventilator, as high-

Table 4. Viscoelastic resistance (*Rvisc*), elastance (*Evisc*), and time constant ($\tau visc$) of the respiratory system (*rs*), lung (*L*) and chest wall (*w*) in anaesthetised, paralysed, normal subjects lying supine

Rvisc,rs, $cmH_2O \cdot s \cdot L^{-1}$	6.14 ± 0.81 (3.78–7.74)
Rvisc,L, $cmH_2O \cdot s \cdot L^{-1}$	3.79 ± 0.62 (1.58–6.06)
Rvisc,w, $cmH_2O \cdot s \cdot L^{-1}$	2.41 ± 0.36 (1.47–3.19)
Evisc,rs, $cmH_2O \cdot L^{-1}$	4.93 ± 0.43 (2.96–6.71)
Evisc,L, $cmH_2O \cdot L^{-1}$	3.04 ± 0.59 (1.35–5.49)
Evisc,w, $cmH_2O \cdot L^{-1}$	1.92 ± 0.26 (1.13–2.44)
τvisc,rs, s	1.28 ± 0.81 (0.84–1.86)
τvisc,L, s	1.27 ± 0.22 (0.30–2.68)
τvisc,w, s	1.27 ± 0.17 (0.53–2.06)

Values are mean ± SE; range in parentheses. Values are from measurements taken in 51 subjects [5, 13, 17], with flows and volumes up to 1.3 $L \cdot s^{-1}$and 3 L above functional residual capacity, respectively

lighted by the introduction of an end-inspiratory pause. A further prolongation of the inspiratory pause produces a decrease in the expiration time, which could lead to gas trapping [63].

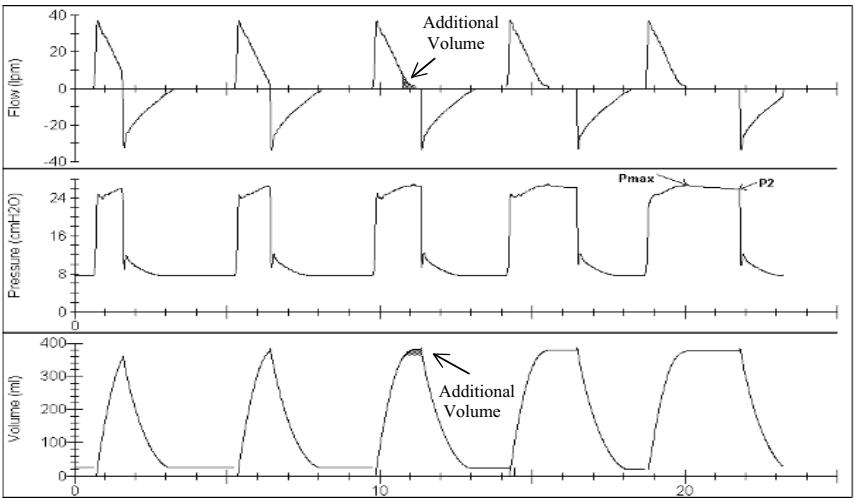

Fig. 7. Pressure-controlled ventilation (PCV), with the characteristic flow wave deceleration. The presence of a pause at end inflation allows identification of the plateau pressure. The prolongation of the duration of inflation in the third cycle produces an additional amount of volume

Generally, two phases occur in the inspiratory flow wave: the initial peak, which corresponds to the system pressurisation, and a second segment, with a decelerated trend and variable slope. The latter is an inverse function, both of respiratory system compliance and of the resistance. As the resistive load increases, the flow loses its characteristic decelerated aspect and becomes almost constant. Conversely, as the compliance decreases, the morphologic features of the flow wave are not altered, except for an early interruption, which leads to a decrease in the delivered volume.

The efficiency of ventilation strategies that use controlled pressure depends on the achievement of the target pressure: during PCV at 25 cmH_2O, a slow attainment of the target pressure does not guarantee an adequate volume, while, by operating on a dedicated function of the ventilator, the characteristic square-shaped pressure curve is eventually achieved and the expected volume is delivered (Fig. 8). An exaggerated pressurisation, which, by the way, is dangerous, may be evidenced by the presence of dampening waves during the remaining inspiration time [64].

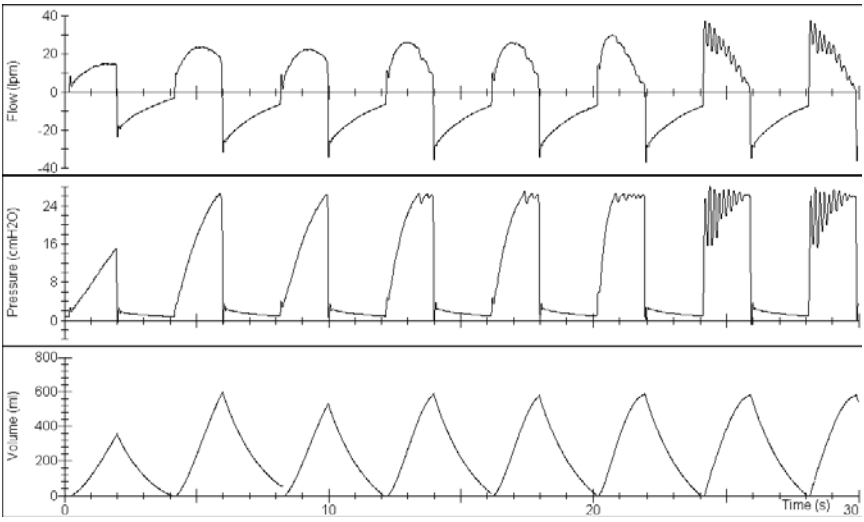

Fig. 8. The first cycle is characterised by a slow increase of pressure, that stops at 16 cmH_2O, well below the target pressure (25 cmH_2O), thus causing hypoventilation. The target pressure is reached by increasing pressurisation in the following breath. Dampening waves are recognisable in the last cycle, indicating excessive pressurisation

Dynamic Performance

Respiratory system mechanics under dynamic conditions in mechanically ventilated patients is often investigated by using a multiple linear regression in order to fit the equation,

$$Ptr = E \cdot \Delta V + R \cdot \dot{V} \qquad (5)$$

to measures of tracheal pressure (Ptr), volume changes from the end-expiratory lung volume (ΔV), and flow ($\dot{V}$) obtained throughout the breathing cycle. Because of viscoelastic properties and marked flow dependence of the expiratory valve of the ventilators, this analysis yields higher correlation coefficients if it is limited to the inflation phase. To account for continuously applied end-expiratory pressures, a constant is often added to the right of Eq. 5. This approach is widely used due to the fact that it is not time-consuming and can be easily implemented. Generally, E and R in the above equation are referred to as respiratory system elastance and resistance, respectively. Substituting transpulmonary or oesophageal pressure for Ptr would yield lung or chest wall E and R, respectively. Provided the breathing pattern is kept fixed, this approach may be useful for studying the changes of gross mechanical features over extended periods of time, the dose–response characteristics of bronchomotor agents [47], and, with adequate refinements, the rapid mechanical changes during drug uptake and clearance [65]. On the other hand, it assumes that E and R are constant throughout the data being analysed, independent of ΔV, $\dot{V}$ and breath timing. Therefore, the single compartment, linear resistance–elastance model in Eq. 5 is unable to fully describe the actual behaviour of the respiratory system and its component parts, particularly when breathing frequency is lower than 0.5 Hz. The viscoelastic elements within the lung and chest wall, in fact, confer time-dependence with respect to elastance and resistance. Moreover, Rrs can be underestimated during low-pressure, support ventilation levels with high respiratory effort [66].

The pressure curve over time has a characteristic feature during constant flow inflation. With the beginning of flow, an almost vertical pressure jump occurs, which is necessary to win the resistance provided by the airways and by the endotracheal tube; then the curve becomes linear, convex or concave, according to volume dependence of compliance [67], reaching its maximum value (Pmax) at the end of inflation. During lung overdistention, the shape of the curve is initially concave, then linear, and finally convex. Inspection of the

pressure–time profile during constant flow inflation in paralysed subjects allows for real-time monitoring of hyperinflation and lung recruitment [68]. From the mathematical analysis of that profile in an animal model, Ranieri et al. [69] have derived a so-called 'stress index,' which is supposed to minimise the risk of ventilatory-induced lung injury (VILI).

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Principles of Respiratory Mechanics and Clinical Correlations

J. Milic-Emili, N.G. Koulouris

During the past 50 years, there have been a number of studies investigating the relationship of forced expiratory volume in the first second (FEV_1) to exercise tolerance and chronic (MRC) dyspnoea in chronic obstructive pulmonary disease (COPD) patients. Because poor correlations were usually found, it was concluded that: a) lung function impairment is a poor predictor of both exercise capacity and dyspnoea; b) the degree of airway obstruction, dyspnoea and exercise curtailment are independent markers of COPD severity; and c) factors other than lung function impairment (e.g. deconditioning and peripheral muscle dysfunction) play a predominant role in limiting exercise capacity in patients with chronic airway obstruction. Recent work, however, suggests that: a) the main cause of exercise intolerance and dyspnoea is dynamic pulmonary hyperinflation (DH) due to tidal expiratory flow limitation; and b) the inspiratory capacity (IC) and FEV_1/ forced vital capacity (FVC), which reflect DH at rest and during exercise, are more powerful predictors of exercise intolerance than FEV_1.

Dynamic Hyperinflation (DH)

In normal subjects at rest, the end-expiratory lung volume, known as the functional residual capacity (FRC), corresponds to the relaxation volume (Vr) of the respiratory system, i.e. the lung volume at which the elastic recoil pressure of the respiratory system is zero [1]. Pulmonary hyperinflation is defined as an increase in FRC above the predictable normal value. This may be due to increased Vr, as a result of loss of recoil (e.g. emphysema) and/or to dynamic pulmonary hyperinflation, which is said to be present when the FRC exceeds Vr. Dynamic hyperinflation exists whenever the duration of expiration is insufficient to allow the lungs to deflate to Vr prior to the next inspiration. This tends to occur under conditions in which expiratory flow is impeded

(e.g. increased airway resistance) or when the expiratory time is shortened (e.g. increased breathing frequency). In COPD patients, DH is commonly due to expiratory flow limitation [2–4].

Expiratory Flow Limitation (FL)

The terms *expiratory flow limitation* should be used only for describing a condition in which flow cannot augment under the prevailing conditions. Thus, FL simply reflects the incapacity to increase expiratory flow by increasing pleural and, therefore, alveolar pressure at that lung volume.

Several factors may contribute to the occurrence of tidal FL. These include airway obstruction, decreased lung volume and body posture. Airway obstruction limits maximal expiratory flow, reducing expiratory flow reserve. Similarly, the reduction of maximal expiratory flow at low lung volumes is crucial in promoting FL during tidal breathing. Reduced lung volumes, as observed in gross obesity, congestive heart failure, etc., are automatically associated with decreased maximal expiratory flow. In supine position, the Vr is lower as a result of gravitational forces and normally the end-expiratory lung volume decreases with recumbency. Since the maximal flow–volume curve shows little variation on assuming the supine position (4), this posture facilitates tidal FL [2].

Increased ventilatory requirements augment the flow requirement because of greater tidal volume and faster respiratory frequency, predisposing to FL [3].

Methods for Assessing Flow Limitation

Comparison between full (or partial) maximal and resting tidal flow–volume loops has been widely used to detect FL, which is assumed to be present when tidal expiratory flow impinges on or exceeds the maximal expiratory flows at the same lung volume [5]. This method, however, is fatally flawed by the different volume and time history of the lung and airways prior to the maximal and tidal expirations, which influence the expiratory flows that are compared in the two manoeuvres [3, 6]. Recently, the negative expiratory pressure (NEP) method was introduced to detect FL [2, 3]. It consists of applying a small negative pressure during tidal expiration (usually between -3 and -5 cm H_2O), thus widening the pressure gradient between the alveoli and the airway opening. In the absence of FL, with NEP there is an increase in expiratory flow, compared with the preceding control breath. In contrast, in the presence of FL, the expiratory flow does not increase throughout the entire or part of the

tidal expiration over that of the preceding control expiration. The NEP method, which has been validated using iso-volume flow–pressure curves [7], does not require cooperation from the subjects, nor use of the plethysmograph, and it is devoid of the interpretative problems caused by the different previous time and volume history of the lung.

Lung Function and Exercise Tolerance

The maximal ventilation that a subject can achieve plays a dominant role in determining exercise capacity, and it may be limited by the highest flow rates that can be generated. Most normal subjects and endurance athletes do not exhibit tidal FL, even during maximal exercise. In contrast, in COPD patients tidal FL is frequently present at rest [2, 3, 8].

Tidal FL promotes dynamic hyperinflation with a concomitant decrease in IC, as shown in Fig. 1 (*right*). Diaz et al. [8] have shown that in most COPD patients who are flow-limited at rest, the IC is lower than normal, while in patients who are not flow-limited at rest the IC is within normal limits. However, reduced IC may also be present in the absence of overall tidal FL (as measured with the NEP method), reflecting regional expiratory flow limitation with concomitant DH.

In normal subjects, there is a substantial expiratory flow reserve, both above and below the FRC, as evidenced by the fact that the maximal expiratory flow rates available are much higher than the flow rates used during resting breathing (Fig. 1 *left*). As a result, the tidal volume during exercise can increase, both at the expense of the inspiratory and expiratory reserve volumes [3]. In contrast, in COPD patients who exhibit FL at rest, the flows available below FRC are insufficient to sustain even resting ventilation (Fig. 1 *right*), and, thus, tidal volume during exercise can increase only at the expense of the inspiratory reserve volume. Because in such patients, IC is already decreased at rest, the exertional increment of tidal volume is limited. Consequently, in COPD patients with FL at rest, the maximal tidal volume during exercise (V_{Tmax}), and hence, exercise tolerance, should be reduced. In fact, recent studies have shown that in COPD patients, there is a much stronger correlation of maximal O_2 uptake (VO_{2max}) with IC than with FEV_1 [3, 8]. Although the correlation of VO_{2max} with IC is relatively high (Fig. 2), the coefficient of determination (r^2) is only 0.56, indicating that IC can explain only 56% of the variance in VO_{2max}. Diaz et al. [8], however, showed that the FEV_1/FVC ratio also plays a significant role in predicting VO_{2max}. Using stepwise multiple regression analysis, they also showed that, taken together, IC and FEV_1/FVC account for 72% of the variance of VO_{2max} (r^2=0.72).

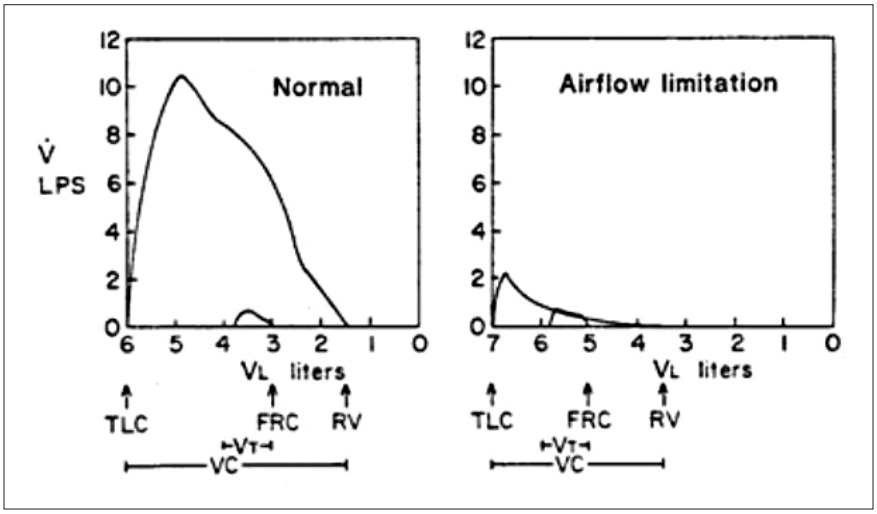

Fig. 1. Flow–volume curves during quiet and forced expiration in a normal subject (*left*) and a patient with severe COPD (*right*). *TLC*, total lung capacity; *FRC*, functional residual capacity; *RV*, residual volume; *VC*, vital capacity; *VT*, tidal volume during quiet breathing. While in the normal subject there is considerable expiratory flow reserve in the resting tidal volume range, in the patient with severe COPD the tidal expiratory flow is maximal, i.e. expiratory flow limitation is present. The latter promotes an increase in FRC with a concomitant reduction of inspiratory capacity (IC = TLC-FRC)

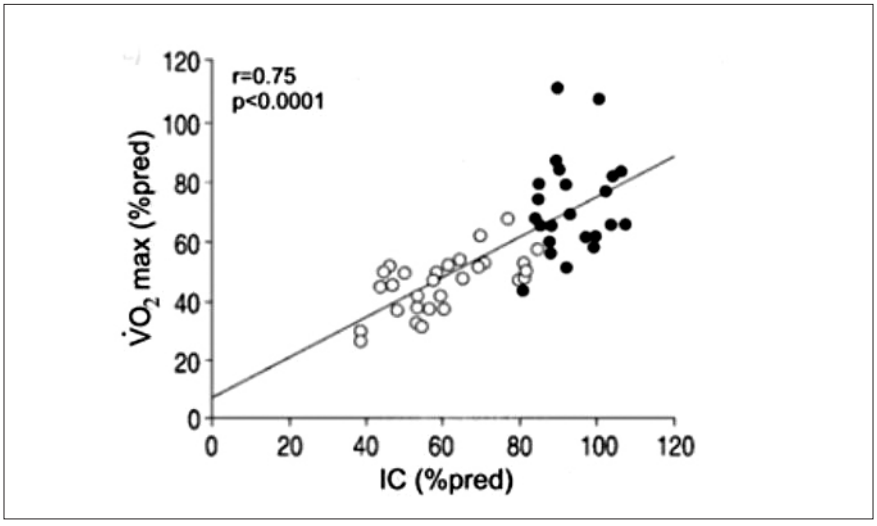

Fig. 2. Relationship of maximal O_2 uptake during exercise (VO_{2max}) to resting inspiratory capacity (IC) in 23 COPD patients without (●) tidal expiratory flow limitation (EFL) at rest, and in 29 COPD patients with (○) tidal EFL at rest

When the above stepwise regression analysis was performed separately for flow-limited and not-flow-limited patients at rest, only IC was selected as a significant contributor for flow-limited patients, while only FEV_1/FVC was selected for not-flow-limited patients. The latter probably reflects the fact that a high FEV_1/FVC ratio expresses a maximal expiratory flow–volume curve, with an upper convexity (Fig. 1, *left*) and, hence, a high flow–reserve over the resting tidal volume range, while a low FEV_1/FVC ratio reflects a curve with an upper concavity (Fig. 1, *right*) and, hence, a low flow–reserve over the resting tidal volume range. Thus, patients who are not flow-limited at rest, but have a low FEV_1/FVC ratio, are more prone to become flow–limited with increasing ventilation during exercise than patients in whom this ratio is high. Accordingly, in the COPD patients who are not flow-limited at rest, VO_{2max} decreases with decreasing FEV_1/FVC ratio [8].

In COPD patients who are FL at rest, the arterial PCO_2 is significantly higher than in not flow-limited patients ($p < 0.04$) and correlates significantly ($r = 0.62$) with IC (% pred) [8]. Thus, hypercapnic COPD patients (the so-called 'blue bloaters') are characterised by a reduction in IC due to dynamic hyperinflation elicited by tidal FL. These patients also exhibit a further significant ($p < 0.002$) increase in arterial PCO_2 at peak exercise associated with a significant ($p < 0.05$) reduction in arterial PO_2 relative to rest [9], which essentially reflects decreased maximum exercise ventilation due to a lower V_{Tmax} in flow-limited than in not flow-limited patients. In fact, V_{Tmax} is closely correlated with IC ($p = 0.0001$), confirming earlier predictions [8, 10].

Dyspnoea and Exercise Limitation

Dyspnoea and exercise limitation are the predominant complaints of patients with COPD, and they are commonly the reason for seeking medical attention. However, routine assessment of lung function is in general based almost entirely on FEV_1 and FVC, although there is ample evidence that in COPD patients these parameters correlate poorly with both dyspnoea and exercise tolerance. Alternatively, maximum exercise power (WR_{max}, % pred) closely correlates with chronic dyspnoea as measured with the modified MRC scale ($r = 0.92$, $p < 0.001$) [11]. Because in COPD, pulmonary hyperinflation plays a central role in eliciting dyspnoea and exercise intolerance, it is not surprising that there is a close correlation of both MRC score ($r = -0.73$, $p < 0.001$) and WR_{max} ($r = -0.79$, $p < 0.001$) with the 5-point FL score, which is a marker of DH, based on the NEP technique.

Assessment of Severity of COPD

Assessment of the severity of COPD is commonly based on the value of FEV_1 (% pred) [2]. To the extent that 'severity' implies curtailment of exercise capacity and increased dyspnoea, the choice of FEV_1 does not seem appropriate in view of the poor correlation of this parameter with both exercise capacity [8–10] and dyspnoea [2]. Separation of COPD patients into two categories, namely flow-limited and not-flow-limited while sitting at rest, is more useful, since it reflects the arterial PCO_2 and PO_2 both at rest and during exercise [8, 9]. However, a three and five point FL scale can also be used to assess the severity of chronic dyspnoea [2] and exercise tolerance [11] in COPD patients.

In conclusion, lung function impairment, as reflected by the reduced FEV_1/FVC and IC, is the main determinant of exercise intolerance in COPD patients. Chronic (MRC) dyspnoea, which is closely related to dynamic hyperinflation, is a close predictor of exercise capacity.

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Understanding the Mechanism of Ventilator-Induced Lung Injury

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Introduction

Mechanical ventilation is the fundamental technique for life support in the intensive care setting. It is an indispensable tool for providing adequate gas exchange, re-establishing sufficient oxygen supply to peripheral organs, and for resting respiratory muscle in many disease states. The major progress in mechanical ventilation occurred during the poliomyelitis epidemic. However, the greatest impetus for technological advancement followed the description of acute respiratory distress syndrome (ARDS) by Ashbaugh et al. in 1967 [1]. ARDS, the most severe form of acute lung injury (ALI), is a common disease with devastating clinical effects.

Actually, one of the most important concepts in the care of critically ill patients is the recognition that mechanical ventilation can worsen, or even cause, lung injury, a condition referred to as ventilator-induced lung injury (VILI). Research in a number of species has shown that mechanical ventilation itself can lead to lung injury that is functionally and histologically indistinguishable from that seen in ARDS [2, 3]. The recognition of this similarity between VILI and ARDS has prompted a number of investigators to suggest that ARDS may in part be a product of the ventilatory management in addition to the progression of the underlying disease. VILI is determined by the dynamic and continuous interaction between the mechanical characteristics of the lung and the ventilator settings. Patients with ARDS often have a number of morphological and functional changes (e.g. surfactant dysfunction, underlying lung disease, malnutrition, oxygen toxicity, infection, atelectasis, alveolar oedema) that not only increase the lungs' susceptibility to injury by mechanical ventilation, but also impair the lungs' ability to repair the damage incurred [4].

Many studies have sought to identify the risk factors, or the potential adverse effects of various forms of mechanical ventilation, and to develop strategies for preventing VILI. The deleterious effects of mechanical ventila-

tion depend on numerous factors, among which, the level of airway pressure applied and resulting volume changes, the end-expiratory lung volume, the overall lung inflation and the extent of the inflammatory process are the most significant.

In the present review, the current clinical status of VILI and insights gained to date from basic scientific studies are discussed. The potential clinical implications of these findings for the management of mechanical ventilation and development of protective strategies are also considered, giving emphasis to patients with ARDS.

Characterisation of VILI

Morphological Changes

The macroscopic and microscopic damage observed in VILI [5–7] is not specific. It closely resembles that observed during human ARDS [8]. However, there is a clear relationship between the duration of mechanical ventilation, the level of harmful stimulus, the extent of the injury, and the overall appearance of the lung.

Macroscopically, the lungs of animals injured by adverse ventilatory strategy display focal zones of atelectasis, severe congestion and enlargement because of oedema [9–11].

In light microscopy studies, interstitial and alveolar oedemas have been reported after mechanical ventilation with high peak airway pressure [5, 9]. The degree of oedema varies with the magnitude of the peak airway pressure and the duration of mechanical ventilation. Oedema is initially confined to the interstitial spaces and is visualised as peribronchovascular cuffs [12, 13]. Severe diffuse alveolar damage, similar to early stages of human ARDS, with hyaline membranes, alveolar haemorrhage and neutrophil infiltration, was demonstrated in animals killed immediately after high-inflation ventilation periods [3]. The microscopic examination of the animals several days after the injury by high-inflation ventilation also demonstrated damaged lungs that looked similar to lungs in late stages of human ARDS, with collapsed alveolar spaces and proliferation of fibroblasts and type II cells [3].

Electron microscopy studies of animal models of VILI showed discontinuities in alveolar type I cells [14], widespread alterations of endothelial and epithelial barriers [5–7], some endothelial detachment from the basement membrane, and occasional breaks in endothelial cells, alveolar flooding and diffuse alveolar damage [5]. Endothelial breaks allowed direct contact between polymorphonuclear neutrophils and the basement membrane [5].

Pulmonary Oedema

Because pressures applied to an air space also impact the capillaries that surround it, the potential for pressures and flows within blood vessels to influence the development and/or evolution of VILI deserves close consideration. Even for the normal lung, alveolar inflation imposes competing vascular stresses on extra-alveolar vessels [15–17] and alveolar microvessels [9, 18]. These competing forces are amplified by the heterogeneity of ARDS [19–21]. The haemodynamics of the microvascular environment is almost certain to vary, depending on the ventilation mode and underlying lung disease. In the framework of ARDS, both alveolar and pulmonary arterial pressures are considerably higher than under normal conditions.

Since the properties of the alveolar–capillary barrier are abnormal in ARDS, it has been essential to ascertain whether mechanical ventilation-induced lung changes would result only in further fluid accumulation, or whether they would create new lesions and/or aggravate existing ones. In their essential contribution to the recognition of VILI, Webb and Tierney demonstrated that mechanical ventilation per se might induce pulmonary oedema [9]. They also verified that the pulmonary oedema developed more rapidly and was more severe in animals ventilated with 45 cmH_2O than in those ventilated with 30 cmH_2O of peak pressure. Other studies subsequently showed that mild interstitial oedema could be developed after only a few (2–5) minutes of ventilation in small animals with such a peak airway pressure [5, 7], while the replication of these observations in larger animals requires much longer periods (several hours) of ventilation [10, 11, 22–24], for reasons that need to be clarified.

Alteration of Alveolar–Capillary Barrier Permeability

The increase in alveolar–capillary permeability seems to be an important mechanism in the pathophysiology of ventilator-induced pulmonary oedema (Fig. 1). Changes in pulmonary epithelial and endothelial permeabilities have been reported for isolated lungs, as well as for open-chest and intact animals, in the presence of high lung volumes. There is an increased epithelial and endothelial permeability to small [25–29] and large solutes [30–33]. Several other experimental studies have demonstrated changes in microvascular permeability, assessed by: the capillary filtration coefficient [34, 35], measuring extravascular lung water and bloodless dry lung weight [5], lymph protein clearance and lymph/plasma protein ratio [23, 24], and ^{125}I-labeled albumin [5]. Findings in electron microscopy have demonstrated severe epithelial and endothelial abnormalities compatible with the increment of permeability [5–7, 14, 36].

Increased Pulmonary Vascular Transmural Pressure

For a long time relatively little was known about the contribution of hydrostatic pressure to the development of pulmonary oedema in VILI. This lack of information can be explained by the difficulty in assessing transmural pressures at the microvascular level. Additionally, no substantial increase in mean transmural vascular pressure that would argue in favour of a hydrostatic origin was reported. Experimental studies on VILI demonstrated only a small magnitude of change in mean transmural microvascular pressure [23, 24]. Additionally, hydrostatic type oedema was not thought to be associated with ultrastructural cellular abnormality, at either the microvascular or epithelial level [37–39]. Now, it is known that hydrostatic pressure is important. For example, under the high permeability conditions at the early phase of ARDS/ALI, minor increases in pulmonary microvascular pressure can lead to increased oedema. Regional differences in lung perfusion and atelectasis might generate larger filtration forces in some areas.

In fact, the role of pulmonary vascular transmural pressure in VILI oedema pathophysiology has been discussed by several authors at length and is well recognised [40]. In elegant experiments undertaken in the laboratories of West et al. [41–44], electron microscopy of the microvasculature demonstrated that capillary stress fractures can occur when microvascular pressures are elevated to very high levels, relative to their usual operating conditions. Other refined structural studies confirmed epithelial breaks, blebbing and endothelial lesions in excised rabbit lungs with vascular pressures around 30 mmHg [45, 46]. Elevated transmural pressure in extra-alveolar vessels may result from the increase in lung volume, as a consequence of lung interdependence – assuming that the luminal pressure remains constant [15–17], whereas increased filtration across alveolar microvessels may be consequent to surfactant inactivation [9, 18] (Fig. 1).

Clearance of Pulmonary Oedema

The clearance of pulmonary fluid is achieved mostly by active Na^+ transport from the alveoli [47–49], independently of its pathogenesis. Even though other mechanisms may contribute, the clearance of pulmonary oedema appears to be mainly performed by the apical sodium (Na^+) channels and the basolaterally located sodium, potassium–ATPases (Na,K–ATPases) in alveolar type II (ATII) cells [50–52]. These mechanisms generate the electrochemical gradient responsible for the vectorial Na^+ flux from air spaces, with isosmotic water movement.

VILI not only increases lung permeability to small and large solutes, it also affects the lungs' ability to clear oedema. An inhibition of active Na^+ transport and a decrease of Na,K-ATPase activity in the ATII cells of rats sub-

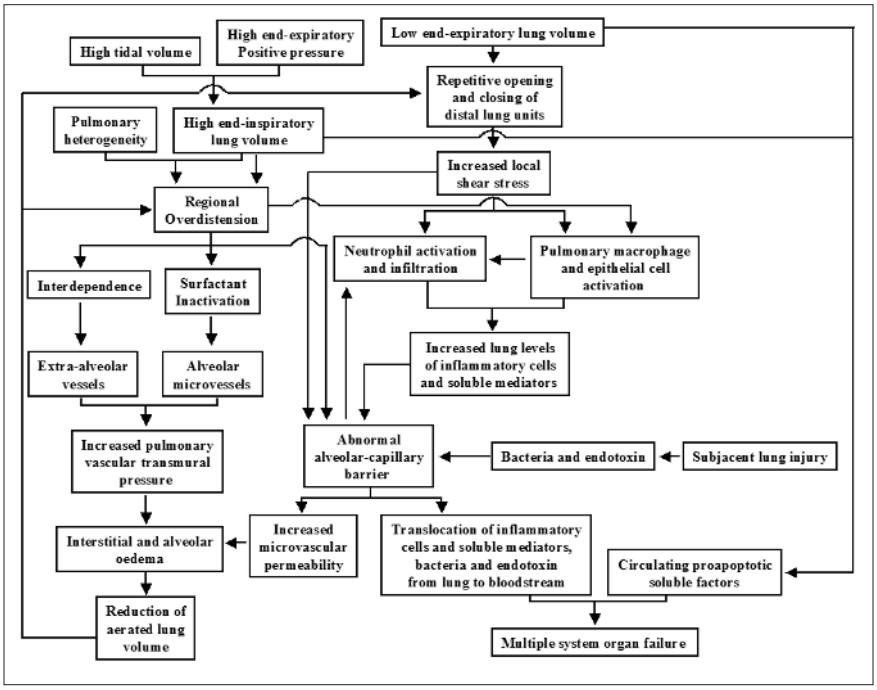

Fig. 1. Diagram summarising the potential determinants of ventilator-induced lung injury and proposed mechanisms for multiple system organ failure

mitted to lung mechanical overstretching was demonstrated in parallel to impair lung oedema clearance [53]. In ATII cells harvested from rats ventilated with moderate and high tidal volume (V_T) for 40 min, Na,K-ATPase activity decreased by ~25% and ~50%, respectively, compared with low V_T in controls (non-ventilated rats). Reduced Na,K-ATPase activity in both moderate V_T and high V_T reflected a lowering in the number of functional pumps in the ATII cells, relative to controls.

Surfactant System

Mechanical ventilation has profound effects on the function of both endogenous and exogenous surfactant [54–57], resulting in an increased tendency for collapse of air spaces (distal airways and alveoli), a need for higher airway pressures to reopen (and keep open) the lung, and increased surface tension at the gas–liquid interface inside the alveoli following an increased transmural capillary pressure gradient (favouring movement of fluid into the lung) [2].

Endogenous surfactant exists within alveolar air spaces in two main structural forms: functionally superior large aggregates (LA) and functionally

inferior small aggregates (SA) [58–60]. Changes in the relative proportions of these aggregates within the air spaces were found in animal models of ALI [61, 62] and in patients with ARDS [63]. Alterations in aggregate forms of surfactant may also be affected by mechanical ventilation [63]. The rate of conversion from LA to SA augments as tidal volume increases. Alterations in the surfactant system may be even greater in lungs with pre-existing lung damage submitted to high-tidal volume ventilation. Two mechanisms should be considered in ventilation-induced surfactant aggregate conversion in injured lungs: (1) the dynamic surface area changes induced by mechanical ventilation itself, and (2) the increased protease activity within air spaces due to increased capillary leakage. High lung inflations may contribute to both mechanisms [6, 10, 64–66].

Major Determinants of VILI

The major determinants of VILI will be discussed under the following headings: barotrauma, volutrauma, atelectrauma and overall lung distension.

Barotrauma

Clinicians quickly recognised that mechanical ventilation could cause disruption of the air space wall and leakage of air, the so-called barotrauma [67]. VILI was, for years, synonymous with barotrauma. The adverse consequences of these macroscopic events, tension pneumothorax, are usually obvious, being the most threatening extra-alveolar accumulation of air. More subtle physiological and morphological alterations require more time to be recognised. Several early experimental and clinical studies suggested that mechanical ventilation might adversely affect lung function and structure [54, 68], but the potential harmful effects remained controversial. Only in 1974 did Webb and Tierney show that mechanical ventilation could also be responsible for ultra-structural injury, independently of air leaks [9]. This was the first comprehensive study in intact animals to demonstrate that mechanical ventilation with high peak airway pressure might severely damage the lung. A number of subsequent studies also demonstrated high inflation pressure-induced diffuse alveolar damage [5, 6, 10, 23].

Volutrauma

Experimental evidence indicates that the degree of lung inflation is more important in determining lung injury than the level of airway pressure, per se. This is supported by the observation that trumpet players commonly achieve airway pressures of 150 cmH_2O without developing lung damage [69]. In this

context, the term volutrauma is therefore more accurate than barotrauma. The relative contribution of pressure and volume to lung injury was first studied by ventilating rats whose tidal excursion was limited by strapping the chest and abdomen [6]. High airway pressure without a high tidal volume did not produce lung injury. In contrast, animals ventilated without a restricted thoracic excursion (achieving high tidal volumes), either with high positive or negative inspiratory pressures, developed severe injury. These results were confirmed in other species [24, 35].

In patients with ARDS the atelectasis of dependent lung regions and the alveolar oedema often present can markedly reduce the aerated lung capacity to as little as 25% of normal [70]. As a result, mechanical ventilation with tidal volumes in the range from 10 to 12 mL/kg may result in overdistension of the remaining aerated lung regions to a level equivalent to that observed in healthy lungs ventilated with tidal volumes of 40–48 mL/kg [71]. If lungs are injured so that only a third of the alveoli can be recruited for ventilation [72], a setting of 6 mL/kg translates into an effective V_T of 18 mL/kg for intact alveoli.

The ARDS Network study demonstrated a reduced mortality (from 39.8 to 31%) in a mixed population of patients with ALI and ARDS ventilated with a V_T equivalent to half of that in the control group [73]. Interestingly enough, results from the ARDS Network trial do not suggest that ventilation with 6 mL/kg is risk free; they simply suggest that this level of ventilation is safer than 12 mL/kg. However, three years later, even in participating centres, clinicians are not routinely using a low V_T strategy for patients with severe respiratory failure [74]. Almost four decades after the first description of ARDS [1], many investigators and physicians [74–77] still apply the same V_T strategy (V_T greater than 10 mL/kg) as in the original description of ARDS.

Atelectrauma

There is a large body of evidence indicating that lung damage may also be caused by ventilation at low lung volume (meaning end-expiratory lung volume). This injury is thought to be related to the cyclic opening and closing of distal airways, ducts and/or alveolar units (hence, the term atelectrauma). Repeated recruitment–derecruitment of terminal units may lead to potential increased local shear stress, particularly if the event is repeated with each breath. Many authors (using various species, diverse lung injury models and different ventilatory strategies) have demonstrated this kind of injury and/or the potential protective effect of positive end-expiratory pressure (PEEP) [9, 65, 78–83]. PEEP application may prevent diffuse alveolar damage by stabilising distal units and maintaining recruitment throughout the ventilatory cycle.

The protective effect of PEEP was first addressed in 1974, in a comprehensive study of intact animals, demonstrating that high inflation-induced lung oedema (45 cmH_2O) was less severe when PEEP (10 cmH_2O) was applied [9]. The beneficial effect of PEEP was attributed to reduced lung tissue stress (by decreasing tidal volume) and capillary filtration (at least in part because of haemodynamic depression), as well as to the preservation of surfactant activity. PEEP is also believed to preserve the integrity of the epithelial layer [80, 84, 85].

Overall Lung Distension

Lung volume at the end of inspiration (i.e. the overall degree of lung distension) seems to be the main determinant of VILI severity. Application of PEEP may result in lung overinflation if it is followed by a significant change in functional residual capacity owing to the increase in end-inspiratory volume. Additionally, depending on the homogeneity of ventilation distribution, this over-inflation will preferentially affect the more distensible areas. Rats ventilated with a low V_T and 15 cmH_2O of PEEP developed pulmonary oedema, whereas rats ventilated with the same V_T but only 10 cmH_2O PEEP did not [65].

Ventilator-Induced Multiple System Organ Failure

Despite the advances in mechanical ventilation, the prognosis for patients with ARDS is poor, with a mortality rate of at least 30% [86–89]. VILI has been estimated to increase mortality in ARDS patients by 3900 to 35 000 patients per year [90]. This estimation is supported by the fact that the vast majority of patients who die with ARDS do not die from their pulmonary disease. Death has traditionally been attributed to multiple system organ dfailure (MSOF) [71]. There are several principal mechanisms by which VILI may lead to the development of MSOF: biotrauma (discussed below), translocation of bacteria or their products from the lung, circulating proapoptotic soluble factors, and suppression of the peripheral immune response (Fig. 1). The potential for intrapulmonary prostaglandins [91], cytokines [92], endotoxin [93] and bacteria [94] to cross an impaired alveolar–capillary barrier following high stretch mechanical ventilation is clear.

Biotrauma

Mechanical ventilation has also been shown to have significant effects on the amount of inflammatory cells in the lungs and soluble mediators (e.g. cytokines) in lung and systemic circulation, a process that has been termed

biotrauma [95]. Both clinical and basic studies have demonstrated that injurious ventilation strategies can initiate or perpetuate local and systemic inflammatory response, which, in turn, can potentially contribute to MSOF [95–97]. The main concept is that inflammatory mediators originating in the lung cross an impaired alveolar–capillary barrier and access the circulation, where they potentially exert detrimental effects.

The possibility that inflammatory cells contribute to the genesis of VILI has been extensively investigated [98–102]. The recruitment and activation of inflammatory cells are components of the lung inflammatory response. In this context, lung overinflation produces an accumulation of leucocytes in the pulmonary microvasculature and macrophages in the alveoli [98]. These results were supported by a subsequent study [3]. Additionally, an adverse ventilatory strategy may induce neutrophil infiltration and activation [3, 103]. Adhesion molecules, such as ICAM-1 and Mac1, play an important role in this phenomenon during VILI [104, 105]. Furthermore, the disruption of endothelial cells may also allow direct contact between polymorphonuclear cells and the basement membrane [106], which may promote leukocyte activation. The harmful effect of lung neutrophil infiltration was confirmed by less important alveolar damage in neutrophil-depleted rabbits, in relation to nondepleted animals [107]. The lungs were proven to contribute to the circulating pool of inflammatory cells.

The participation of inflammatory cytokines in the course of VILI has been the subject of numerous studies. Injurious mechanical ventilation with alveolar overstretching and high shear forces generated by repetitive opening and collapsing of atelectatic regions can lead to an increase in pulmonary and systemic levels of various inflammatory mediators. Evidences from in vitro systems [108–111], ex vivo models [92], in vivo experiments [112–117] and clinical studies [73, 96, 118, 119] support this hypothesis. Stretching alveolar macrophages results in the release of interleukin (IL)-8 [108, 109], a chemokine involved in neutrophil recruitment. Alveolar epithelial cells, when submitted to overstretch, may also contribute to increased secretion of IL-8 [110, 111]. IL-8 (or MIP-2 in rodents) is the only mediator that was constantly released during overinflation in in vitro [108, 110], ex vivo [92, 120] and in vivo models [121, 122]. The importance of this chemokine was confirmed by the demonstration that knockout mice for MIP-2 receptor presented less VILI [122]. Other inflammatory mediators, in particular tumour necrosis factor (TNF)-α, are not universal [120, 123, 124]. IL-1 may be an important cytokine in the development of VILI, even though it has not received much attention. Recombinant IL-1 receptor antagonist (IL1-ra) decreases the severity of hyperoxia and overinflation-induced lung injury [100]. Another cytokine that should receive more attention is IL-6, which has been suggested as a pivotal mediator in biotrauma-induced MSOF. The clinical significance of this

hypothesis became apparent after the ARDS network demonstrated that a lung protective approach – lowering V_T to 6 mL/kg – was associated with significantly reduced 3-day plasma IL-6 concentrations and increased survival in patients with ARDS [73]. Reduced systemic inflammatory response secondary to the lung protective strategy could have contributed to less MSOF and lower mortality in the group ventilated with V_T of 6 mL/kg than in that ventilated with 12 mL/kg. A post-hoc analysis of the relation between organ failures and cytokine concentrations revealed a correlation between increased IL-6 plasma concentrations and the development of MSOF [118].

Translocation of Bacteria and/or Their Products from the Lung

Injurious mechanical ventilation may also promote the translocation of bacteria and/or their products from the lung into the bloodstream, thereby contributing to the development of MSOF [71, 125]. Overall lung distension associated with the repetitive opening and closing of distal units has been proven to facilitate translocation to the bloodstream of bacteria that had previously been instilled intratracheally [94, 123] as a result of alveolar–capillary barrier damage. The administration of PEEP diminishes this effect [123]. Adverse ventilatory strategies may also affect the pulmonary-to-systemic translocation of endotoxin [93]. Ventilator-induced high plasma levels of endotoxin and bacteria are associated with an increased mortality rate [93, 126].

Circulating Proapoptotic Soluble Factors

It has been recently demonstrated that an adverse mechanical strategy can lead to distal organ epithelial cell apoptosis. Circulating proapoptotic soluble factors (soluble Fas ligand) produced by injurious ventilatory strategies may be involved in this mechanism. Epithelial cell apoptosis in the kidney and small intestine is increased by injurious ventilatory strategies [127]. Plasma from adversely ventilated animals induced in vitro apoptosis in renal tubular cells, which was reduced by a fusion protein that blocks soluble Fas ligand [127]. Finally, it is well known that the dysregulation of apoptotic pathways can contribute to the epithelial injury observed in patients with ARDS [128].

Conclusions

Mechanical ventilation is a mainstay in the therapy of critically ill patients with respiratory failure. This is in spite of the fact that data accumulated in recent decades strongly suggest that ventilatory strategies associated with excessive end-inspiratory stretch and/or collapse/recruitment of lung units

can cause further injury to the lung and perhaps lead to multiple system organ failure. The development of MSOF is a multifactorial process (Fig. 1). Insights into the mechanisms causing this ventilation injury and consequent MSOF will hopefully lead to the development of novel therapeutic approaches to abrogate or prevent detrimental consequences. We suggest that biochemical and biomolecular scientific advances will offer new strategies for the prevention of MSOF secondary to VILI. More randomised, controlled clinical trials are also necessary to confirm experimental findings.

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Lung Parenchyma Remodelling in the Acute Respiratory Distress Syndrome

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Introduction

The acute respiratory distress syndrome (ARDS) is a catastrophic condition with exudation, inflammation and often fibrosis throughout the lung [1]. Interestingly, despite the extensive damage, it can be fully repaired [2]. This recovery requires the resolution of inflammation, clearance of inflammatory cells and oedema and reversal of fibrosis, allowing the lung tissue to return to its normal structure and function. The repair process is very complex and modulated not only by several growth factors and cytokines released in the alveolar space during lung injury, but also by a variety of components of the extracellular matrix (ECM) [3].

In 1994, the American–European Consensus Conference established a definition of ARDS consisting of four criteria: (1) acute onset, (2) ratio of PaO_2 to FiO_2 of 200 or less (regardless of the positive end-expiratory pressure level [PEEP] needed to support oxygenation), (3) bilateral infiltrates seen on frontal chest radiograph, and (4) pulmonary artery wedge pressure not larger than 18 mmHg or, in other words, no clinical evidence of left atrial hypertension. The criteria for acute lung injury (ALI) are identical to those for ARDS, except for a difference in PaO_2/FiO_2, which must be 300 or less [4].

The American–European Consensus Conference also defined two pathogenetic pathways leading to ARDS: a direct (primary or pulmonary) insult, which directly affects lung parenchyma, and an indirect (secondary or extrapulmonary) insult, which results from an acute systemic inflammatory response [4]. Although various causes of ARDS result in a uniform pathological condition in the late stage, there is evidence that the pathophysiology of early ARDS may differ according to the type of the initial insult [5–8].

The exact incidence of ARDS is difficult to measure, in part because of the lack of a clinical diagnostic test and in part because ARDS courses largely undiagnosed. The incidence of ARDS in at-risk populations is not certain, but various estimates range from 1.5 to 75 cases per 100 000 persons per year [9].

Overall, approximately 7% of patients admitted to the intensive care unit will develop ALI/ARDS, and among mechanically ventilated patients with acute respiratory failure, the incidence varies from 11–23% [10]. The most common cause of ARDS, severe infection, accounts for approximately half the cases [11].

ARDS is associated with high morbidity and mortality [12]. Despite advances in therapy, the mortality rate is between 35–60% [9]. In addition, survivors must endure a debilitating, long-term disability [13, 14]. Factors like age, organ dysfunction, co-morbid diseases – including chronic liver disease and severity of illness – constitute important predictors of mortality [9]. Finally, multiple organ failure represents the major cause of death in patients with ARDS [11]. In this context, the present review analyses the pathologic findings and the different mechanisms associated with lung parenchyma remodelling in ARDS.

Pathologic Findings

Diffuse alveolar damage (DAD) is the most common histopathologic diagnosis in patients with ARDS [15]. This damage involves both the endothelial and epithelial surfaces of the alveolar–capillary membrane, and involves flooding the alveolar spaces, inactivating surfactant, causing inflammation and producing severe gas exchange abnormalities and loss of lung compliance.

The histological appearance of DAD has been divided into two distinct but overlapping stages: the early exudative phase and the late proliferative phase [16–19]. In the exudative phase, the widespread injury and stress failure of the alveolar–capillary membrane results in increased permeability, demonstrating interstitial and alveolar, protein-rich oedema, haemorrhage and hyaline membranes. Hyaline membranes are homogeneous eosinophilic structures, usually accompanied by intraalveolar proteinaceous exudates, lining the alveolar septa. Ultrastructurally, they contain fibrin as well as cytoplasmic and nuclear debris from sloughed cells. At this stage, fibrin thrombi can often be present in alveolar capillary and small pulmonary arteries [15].

Toward the end of the acute stage of DAD, hyperplasia of alveolar type II cells develops, and a reparative phenomenon, in which type II cells replace the sloughed type I cells, can be observed. In this situation, type II cells display features of atypia, namely nuclear enlargement, clumped nuclear chromatin, large eosinophilic nucleoli and cellular polymorphism. Intracytoplasmic lipid accumulation and cytoplasmic hyaline changes can be seen in these cells as well [20].

The alveolar type II cells play a critical role in both ion and fluid transport

and surfactant secretion. In the setting of ARDS, decreased synthesis and uptake of surfactant, as well as an increase in alveolar epithelial permeability, may contribute to an inadequate amount of functional surface–active material in the distal air spaces of the lung, contributing to the alveolar collapse. Furthermore, surfactant composition and function can be impaired by inhibitory factors from protein-rich pulmonary oedema fluid or by degradation in the alveolar space, due to lipases and proteinases [21].

The proliferative phase characteristically displays a fibroblast proliferation in the interstitium and air spaces. Alveolar macrophages engage in the phagocytosis of hyaline membranes and cellular debris. Residual alveolar exudates may be incorporated into the alveolar septa or organised in the luminal surface of the alveolar walls [17]. Thrombi, arterial medial hypertrophy and intimal fibrosis, resulting in obliteration of the vascular bed, constitute the typical vascular alterations [22].

Experimental models of ALI/ARDS present different responses and morphologic alterations of lung parenchyma as consequences of direct or indirect insults. The pulmonary epithelium is the primary structure injured after a direct insult. The alveolar epithelium lesion leads to activation of alveolar macrophages and the inflammatory network, resulting in the onset of pulmonary inflammation. The epithelial damage brings about: (1) alveolar flooding, (2) reduced removal of oedema fluid from the alveolar space (loss of epithelial integrity and injury of type II cells disrupt normal epithelial fluid transport), (3) lessening of the production and turnover of surfactant (lesion of type II cells), and (4) fibrosis [5]. Thus, the prevalent damage after the direct insult consists of alveolar filling due to oedema, fibrin, collagen, neutrophilic aggregates and/or haemorrhage [7]. The indirect insult is caused by mediators released by extrapulmonary foci into the blood, which creates the pulmonary lesions. The main target damage is the pulmonary endothelial cell. Activation of the inflammatory network results in increased permeability of the endothelial barrier and recruitment of monocytes, neutrophils, platelets and other cells [23]. Thus, microvascular congestion and interstitial oedema, with a relative sparing of the intraalveolar spaces, represents the main pathologic finding in the indirect insult [7].

The acute phase may resolve or progress to fibrosis with persistent hypoxaemia, increased dead space, pulmonary hypertension and further loss of lung compliance. Pathological examination of the lung discloses fibrosis with collagen deposition, acute and chronic inflammation, and incomplete resolution of oedema. Resolution of hypoxaemia and improvement in dead space and lung compliance characterises the recovery phase of ARDS. Although radiographic abnormalities usually resolve, microscopic fibrosis remains [11] (Fig. 1).

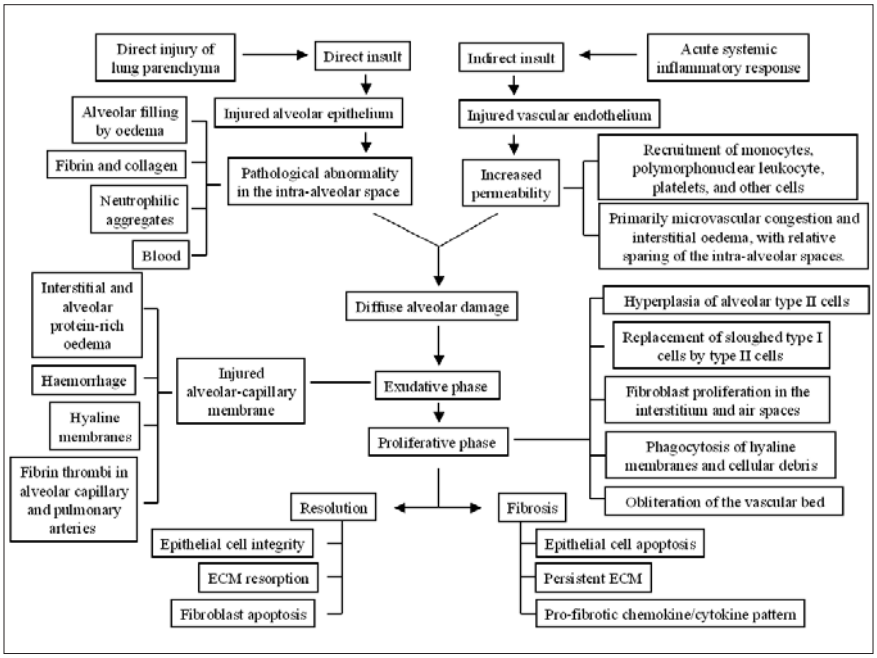

Fig. 1. Diagram summarising the major events occurring in the acute respiratory distress syndrome of direct and indirect aetiology

Extracellular Matrix Organisation

In normal lungs, matrix cells (mainly fibroblasts and myofibroblasts) locally secrete extracellular matrix (ECM) proteins, which form a net surrounding the cells. Three groups of macromolecules physically associate to form and regulate the ECM: (1) collagen and elastic fibres, (2) proteoglycans, and (3) metalloproteinases (MMP) and tissue inhibitors of metalloproteinases (TIMP).

Collagen fibres constitute the principal component of ECM. Despite their broad diversity in the connective tissue, collagen fibre types I, II, and III (fibrillar) and IV, V and VI (non-fibrillar or amorphous) are the primary ones present. The turnover of the collagen fibres is a dynamic process, necessary for the maintenance of the normal lung architecture [24]. The amount of collagen deposition depends on the extension of the alveolar injury and on the intensity of release of inflammatory mediators in the lung parenchyma. Several factors, including growth factors – platelet-derived growth factor (PDGF), FGF (fibroblast growth factor) and transforming growth factor (TGF)-β – and cytokines –interleukin (IL)-1 and IL-4, which are secreted by leucocytes and fibroblasts – intensify collagen synthesis. However, the final collagen accumulation depends not only on its synthesis, but also on its degradation [25].

Elastic fibres represent another important component of the ECM. Many types of cells, including condroblasts, myofibroblasts and smooth muscle cells, synthesise these fibres. The amount of elastic fibres increases with lung growth, and, indeed, elastin responds to alveolar formation [23]. Early in development, the elastic fibre composition consists of microfibrils that define fibre location and morphology. Over time, tropoelastin accumulates within the bed of microfibrils to form the functional protein known as elastin.

Elastic fibres comprise three components, which are defined according to the amount of elastin they contain and fibril orientation: (1) oxytalan fibres are composed of a bundle of microfibrils; (2) elaunin fibres are made up of microfibrils and a small amount of elastin; and (3) fully developed elastic fibres consist of microfibrils and abundant elastin [26, 27]. The properties of the elastic fibres depend on their amorphous component, elastin. Oxytalan fibres do not elongate under mechanical stress and prevent excessive tissue stretch, whereas the elaunin fibres present intermediate elastic properties.

Some authors have observed an increased number of myofibroblasts and procollagen-producing cells (types I and III) early in the course of ARDS, suggesting that the proliferative phase begins much sooner than had been previously thought [28–31]. In this context, Rocco et al. disclosed that collagen and elastic fibres were already elevated 24 h after tissue damage in an animal model of ALI induced by paraquat, thus indicating that the biochemical processes implicated in the synthesis of these fibres react very quickly to assault [18, 19].

In the connective tissue, proteoglycans (PGs) form a gelatinous and hydrated substance embedding the fibrous proteins. Proteoglycans consist of a central protein bound to one or more polysaccharides, which are referred to as glycosaminoglycans (GAGs). Because of their hydrophilic structure, GAGs can attract water into the ECM, thereby altering tissue turgor and the viscoelastic properties of the matrix. PGs interact with various cytokines and growth factors and affect cell migration and proliferation. Furthermore, PGs influence the formation of collagen fibres. Proteoglycans are frequently bound to collagen and elastic fibres, participating in ECM organisation. In the fibroproliferative phase of ARDS, an increased deposition of proteoglycans on the pulmonary interstitium takes place [32].

MMPs comprise a family of 23 related, yet distinct enzymes. They are discretely expressed in normal adult tissues, but elevated during embryonic development, tissue repair, inflammation, tumour invasion and metastasis. Growth factors and cytokines can induce or inhibit the transcription of MMPs [33]. Two major physiological inhibitors of the MMPs exist in vivo: (1) α-2 macroglobulin (restricted to its sites of activity owing to its large size), and (2) the family of specific tissue inhibitors of metalloproteinases (TIMPs), naturally occurring proteins specifically inhibiting these proteases and pro-

duced by many cell types [34]. A local imbalance between MMP and TIMP expression may lead to the accumulation of ECM in the interstitial space [33]. MMPs can destroy the normal parenchymal architecture of the lung, but they may also function in remodelling by removing excess matrix in areas of fibrosis. Thus, these enzymes are likely important in cell migration and can degrade a broad range of matrix macromolecules.

The bronchoalveolar lavage fluid (BALF) of patients with ARDS contains high levels of MMPs and their TIMPs [35]. Collagenase (MMP-1) cleaves types I, II and III collagen fibres. The resulting fragments present high susceptibility to digestion by gelatinases (MMP-2 and MMP-9), thus facilitating their removal from the tissue. Gelatinase A (MMP-2) and gelatinase B (MMP-9) degrade collagen IV, fibronectin and elastin. MMP-2 spreads throughout lung parenchyma, whereas MMP-9 is found in intra-alveolar macrophages and alveolar epithelial cells [34]. Stromelysins and matrilysins decompose proteoglycans, fibronectin and laminin. Membrane MMPs degrade several cell surface proteins, and elastase destroys elastin and fibronectin [36].

Mechanisms of Remodelling

Fibroproliferation is a stereotypical reparative response to injury, which can yield disastrous consequences if not closely regulated. Excessive fibrosis occurring in the airspaces, interstitium, respiratory bronchioles and wall of the intra-acinar microvessels may occur.

Inflammatory mediators that stimulate local fibroblasts to migrate, replicate and produce excessive connective tissue quite possibly generate the fibrotic response. In fact, this phenomenon results in a complex interplay between collagen deposition and degradation, with the balance shifted towards deposition [37, 38].

Inflammation can occur without subsequent fibrosis. In ARDS, however, the two processes are probably intimately linked, although the exact degree to which inflammation drives fibrosis remains unclear. It is likely, however, that the resolution of inflammation contributes in important ways to the termination of fibroproliferation. To halt the aggressive lung fibrosis and limit the exuberant alveolar type II cell response, the fibroproliferative response must be turned off and the excess of mesenchymal cells cleared by apoptosis. An intact epithelial basal lamina is also important, as it plays a fundamental role in the repair of the injured lung [38].

Pulmonary Epithelium

The factors determining whether pulmonary fibrosis or restoration of the

normal pulmonary architecture will occur after ARDS remain unknown. One important step is the rapid and efficient restoration of the denuded basement membrane. Efficient alveolar epithelial repair may reduce the development of fibrosis, since the presence of an intact alveolar epithelial layer suppresses fibroblast proliferation and matrix deposition. Epithelial repair involves close coordination of several complex molecular mechanisms. The process includes interactions between the alveolar type II cell and the matrix, which are coordinated by a variety of soluble mediators released into the alveolar space in ARDS [33].

Optimal repair also requires a provisional fibrin matrix on the basement membrane to provide a platform for cell adhesion, spreading and migration. This provisional matrix formed in the context of injury emits signals to activate an inflammatory response, provoking an expansion of connective tissue elements that leads to persistent, and sometimes permanent, matrix reordering [39]. The alveolar proteinaceous exudate provides the substrate for thrombin activation and fibrin formation. Concurrently, low but significant levels of the plasminogen activator, urokinase, are continuously released along alveolar surfaces to facilitate timely resolution of extensive fibrin deposition on the basement membrane [40]. Therefore, the insoluble matrix accumulated in alveolar spaces contains both chemotactic and growth factors to support an influx of fibroblasts and fibroproliferation.

Most modulators that promote alveolar epithelial cell migration are heparin-binding proteins, such as epithelial growth factor (EGF), TGF-α, keratinocyte growth factor (KGF), hepatocyte growth factor (HGF) and FGF [41]. Other biologically active mediators capable of enhancing alveolar epithelial repair in vitro are released into the alveolar space in patients with ARDS. For instance, IL-1β, which seems to mediate epithelial repair activity, proved biologically active in pulmonary oedema fluid from patients with early ARDS [31].

Pulmonary Endothelium

Vascular endothelium, a highly specialised metabolically active organ, serves numerous physiological, immunological and synthetic functions. The pulmonary endothelium contains numerous enzymes, receptors and transduction molecules, which interact with other vessel wall constituents and circulating blood cells [42].

Increased pulmonary vascular permeability – which may be induced by cytokines or other agents, and also via cytoskeletal-related mechanisms of endothelial cells in response to stimuli such as thrombin or mechanical stretch – represents a hallmark of ARDS pathogenesis [43].

Vascular endothelial growth factor (VEGF) is a potent vascular perme-

ability inducer. The systemic expression of VEGF causes widespread multiorgan capillary leakage, suggesting that the overexpression of VEGF plays a pivotal role in the development of pulmonary oedema [44]. Furthermore, VEGF and related molecules, by regulating cell proliferation, angiogenesis and monocytes recruitment, have profound effects on endothelial cell biology. Although endothelial cells stand out as primary targets of VEGF, it can also stimulate the production of surfactant by alveolar type II cells [45], in addition to stimulating growth of lung airway epithelial cells in vitro [46]. Hence, VEGF has also been characterised as an endothelial survival factor, since it prevents microvascular apoptotic cell loss [47].

The expression and function of the VEGF system in ARDS varies, depending on the pathophysiological conditions, timing and degree of damage in the epithelial and endothelial cells. Possibly, in the early phase of lung injury, acute inflammatory response-induced VEGF released by alveolar epithelial cells and leukocytes increases the permeability of the endothelial layer of the barrier and contributes to the formation of interstitial oedema. With the further development of pulmonary oedema, the damage of the alveolar epithelial layer may reduce the production of VEGF. During the recovery period, VEGF may participate in the angiogenesis process, an important component of lung repair [48].

Pulmonary endothelium is also actively involved in the fibrinolytic process, expressing plasminogen activators as well as their inhibitors. The endothelial cell fibrinolytic activity appears to be affected by several ARDS-related mediators, including endotoxin, IL-1, tumour necrosis factor (TNF)-α and thrombin [49].

Pulmonary endothelium releases nitric oxide (NO), a free radical with a very short half-life. NO can exert either pro- or anti-oxidative effects, depending on the type and quantity of oxygen radicals present. In addition to vascular smooth muscle cell relaxation, NO can inhibit platelet aggregation, leukocyte adhesion, and promote cellular proliferation. Furthermore, NO may modulate hypoxic pulmonary vasoconstriction (HPV), a protective feature of lungs to hypoxia. Since hypoxia reduces NO synthesis [50], HPV is lost in ARDS.

Apoptosis

Recent studies have shown that apoptosis contributes to the pathogenesis of lung fibrosis, as well as to its resolution [51, 52]. Apoptosis can be detrimental or beneficial, depending on the cell type, circumstances and timing. Stimulation of apoptosis in myofibroblasts and fibroblasts in the fibrotic lung, for example, can be beneficial because these cells are the major source of excess ECM. Apoptosis of inflammatory cells may also be beneficial [53], but

excessive epithelial cell apoptosis can lead to the destruction of alveolar septa and a fibrotic response [54].

Apoptotic epithelial cells have been found in the damaged alveolar epithelium of patients with ARDS. In the resolution phase, apoptosis of type II pneumocytes is largely responsible for the disappearance of excess epithelial cells [55, 56]. BALF from patients with ARDS contains elevated concentrations of soluble Fas and Fas ligand [57], suggesting that the Fas system may play a role in apoptosis.

The consequences of lung injury depend to a great extent on the apoptosis of neutrophils. Sookhai et al. [58] induced apoptosis of pulmonary neutrophil by administering aerosolised dead *Escherichia coli* before reperfusion injury occurred. They reported a significant improvement in lung injury and survival. Thus, apoptosis of neutrophils probably plays an important role in attenuating lung injury and may ultimately benefit the outcome of patients with ARDS.

Apoptosis of epithelial cells and neutrophils are interrelated events. In response to Fas ligand or TNF-α, bronchiolar epithelial cells undergo apoptosis and secrete IL-8 and nuclear factor (NF)-κB [59], which in turn suppresses the apoptosis of neutrophils, increasing lung injury.

Conclusions

In ARDS, the pathological features represent the consequences of an intense inflammation, resulting in significant and often fatal injury. The remarkable fact is that, despite this extensive damage, ARDS can fully resolve, in a process that requires clearance of the inflammatory cells and mediators, and reversal of pulmonary fibrosis. The regulation of the remodelling of ECM results in a complex integrative mechanism, which transcripts elements that degrade matrix proteins and produces activation/inhibition of several lung tissue cell types.

Understanding the pathogenesis of ARDS is essential, both in determining effective therapeutic strategies and in the search for new tools for controlling the condition.

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Strategies To Modify Lung Remodelling in the Acute Respiratory Distress Syndrome

G.J. Laurent

Acute and chronic lung disorders, such as the acute respiratory distress syndrome (ARDS), asthma, chronic obstructive pulmonary diseases and interstitial lung diseases, are a major cause of morbidity and mortality, and an enormous burden on world healthcare systems. A feature of these diseases is the destruction and remodelling of the lung's support structures, including its extracellular matrix. When this occurs in the fine structures of the lung, it has deleterious effects on lung function. This is seen in many disease settings, including diseases of the airways such as asthma and chronic obstructive pulmonary disease (COPD) – where excessive matrix deposition may occur in large or small airways – and in parenchymal diseases, such as ARDS and idiopathic pulmonary fibrosis (IPF), where there is excessive deposition in alveolar structures and severely compromised gas exchange.

In recent years, we have characterised the key processes in remodelling and identified the diverse structural components of lung airway and parenchymal structures [1]. Collagen types I and III are the most abundant proteins found in airways and blood vessels, as well as in alveolar septa, and it is these collagens that are predominate in parenchymal fibrosis [2] and asthma [3]. The collagens are synthesised by many cells, but predominantly by mesenchymal cells – fibroblasts, smooth muscle cells and myofibroblasts, as well as by epithelial cells [4]. Recent data suggest that there is plasticity between these cells in vivo and that cytokines can promote trans-differentiation processes.

Microarray Studies and the Fibrotic Phenotype

Fibroblasts are widely distributed in all lung structures and have long been recognised to be extremely dynamic. They are continuously synthesizing and degrading collagens and expressing the diverse matrix metalloproteases that can degrade all collagens. When activated, they express a large number of

genes. We recently profiled human foetal lung fibroblast global gene expression in response to transforming growth factor (TGF)-β_1 using oligonucleotide microarrays. Almost 150 genes were up-regulated at least two-fold, representing several major functional categories, including genes involved in cytoskeletal reorganisation, matrix formation, metabolism and protein biosynthesis, cell signalling, proliferation and survival, and gene transcription. An additional 80 genes not previously reported to be TGF-β_1-responsive were up-regulated [5]. This diversity is reflected in in vivo with studies of pulmonary fibrosis in human and animal models showing that almost 500 genes are expressed more than two-fold, including many of those mentioned above, as well as a large cluster of diverse matrix genes [6].

Pro-fibrogenic Cytokines and Pulmonary Fibrosis

A large number of molecules, produced by many different cell types, are known to promote fibroblast proliferation, collagen synthesis, and migration or trans-differentiation [7–9]. These changes when they occur in the lung lead to excessive collagen deposition, the hallmark of fibrosis. Studies in human and experimental models have implicated many of these molecules in the pathogenesis of acute and chronic lung diseases. Understanding this network of mediators, as well as the redundancy in the inflammatory and tissue repair cascade, involves a number of challenges, as we seek to develop new approaches to treat patients suffering with these diseases.

TGF-β is one of the most potent profibrotic molecules in vitro and a strong candidate as a central player in remodelling diseases, including asthma [10], fibrosis and pulmonary fibrosis [8]. Blocking this molecule using a number of strategies blocks pulmonary fibrosis, and several groups in academia and industry are exploring inhibitors of the TGF-β as a strategy to prevent fibrosis. A serious reservation, however, is the role TGF-β plays as an inhibitor of immune responses, since mice deficient in this cytokine exhibit a severe wasting syndrome with evidence of mononuclear cell infiltration in the heart and lungs [11].

Proteases in the Regulation of Fibroblast Function and Remodelling

The serine and matrix metalloproteases have long been thought to be involved in emphysema, where degradation of matrix and destruction of parenchymal lung structures is a feature. There is also compelling evidence that these molecules may be involved in acute lung injury and pulmonary fibrosis [12]. Thus, inhibitors of neutrophil elastase inhibit lung injury and

fibrosis, and, as recently we have demonstrated, mice deficient in this protease are protected from lung fibrosis [13].

It is also clear that proteases of the coagulation cascade, including tissue factor, factor Xa and thrombin, have pro-inflammatory and pro-fibrotic properties and likely play key roles in acute lung injury and remodelling disorders of the lung [14–16]. These molecules activate cells via a family of at least four proteolytically activated receptors (PARs). The receptors have emerged as interesting targets to prevent fibrosis, given that thrombin inhibitors can partially block fibrosis [17] and animals deficient in the main thrombin and factor Xa receptor (PAR-1) are protected from lung fibrosis.

Evidence That Epithelial Cells Are Central to Remodelling

Recent evidence has focussed on epithelial–fibroblast interactions as central to remodelling both in the airways [18] and in the fibrotic foci found in the alveoli of patients with IPF [19, 20]. Epithelial cells release many pro-fibrotic cytokines, including TGF-β, insulin-like growth factor-1 and endothelin-1, all of which stimulate fibroblast proliferation and procollagen production by fibroblasts. Furthermore, these cells may play key roles in the activation of growth factors via cell surface integrins. One of these molecules, expressed only by epithelial cells, is $\alpha_v\beta_6$. Mice deficient in this integrin are protected from pulmonary fibrosis and lack the ability to activate TGF-β. These data, together with the sparcity of inflammatory cells in some fibrotic conditions, and the ineffectiveness of current anti-inflammatory drugs, have lead to the suggestion that remodelling and fibrosis may proceed independently of inflammation.

Endothelin and Angiotensin: Vasoconstrictors That Regulate Remodelling Processes

There are parallels between the actions of agents regulating tone in the vasculature and their effects on fibroblasts – vasoconstrictors often induce remodelling, whereas vasodilators are inhibitors. Two examples are endothelins and angiotensin II. Both agents exhibit pro-fibrotic features in vitro [21, 22], and receptor antagonists for these agents have shown some success in blocking fibrosis in animal models. The relevance to humans remains uncertain and awaits the results of trials with drugs currently used in humans in other settings, but it is of interest that a polymorphism in angiotensin-converting enzyme has been shown to influence outcome in patients with ARDS [23].

Targeting Inflammation and Immune Processes

There is strong evidence that inflammatory processes are important in remodelling. Inflammation is a feature of all the diseases where remodelling occurs, although the precise temporal relationship is uncertain and a causal link remains unproven in humans. In animal models agents that block inflammation via a variety of mechanisms have been shown to reduce the extent of the subsequent fibrosis. For example, agents targeting inflammatory cell migration, activation or gene expression can reduce fibrosis. Until the facts come in on the importance of inflammatory events, we should explore with vigour agents that can influence inflammation and, where possible, test these agents in humans. New generation agents, such as the TNF-α antagonists, need to be assessed in the hope that they will prove to be better than corticosteroids.

Immune modifying drugs are also being explored as agents that might interfere with remodelling processes. Many diseases in which remodelling is a feature are characterised by a predominant Th2 profile (e.g. IL4, 9 and 13) and a diminished Th1 response (IFNγ) – molecules which are broadly fibrotic and anti-fibrotic, respectively, in vitro. Thus, agents that might alter this balance are being explored. Immune suppressants, such as azothioprine, have also been used to treat patients with idiopathic pulmonary fibrosis (IPF). The reports on its effectiveness have not been encouraging; however, the new macrolide immunosuppresants, such as the rapamycin analogue SDZ-RAD, has more recently shown promise by inhibiting bleomycin-induced lung fibrosis [24]. This drug is currently being explored in patients with IPF.

Cytokines and Lipid Mediators As Inhibitors of Fibroblast Function and Fibrosis

For a time, there is considerable interest in the use of anti-fibrotic molecules to inhibit lung fibrosis. This gained impetus as a result of reports in a small group of patients that interferon gamma was an effective treatment for IPF [25]. Unfortunately, this early promise was not born out in more recent multicentred trials with large numbers of patients. Another molecule of interest is prostaglandin E_2, the cyclo-oxygenase product of arachidonic acid metabolism. PGE_2 is a paracrine and autocrine inhibitor of collagen deposition, and its production is reduced in fibroblasts from patients with fibrosis following stimulation with mediators such as IL1 [26] or TGF-β [27]. Furthermore, COX-2 'knockout' mice are more susceptible to bleomycin-induced pulmonary fibrosis [27]. Taken together, these observations support the hypothesis that there is a defect in PGE_2 production in patients developing fibrosis. These data also suggest that strategies to target specific pro-fibrotic genes or

over-express anti-fibrotic molecules might be fruitful. To begin to explore this, we have developed an integrin-targeting gene delivery system which shows high delivery efficiency, while avoiding the immune and inflammatory side effects associated with the use of adenoviral vectors [28].

Apoptosis and Pulmonary Fibrosis

Apoptotic pathways are also key to the resolution of inflammation and fibrosis following lung injury [29, 30]. For example, the clearance of inflammatory cells or fibroblasts may be vital in remodelling, and there is evidence of a diminution of pro-apoptotic pathways in fibroblasts taken from patients with pulmonary fibrosis [31]. Furthermore, fibroblasts derived from injured lungs can induce apoptosis of epithelial cells. It has also been shown that excessive apoptosis of epithelial cells is a feature of experimental fibrosis, and that inhibitors of the pro-apoptotic molecule, Fas, or the caspases, which signal from the death receptors, inhibited fibrosis [32, 33].

Stem Cell and Cell Plasticity in Relation to Remodelling

Recent studies have challenged the concept that resident fibroblasts are the only cells that produce the matrix proteins characteristic of the remodelling resAQnse. For example, epithelial cells have been identified as possible precursors of fibroblasts in chronic renal disease, and TGF-β_1 has been implicated in the trans-differentiation process [34, 35]. The source of differentiated fibroblasts is uncertain in remodelling disorders of the lung, but one recent study showed that bone marrow-derived cells expressing type I collagen populated the lung in bleomycin-induced fibrosis [36].

Final Common Pathways Leading to Remodelling

To date, over 30 molecules have been identified as potential players in fibrosis, challenging us to find final common pathways leading to (or inhibiting) remodelling and fibrosis. There is growing evidence that TGF-β_1, connective tissue growth factor [37] and prostaglandin E2 may be such key molecules. As such, they are primary targets for new therapeutic approaches. Finally, new approaches to target cell proliferation, apoptosis and cell trans-differentiation are also being explored. For example, agents to activate epithelial cell proliferation and aid repopulation of the damaged epithelium are being explored; as are agents to block transformations of mesenchymal cells, including fibroblasts and epithelial cells, to myofibroblasts. Research is there-

fore providing us with promising new ways to treat fibrosis and halt the inexorable progression that is a feature of so many fibrotic and remodelling disorders.

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Application of the Negative Expiratory Pressure Technique in Clinical Research

N.G. Koulouris, J. Milic-Emili

Tidal Expiratory Flow Limitation and Its Measurement

Conventional Techniques

The term expiratory flow limitation (EFL) is used to indicate that maximal expiratory flow is achieved during tidal breathing and is characteristic of intrathoracic airflow obstruction. It should be noted that some experts use the term chronic airflow limitation as a synonym for chronic obstructive pulmonary disease (COPD) to indicate the reduction in maximum expiratory flow that occurs in this disease (and, indeed, in other pulmonary diseases); the latter term does not imply that expiratory flow limitation actually occurs during tidal breathing [1–3].

The presence of EFL during tidal breathing results in dynamic hyperinflation (DH) of lung and intrinsic positive end-expiratory pressure (PEEPi), with a concomitant increase in the effort of breathing, functional impairment of inspiratory muscle function and adverse effects on haemodynamics [4]. These conditions, together with flow-limiting dynamic airway compression during tidal breathing, may contribute to dyspnoea [5].

According to a recently proposed hypothesis [6], in smokers who are destined to develop COPD the transition from peripheral airway disease to overt COPD is characterised by three sequential stages in which EFL plays a central role: *Stage I*, during which the closing volume eventually exceeds the functional residual capacity; *Stage II*, during which EFL first develops; and *Stage III*, during which DH progressively increases, leading to dyspnoea and exercise limitation. The presence of airway closure (*Stage I*) and EFL (*Stage II*) in the tidal volume (V_T) range may promote peripheral airway injury and accelerate abnormalities in lung function [7–9]. This enhances inflammation due to smoking, per se, leading to severe functional and structural abnormalities within the lung. This vicious cycle cannot be reversed, with the possible exception of *Stage I*.

Despite the severe consequences of flow limitation, the prevalence and clinical significance of the above phenomenon have not been adequately studied in COPD, asthma or other pulmonary and non-pulmonary diseases.

By definition, demonstration of expiratory flow limitation requires the demonstration of an increase in trans-pulmonary pressure with no increase in expiratory flow. Therefore, the direct assessment of expiratory flow limitation requires a determination of iso-volume relationships between flow and trans-pulmonary pressure ($\dot{V}$–P). However, this method is technically complex, time consuming and invasive, because it requires the passage of an oesophageal balloon [10, 11].

Until recently, the conventional method used to detect expiratory flow limitation during tidal breathing was the one proposed by Hyatt [3] in 1961. It consists in correctly superimposing a flow–volume loop ($\dot{V}$–V) of a tidal breath within a maximum flow–volume curve. This analysis and the 'concept of EFL' have provided the foundation for understanding respiratory dynamics. Flow limitation is not present when the patient breathes below the maximal expiratory flow–volume (MEFV) curve. According to this technique, normal subjects do not reach a flow limitation even at maximum exercise [1, 2]. In contrast, flow limitation is present when a patient seeks to breathe tidally along or higher than the MEFV curve. It has long been thought that patients with severe chronic obstructive pulmonary disease (COPD) may exhibit flow limitation even at rest, as reflected by the fact that they breathe tidally along or above their maximal flow–volume curve [1–6]. However, the conventional method used to detect flow limitation, based on comparison of maximal and tidal expiratory flow–volume curves, has several methodological deficiencies. These include:

a) *Thoracic gas compression artefacts.* To minimise such errors, volume should be measured with a body plethysmograph, instead of using, as is common practice, a pneumotachograph or a spirometer [12]. The corollary of this is that, in practice, flow limitation may be assessed only in seated subjects at rest.
b) *Incorrect alignment of tidal and maximal expiratory $\dot{V}$-V curves.* Such alignment is usually made using the total lung capacity (TLC) as the fixed reference point. This assumption may not always be valid [13, 14].
c) *Effect of previous volume and time history.* Since the previous volume and time history of a spontaneous tidal breath is necessarily different from that of an forced vital capacity (FVC) manoeuvre, it is axiomatic that comparison of tidal with maximal $\dot{V}$–V curves is problematic. In fact, there is not a single maximal $\dot{V}$–V curve, but rather a family of different curves, which depend on the time course of the inspiration preceding the FVC manoeuvre [15–17]. Therefore, the concept of making a comparison of tidal and maximal $\dot{V}$–V curves is technically incorrect.

d) *Respiratory mechanics and time constant inequalities.* These are different during the tidal and maximal expiratory efforts, also making comparisons of the two $\dot{V}$–V curves problematic [18–20].
e) *Exercise.* This may result in either bronchodilation or bronchoconstriction and other changes of lung mechanics, which may also affect correct comparisons of the two $\dot{V}$–V curves [21].
f) *Patient cooperation.* Another important limitation of the conventional method is that it requires patient cooperation. This is not always feasible [13, 14].

From the above considerations, it can be seen that the detection of expiratory flow-limitation based on a comparison of tidal with maximal $\dot{V}$–V curves is not valid even when a body-box is used. In fact, this has been clearly demonstrated in several studies [22–25]. As a result, the use of this method is no longer recommended.

The Negative Expiratory Pressure (NEP) Technique

In order to overcome the above technical and conceptual difficulties, the negative expiratory pressure (NEP) method was recently introduced [22–25] (Fig. 1). The NEP technique has been applied and validated in mechanically ventilated intensive care unit (ICU) patients by concomitant determination of isovolume flow–pressure relationships [23, 26] (Fig. 2). This method does not require the performance of FVC manoeuvres, collaboration on the part of the patient or the use of a body plethysmograph, and it can be used during spontaneous breathing in any body position [27], during exercise [24, 28, 29], or in the ICU setting [7, 8, 23, 30–32]. With this method the volume and time history of the control and test expiration are the same.

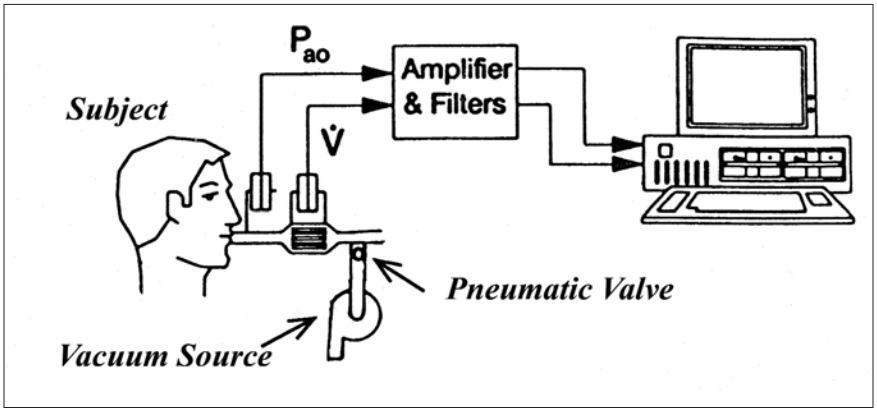

Fig. 1. Schematic diagram of equipment setup (modified from [22])

Figure 1 depicts the experimental setup used to assess expiratory flow limitation [22]. A flanged plastic mouthpiece is connected in series to a pneumotachograph and a T-tube. One side of the T-tube is open to the atmosphere, while the other side is equipped with a one-way pneumatic valve, which allows for the subject to be rapidly switched to negative pressure generated by a vacuum cleaner or a Venturi device. The pneumatic valve consists of an inflatable balloon connected to a gas cylinder filled with helium and a manual pneumatic controller. The latter permits remote control balloon deflation, which is accomplished quickly (30–60 ms) and quietly, allowing rapid exposure to negative pressure during expiration (NEP). Alternatively, a solenoid rapid valve can be used. The NEP (usually set at about -3 to -5 cmH_2O) can be adjusted with a potentiometer on the vacuum cleaner or by controlling the Venturi device. Airflow ($\dot{V}$) is measured with the heated pneumotachograph, and pressure at the airway opening (PaO) is simultaneously measured through a side port on the mouthpiece. Volume (V) is obtained by digital integration of the flow signal [22–25].

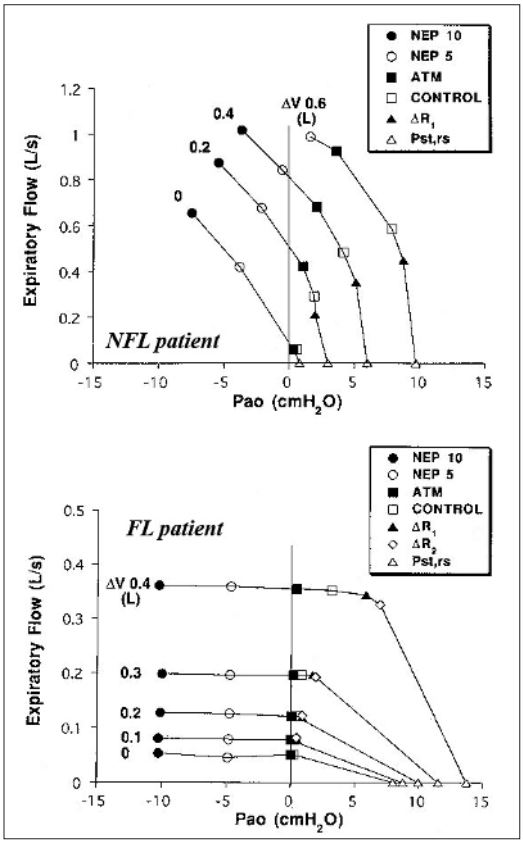

Fig. 2. Expiratory iso-volume flow–pressure relationships under control conditions and during test breaths with different methods of assessing flow-limitation in two, mechanically ventilated patients. *NEP 10*, negative expiratory pressure of -10 cmH_2O; *NEP 5*, negative expiratory pressure of -5 cmH_2O; *ATM*, expiration into atmosphere; ΔR_1 and ΔR_2, expiration with added expiratory resistance; *Pst,rs*, static pressure of respiratory system during lung deflation. *Upper panel*: A representative non flow-limited patient (*NFL*), as indicated by the increase in flow with NEP and ATM, compared with control. *Lower panel*: A representative flow-limited (*FL*) patient, as indicated by unchanged expiratory flow and ATM, compared with control (modified from [23])

During testing, subjects should be watched closely for leaks at the mouthpiece. By monitoring the volume record over time on the chart recorder, the absence of leaks and electrical drift can be ensured by the fact that, after the NEP tests, the end-expiratory lung volume (EELV) returns to the pre-NEP level. Only tests in which there is no leak are valid [33].

The NEP method is based on the principle that, in the absence of preexisting flow limitation, the increase in pressure gradient between the alveoli and the airway opening caused by NEP should result in increased expiratory flow. In contrast, the application of NEP in flow-limited subjects should not change the expiratory flow. Our analysis essentially consists in comparing the expiratory $\dot{V}$–V curve obtained during a control breath with that obtained during the subsequent expiration in which NEP is applied [22, 23].

Subjects in whom application of NEP does not elicit an increase of flow during part or all of the tidal expiration (Fig. 3, *right*) are considered flow-limited (EFL). In contrast, subjects in whom flow increases with NEP throughout the control V_T range (Fig. 3, *left*) are considered as non flow-limited (NFL). If EFL is present when NEP is applied, there is a transient increase of flow (spike), which mainly reflects a sudden reduction in volume of the compliant oral and neck structures. To a lesser extent, a small artefact due to common-mode rejection ratio of the system of measuring flow may also contribute to the flow transients [22–24]. Such spikes are useful markers of EFL.

Using any one of three different EFL indices, the degree of flow limitation

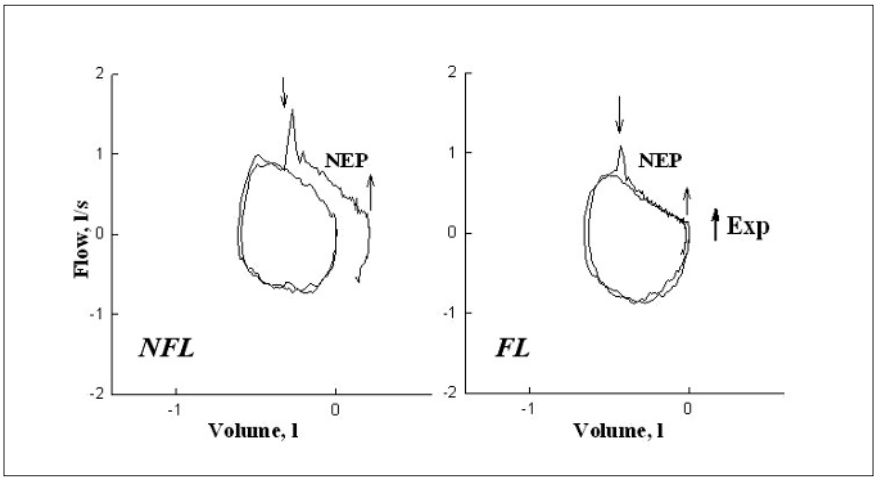

Fig. 3. Flow–volume loops of test breaths and preceding control breaths of two representative bronchiectatic patients with different degrees of flow-limitation: non flow-limited (*NFL*) (*left*) and flow-limited (*FL*) over less than 50% tidal volume (V_T) (*right*). Arrows indicate points at which NEP was applied and removed (modified from [34])

can be assessed as: a) a continuous variable expressed as $\%V_T$ in both seated and supine positions [22] (Fig. 3); b) a discrete variable in the form of three categories of classification – i.e. NFL both seated and supine, EFL supine but not seated, EFL both seated and supine [22]; and c) a discrete variable based on the five classification categories (the 5-point EFL score) [25].

Application of NEP is not associated with any unpleasant sensation, cough or other side effects [22–25]. However, there is a potential limitation of the NEP technique, which concerns normal snorers and patients with obstructive sleep apnoea syndromes (OSAS) [35–38]. A typical example is clearly illustrated in Fig. 4. On the left (a), the figure illustrates a flow-volume loop obtained with NEP and preceding control tidal breath in a sitting snorer at rest. The arrows indicate the onset and end of NEP application (-5 cmH_2O). The NEP expiratory flow shows a transient drop below control flow, reflecting a temporary increase in upper airway resistance. After this transient decrease in flow, expiratory flow with NEP exceeds control flow, indicating that there is no intrathoracic flow limitation. The right (b) is the same as the left, except that flow with NEP remains below control throughout expiration, reflecting a prolonged increase in upper airway resistance. In this case, the NEP test is not valid for assessing intrathoracic flow limitation. However, this phenomenon is uncommon in non-obstructive sleep apnoea hypopnoea syndrome (OSAHS) subjects [38]. Furthermore, valid measurements may be obtained with repeated NEP tests using lower levels of NEP (e.g., -3 cmH_2O).

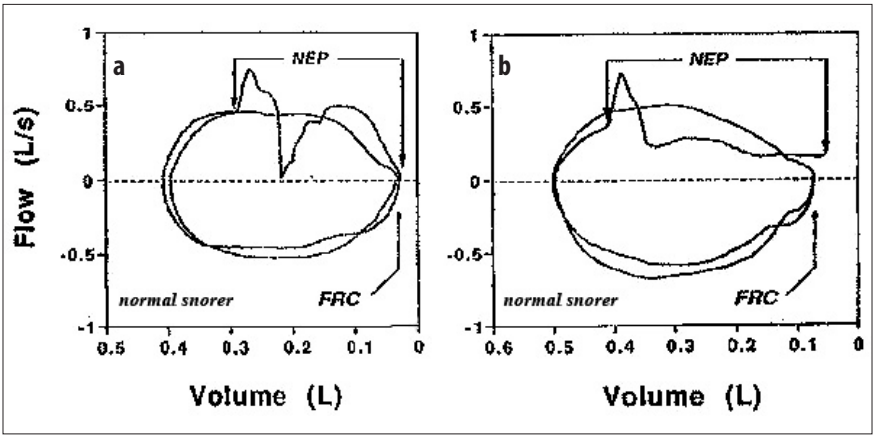

Fig. 4. Flow–volume loops obtained with NEP and preceding control tidal breath in two representative sitting snorers (**a**, **b**) at rest (modified from [35]). For explanation, see text

In non-OSAHS and OSAHS patients [37, 38], in whom there is a consistent upper airway collapse in response to the application of NEP, EFL can be assessed by: a) sub-maximal expiratory manoeuvres initiated immediately after end-tidal inspiration; or b) by squeezing the abdomen during expiration (see below).

Turning this apparent drawback into advantage, Liistro et al. [36] and Verin et al. [37] found significant correlations between the degree of flow limitation expressed as $\%V_T$ in the supine position with the desaturation index (DI) and the apnoea/hypopnoea index (AHI) in OSAHS patients with no evidence of intra-thoracic obstruction.

Clinical Applications

Since its introduction, the NEP technique has been used to detect flow limitation, or to examine the effect of negative pressure, under a variety of conditions, i.e. in different body postures [27] during rest and exercise [24, 28, 29], in spontaneously breathing and mechanically ventilated subjects [7, 8, 23, 30–32], and in paediatric [26, 39], neurological [40] and geriatric settings [41, 42].

EFL has been determined to be present during resting breathing in sitting and supine positions in 117 stable COPD patients [25]. Although, on average, the patients who experienced EFL when both seated and supine had a lower forced expiratory volume in the first second (FEV_1) as percentage predicted (% pred) than those who were not experiencing EFL, there was a marked scatter of the data. Indeed, 60% of the NFL group had an $FEV_1 < 49$ % pred, and were classified as having severe-to-very-severe airway obstruction. Thus, FEV_1 is not a specific predictor of EFL in COPD patients.

Intuitively, one would expect patients with the most severe airway obstruction, as assessed by 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. In fact, many studies have shown that the correlation between chronic dyspnoea and FEV_1 is weak. EFL measured with the NEP technique, however, has proved to be a much better predictor of chronic dyspnoea than FEV_1 in COPD patients [25]. Furthermore, the NEP technique has revealed a high prevalence of orthopnoea in these patients [43].

It appears that in stable COPD patients, there is a high prevalence of flow limitation even when taking into account the severity of airway obstruction in terms of FEV_1. Indeed, 48% of COPD patients were EFL, compared with 15% of asthmatics at comparable FEV_1 values [22, 25, 43–45]. In contrast to COPD patients, most asthmatics do not exhibit EFL during resting breathing

seated and/or supine [28, 43–47]. This discrepancy between asthma and COPD may reflect lower elastic recoil in the latter condition.

Tantucci et al. [44] were the first to assess the effect of a bronchodilator (salbutamol) on resting inspiratory capacity (IC). In a group of COPD patients divided according to the presence or absence of tidal EFL and with similar baseline FEV1% pred, the acute administration of a bronchodilator induced a significant (greater than 10% of baseline) increase in IC, but only in the tidal EFL COPD patients (about 75% of the entire group of patients). It should be noted that only 6% (using ERS criteria) or 16% (using ATS criteria) of all COPD patients examined demonstrated reversibility of the airway obstruction after bronchodilator. Moreover, a significant post-bronchodilator decrease in EELV (or dynamic FRC) was observed only in the COPD subgroup with tidal EFL.

Subsequently, it has been shown that the increase in IC after anticholinergic and salbutamol therapy best reflects improvement in exercise tolerance [48]. Both a significant reduction in exertional dyspnoea (ΔBorg, exercise) and a close relationship between ΔBorg, exercise (decrease) and ΔIC at rest (%pre) (increase) were found after salbutamol, regardless the change in FEV1 in the group of COPD patients with tidal EFL at rest. In contrast, no change in ΔIC at rest (%pre) or in ΔBorg, exercise was observed in the group of COPD patients without tidal EFL at rest. Therefore, in COPD patients the reduction in breathlessness during mild-to-moderate exercise following the administration of bronchodilator is heralded by an increase in IC at rest.

The improvement of IC after bronchodilator administration, which is mainly limited to patients with EFL at rest who exhibit a reduction of baseline IC, entails reduction in dyspnoea both at rest and during light exercise [48]. Thus, in obstructive lung disease, the benefit of bronchodilator therapy should be assessed not only in terms of changes in FEV_1, but also, and more importantly, in terms of increases in IC. In connection with this, it should be noted that, because performance of IC precedes the FVC manoeuvre, FEV_1 and IC are, in general, recorded together during bronchodilator testing.

Although, traditionally, bronchodilator testing has focused on changes in FEV_1, the scrutiny of changes in IC should be mandatory, due to the fact that IC provides more useful information than FEV_1, for both dyspnoea and exercise tolerance. The detection of EFL alone with the NEP technique is not an appropriate measurement of acute bronchodilator responsiveness [49]. However, the fact that, after bronchodilator administration, there is a significant reduction of DH only in patients with EFL at rest in sitting position, further supports the usefulness of stratifying COPD patients into subgroups of those with and those without EFL in order to predict an improvement in DH. Thus, measurement of IC and detection of EFL are complementary techniques for assessing bronchodilator responsiveness in COPD patients [44, 48].

We studied the feasibility of using the NEP technique during exercise and assessed the implications of flow limitation on exercise performance [24, 28, 29]. Figure 5 shows the flow–volume curves of a COPD patient, both at rest and at two levels of exercise [24]. With NEP, flow increased at rest, but not during exercise, indicating that expiratory flow limitation was present at both levels of exercise but not at rest. With the conventional test, i.e. comparing the tidal flow–volume to the maximal flow–volume curve, this patient would be classified as flow-limited both at rest and during exercise. The NEP technique has an enormous advantage in that it allows for the occurrence during exercise of all the effects discussed earlier, including bronchoconstriction or bronchodilation [28]. In this context, Murciano et al. [29] were able to show using the NEP test that, although after single lung transplantation patients were not flow-limited at rest, most of them become flow-limited during exercise.

Figure 6 shows subdivisions of lung volume, expressed as a percent of total lung capacity (%TLC), at rest and at different exercise levels in three groups of COPD patients: flow limited (EFL) at rest, at 1/3 WR_{max}, and EFL or NFL at 2/3 WR_{max}. The presence of flow-limitation at rest implies that the increased ventilation during exercise should be associated with dynamic pulmonary hyperinflation. Indeed, in our COPD patients who were EFL at rest, the EELV

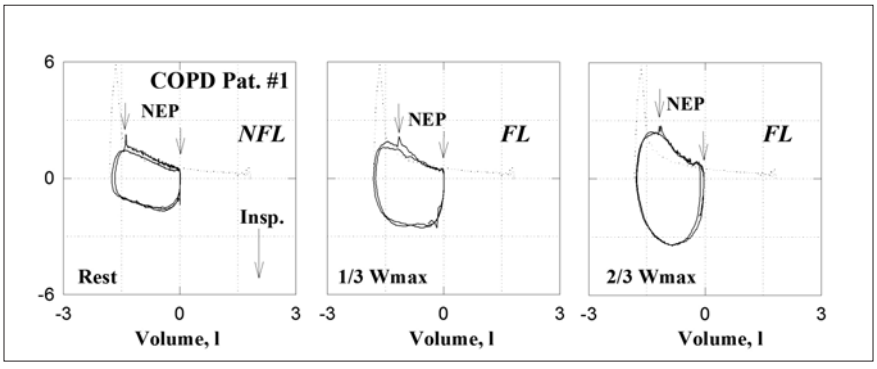

Fig. 5. Flow–volume curves obtained in a patient with COPD (FEV_1: 45% pred) at rest and at two different levels of exercise, expressed as a fraction of maximal power output (Wmax). Zero volume represents the end-expiratory lung volume (EELV) at rest. In each instance, the flow–volume loops of two consecutive breathing cycles are shown: that of a test breath, during which a negative pressure (NEP) of -5 cmH_2O was applied during expiration, and that of the preceding control breath. NEP was applied during early expiration (*first arrow*) and maintained throughout expiration (*second arrow*). With NEP, flow increased at rest but not during exercise, indicating that expiratory flow-limitation was present at both levels of exercise, but not at rest. Also shown by the dotted line is the expiratory flow–volume curve obtained during an FVC manoeuvre. With the latter test, the patient would be classified as flow-limited at rest and during exercise (modified from [24])

increased significantly at both exercise levels studied (Fig. 6, *left*). Similarly, in the patients who became EFL at 1/3 WR_{max}, there was a significant increase of EELV only at 2/3 WR_{max} (Fig. 6, *middle*). In contrast, in the other patients, there was no significant change in EELV over the entire exercise range studied (Fig. 6, *right*). The five COPD patients who were EFL at rest exhibited a significantly lower IC % pred, compared with the other COPD patients. If flow limitation is present at rest, with a concomitant decrease in IC, the maximal tidal volume (V_{Tmax}) during exercise should also be reduced. Indeed, a very low V_{Tmax} was a characteristic feature of the five COPD patients who were EFL at rest. Hence, it may be concluded that the lower the resting IC, the lower the V_{Tmax} attained.

Along similar lines, Diaz et al. [50] found that IC was the only spirometric parameter in which there was almost no overlap between NFL and EFL COPD patients, and that almost all the NFL patients had normal IC, while, in a group of 52 COPD patients, the EFL patients all had < 80 % pred. Furthermore, they documented a close correlation between V_{Tmax} and IC ($r = 0.77$, $p < 0.0001$). In this group of COPD patients, Diaz et al. also confirmed our initial observation in a smaller group of COPD patients that V_{Tmax} is closely correlated with exercise capacity expressed as VO_{2max} L/min [24, 51].

Hence, it is not surprising that linear regression analysis performed separately for EFL and non-EFL patients showed that, in the EFL patients, the sole predictor of exercise capacity was IC (% pred), while in the non-EFL patients, the ratio FEV_1/FVC (% pred) was the sole predictor. The significant correlation of VO_{2max} with a high FEV_1/FVC ratio in patients without EFL is mainly

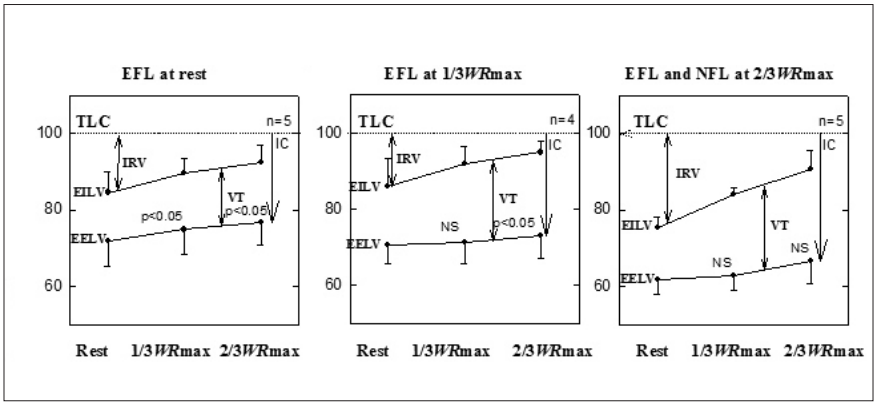

Fig. 6. Subdivisions of lung volume, expressed as a percentage of total lung capacity (*TLC*), at rest and at different exercise levels in three groups of patients with COPD: flow limited (*EFL*) at rest; EFL at one-third Wr_{max}; and EFL or NFL at two-thirds Wr_{max}.
• indicate average values; error bars, SE (modified from [24])

due to the fact that a high FEV_1/FVC ratio reflects a MEFV curve with an upward convexity, which implies a large flow reserve, i.e. beyond the resting V_T range, while a low FEV_1/FVC ratio reflects a curve with an upward concavity and little expiratory flow-reserve over the resting V_T range. Thus, patients without EFL at rest, but with a low FEV_1/FVC ratio, are more prone to developing EFL during exercise than patients in whom this ratio is high. Development of EFL during exercise limits V_{Tmax}, and, hence, maximal exercise ventilation and exercise tolerance. Accordingly, in COPD patients without EFL at rest, VO_{2max} correlates directly with FEV_1/FVC (% pred). Thus, the main finding of these studies is that the detection of EFL at rest plays an important role in identifying the factors that limit exercise tolerance; this is because resting EFL clearly separates two populations of patients exhibiting significant differences in exercise tolerance. More importantly, this finding provides useful information about the mechanisms limiting exercise tolerance. In the presence of EFL, DH appears to be the main determinant of exercise performance, and the magnitude of resting IC, a well-recognised marker of DH, appears to be the best clinical predictor.

In a similar manner, a more recent study showed that most patients with stable asthma exhibit tidal EFL and DH during exercise, even if their baseline FEV_1 and PEF are within normal limits and they have no exercise-induced asthma [28]. In asthmatics with exercise-induced tidal EFL, the exercise capacity is reduced as a result of DH. This finding has important clinical implications because it is possible that administration of bronchodilators immediately before exercise may abolish tidal EFL and DH during exercise and improve exercise capacity.

It should be noted, however, that during metacholine (MCh)-induced bronchoconstriction, DH, as reflected by decreased IC, commonly occurs in the absence of tidal EFL. Therefore, the presence of EFL may not result in DH, if the available expiratory flow is sufficient to sustain resting ventilation (without the need to increase EELV). This is demonstrated by the fact that there are patients with EFL and normal IC.

In contrast, it has been found that, during exercise, DH is closely associated with tidal EFL, not only in COPD patients [24] but also in asthmatics [28]. This discrepancy may be due to the fact that, during MCh-challenge, DH is associated with increased expiratory resistance linked to persistent activity of the inspiratory muscles and expiratory narrowing of the glottis during the breathing cycle. While some of these mechanisms may have contributed to the exercise-induced DH in our patients, EFL seems to be the principal factor since it was present in all of our patients who exhibited DH, while absent in all our patients who did not exhibit DH. It is possible that the exercise-induced bronchoconstriction is more homogeneous than MCh-induced bronchoconstriction. With non-homogeneous bronchoconstriction, some

regions may develop EFL, with concurrent DH, while others empty normally; hence, overall EFL (as measured with NEP) may be absent. In such cases, IC may be decreased in the absence of overall EFL. In contrast, with homogeneous bronchoconstriction, overall EFL and DH should reflect homogeneously distributed mechanical impairment within the lungs [28].

The NEP technique has also been used to detect flow limitations in mechanically ventilated patients [7, 8, 23, 30–32]. In fact, initially, the NEP method was validated using mechanical ventilation in various body postures [23]. Dimitroulis et al. found that almost all COPD patients who require mechanical ventilation are flow-limited over the entire range of tidal expiration, and that the supine posture increases flow limitation. It should be noted that flow limitation is reversed in lateral decubitus and in spontaneous breathing COPD patients on hands-and-knees positions [27]. Studies by other authors have shown that most patients with acute respiratory failure of pulmonary origin present with tidal expiratory flow limitation, while patients with acute respiratory failure of extra-pulmonary origin do not [30]. The same authors found that most ARDS patients exhibit expiratory flow limitation, probably associated with the closure of small airways and a concomitant PEEPi [7]. The presence of EFL, which implies concurrent cyclic dynamic compression and re-expansion of the airways, increases the risk of low-lung volume injury. In all ARDS patients, the application of 10 cmH_2O of PEEP abolished EFL and improved arterial oxygenation, as a result of alveolar recruitment in NFL patients and reduced intrapulmonary PEEPi inequality in EFL patients [8].

Tidal EFL and PEEPi are also common in supine, morbidly obese sedated (or paralysed) subjects after abdominal surgery [32]. This implies that the therapeutic administration of external PEEP must be monitored with concurrent assessment of EFL and PEEPi. The presence of EFL and peripheral airway closure implies possible risk of low volume injury. Accordingly, it also seems prudent to apply PEEP in order to avoid peripheral airway closure and EFL. Thus, NEP is a potentially useful bedside technique for obtaining information concerning the respiratory mechanics in the assessment of EFL in mechanically ventilated patients.

In the past, there was no online method available for assessing whether the flows during FVC manoeuvres were maximal or not. Recently, however, a simple method for assessing FVC performance has been developed [26, 52]. It is based on a variation of the NEP technique, and consists in the application of short NEP pulses (-10 cmH_2O) during the FVC manoeuvre. If the expiratory flow increases during the application of the NEP pulse, the expiratory flow is sub-maximal. In contrast, if flow does not increase with the negative pressure, expiratory flow limitation has been reached. Thus, with this method it is possible to determine whether the maximal flows are low as a result of insuf-

ficient respiratory effort (e.g., weak respiratory muscles, lack of coordination, malingering) or as a result of the presence of a lung disorder.

In summary, the NEP technique has been used clinically in studies a) with COPD (during mechanical ventilation and exercise, and in correlation with dyspnoea, orthopnoea and other lung function indexes, both before and after bronchodilatation and in various postures) [22–25, 27, 33, 43, 44, 50, 51]; b) with asthma (i.e. stable asthma, during methacholine bronchoconstriction and during exercise) [28, 45–47]; c) with cystic fibrosis [53, 54] and bronchiectasis [34]; d) with restrictive lung disease [33, 37]; e) with obesity [32, 55, 56]; f) with mechanical ventilation with acute respiratory failure and ARDS [7, 8, 23, 30–32]; g) with left heart failure [57]; h) after single lung transplantation [29, 58]; i) with euthyroid goitre [59]; and j) in assessments of bronchial hyperreactivity [60]. The use of the NEP technique during tidal flow–volume analysis studies has revealed the importance of expiratory flow limitation in exertional dyspnoea and ventilatory impairment for a surprisingly wide range of clinical conditions [61]. As a result, the NEP technique has demonstrated itself to be a useful, new research and clinical lung function tool.

Conclusions

In conclusion, the NEP technique provides a simple, rapid, non-invasive and reliable test for detecting tidal expiratory flow limitation [61–63]. Advantages of the technique are that:

a) It does not require a body-box or any cooperation on the patient's part.
b) It can be applied in any body position, during mechanical ventilation and during exercise.
c) It may provide new insights into the physiology and pathophysiology of a variety of diseases, including those characterised by symptoms of dyspnoea.

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Non-Invasive Ventilation

A. Peratoner, V. Antonaglia, U. Lucangelo

Mechanical ventilation represents the most widely used supportive technique in the intensive care unit (ICU). Without mechanical support for respiration, many patients would die within a few hours due to acute hypoxaemic and hypercapnic respiratory failure. Several forms of external support for respiration have been described in the literature to assist the failing ventilatory system. Chief among these is endotracheal intubation (ETI) [1–3], which constitutes a major advance in the management of patients with respiratory distress. The technique involves the insertion of a tube into the mouth, through the trachea and down into the lungs. Although it can be life-saving, ETI poses a risk of morbidity, including upper airway trauma, nosocomial pneumonia and sinusitis. In addition, ETI may prolong the length of the ICU and hospital stay, as a result of additional time that may be necessary for weaning from ventilation and for the treatment of complications [4–6].

Observational, physiological and case-control studies form a strong body of evidence that, in many clinical situations, non-invasive ventilation (NIV) can be used to decrease patient dyspnoea and improve gas exchange, thereby avoiding the need for ETI [1–3]. Randomised controlled trials have confirmed this and helped delineate when NIV should be used as a first line treatment. Studies conducted outside the context of clinical trials are also of great importance and demonstrate that the results of the trials can be obtained in real life clinical practice [7–9]. It is important to point out, however, that NIV is a complementary technique and not intended to replace ETI in all instances.

The potential benefit of continuous positive airway pressure (CPAP) using a face mask in patients with acute respiratory failure was recognised decades ago [10, 11]. In more recent years, non-invasive positive pressure ventilation (i.e. the combination of pressure support and positive end-expiratory pressure [PEEP]) delivered via facial or nasal mask or helmet has been used increasingly to avoid ETI and its complications in patients with acute respiratory failure.

NIV can be initiated at an earlier stage, before mechanical ventilation would normally be considered necessary. Increasingly, NIV is being used with good results outside intensive care units, either in general wards or emergency departments. With adequate staff training, the early implementation of NIV on a general ward results in a better outcome for patients that might otherwise receive respiratory support. Moreover, intermittent ventilatory assistance is possible with NIV, thereby allowing normal eating, drinking and communication, as well as gradual weaning.

The physiological effects of NIV vary greatly and depend on the pathophysiology of the patient's respiratory failure, the severity of the respiratory dysfunction, the mode of NIV and the level of pressure applied and, finally, the efficiency of breathing circuit. The possible benefits of NIV on respiratory and cardiac function include:

- Improved gas exchange
- Improved alveolar ventilation
- Reduced work of breathing
- Reduced cardiac transmural pressure
- Decrease afterload
- Improved cardiac performance.

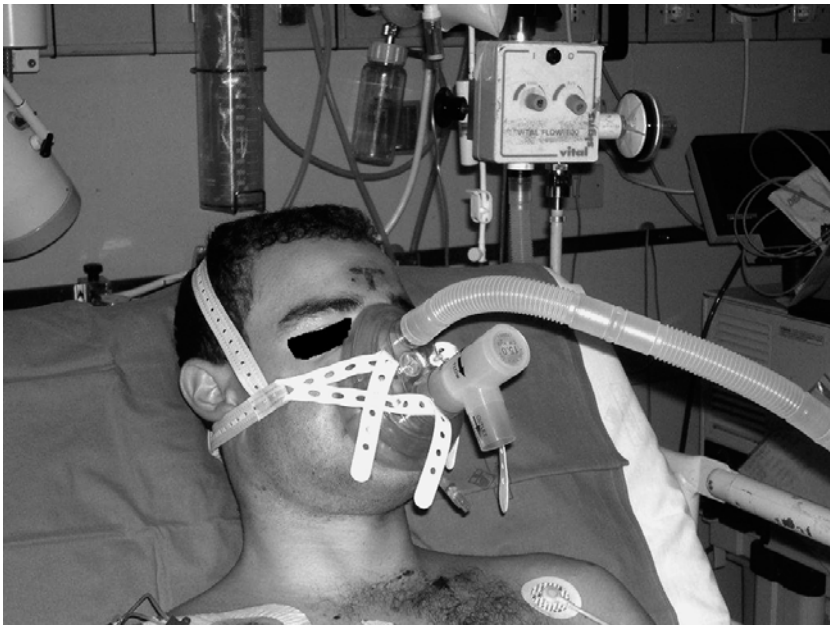

Fig. 1. Non-invasive ventilation delivered by full face mask

NIV is not suitable for all patients with respiratory failure. If used indiscriminately, patients who would be managed more appropriately using ETI may receive suboptimal treatment.

The use of NIV in patients in whom it is unlikely to be beneficial is also undesirable. Furthermore, it is essential that NIV be applied in an appropriate clinical setting by appropriately trained staff, using the optimal ventilator mode, settings and interface, as well as adequate monitoring.

Indications for NIV depend on the goals of therapy at the time of intervention. Due to the absence of large-scale, controlled studies, NIV should not be used unequivocally in all patients with respiratory failure. Reasonable therapeutic goals include the avoidance of ETI, unloading respiratory muscles (decreasing respiratory rate and the sensation of dyspnoea and increasing patient comfort), improving gas exchange and thus oxygenation and acidosis, decreasing heart rate and improving haemodynamics, decreasing ICU length of stay and associated complications (such as nosocomial infections) and, finally, decreasing hospital stay and mortality. On the basis of these criteria most patients with respiratory impairment should be given the opportunity to receive NIV and its associated benefit. There are three levels at which NIV may be used:

1) As a holding measure to assist ventilation in patients at an earlier stage than that at which ETI would be considered.
2) As a trial measure before initiating ETI.
3) As a treatment for patients who are not candidates for ETI.

A decision about the use of ETI, in the event that NIV fails, should be made early in the treatment, in consultation with ICU staff, taking into account the severity of the underlying disease and the level of disability. The wishes of the patient and family should also, of course, be taken into consideration, and the final decision should be verified with senior medical staff. Finally, if appropriate, there should be a consultation with ICU staff.

Although the boundaries for the use of NIV continue to expand, ETI and conventional ventilation remain the gold standard of therapy for many patients with acute respiratory failure. Local protocols need to be developed in order to avoid inappropriate trials of NIV in patients who require urgent ETI. NIV is not appropriate in well documented, end-stage disease, or when several comorbidities are present. While there are no 'absolute' contraindications, a number have been suggested [12, 13], based on procedures followed during the controlled trials. Other contraindications, such as the failure of pH to improve within 1 h [13] are more on the order of self-fulfilling prophecies, if they have been determined from the outset to indicate a failure of treatment. Whether NIV should be contraindicated or not really depends on the individual circumstances. If invasive ventilation is not considered appropri-

ate but NIV would be acceptable, there is nothing to lose by trying NIV. The many controlled trials undertaken have resulted in a balanced picture regarding appropriate indications and contraindications for NIV. Generally accepted criteria, as well as contraindications, are indicated below.

Selection Criteria

- Moderate-to-severe respiratory distress
- Tachypnoea (respiratory rate > 30–35 or > 24, in the case of chronic obstructive pulmonary disease [COPD])
- Accessory muscle use or abdominal paradox breathing
- Blood gas derangement: $PaCO_2$ > 45 cmH_2O and/or pH < 7.32, or PaO_2/FiO_2 < 200.

Patient Inclusion Criteria

- Awake and cooperative
- Haemodynamic stability
- No copious respiratory secretions
- Ability to expectorate
- Ability to protect airway.

Contraindications

- Cardiac or respiratory arrest
- Severe encephalopathy (e.g. Glasgow Coma Scale < 10)
- Severe upper gastrointestinal bleeding
- Haemodynamic instability or unstable arrhythmia
- Inability to cooperate and protect airway
- Inability to clear respiratory secretions
- Upper airway obstruction
- High risk for aspiration
- Facial surgery, trauma or burns
- Undrained pneumothorax.

Clinical Applications

Increasingly, NIV is being used for diseases causing acute respiratory dysfunction in a effort to avoid ETI and/or accelerate the discontinuation of mechanical

ventilation. The literature indicates that COPD exacerbation and cardiogenic pulmonary oedema are the clinical settings in which NIV has been used most successfully [14]. Randomised, controlled studies also support the use of NIV, rather than ETI, in immunocompromised patients and patients who are recovering from thoracic surgery. Evidence of the efficacy of NIV is rapidly accumulating in a variety of different areas, as summarised below.

Good Evidence of Efficacy

- COPD exacerbation
- Cardiogenic pulmonary oedema
- Respiratory failure in the immunocompromised.

Intermediate Evidence of Efficacy

- Postoperative respiratory failure
- Facilitation of weaning
- 'Do not intubate' patient
- Pneumonia
- Asthma
- Restrictive lung disease
- Cystic fibrosis.

Weak Evidence of Efficacy

- Trauma
- Acute respiratory distress syndrome (ARDS)
- Upper airway obstruction
- Obstructive sleep apnoea.

COPD Exacerbation

Patients with COPD are prone to respiratory failure, often resulting in admission to the ICU. Between 20–33% of the patients admitted with hypercapnic respiratory failure due to acute COPD exacerbation will die in the hospital, despite mechanical ventilation [15–19]. Although, traditionally, patients who do not respond to conventional treatment are given invasive ventilation, this procedure is associated with high morbidity. It can also be very difficult to wean these patients from ventilation [20, 21]. Furthermore, complications resulting from the ETI procedure or ventilation (consisting of damage to local tissues, or ventilator-associated pneumonia, respectively) can prolong the length of time in ICU. COPD patients with acute exacerbations represent the

single largest group of patients that have been treated successfully with NIV techniques [3]; and over the past decade the use of NIV in this clinical setting has become widespread. Several authors [18, 22–26] have published enthusiastic reports about the treatment of acute COPD exacerbations with NIV, which has significantly reduced mortality.

In patients with severe COPD, the respiratory muscle pump is often functioning at the point at which it can no longer maintain effective ventilation. There are excessive elastic and resistive loads on it, due to hyperinflation and airway obstruction, respectively. There is also reduced capacity, due to the fact that hyperinflation causes the respiratory muscles to operate at a mechanical disadvantage. In addition, the presence of an intrinsic-positive end-expiratory pressure (PEEPi) results in an inspiratory threshold load. During an acute exacerbation, when the load on the respiratory muscles' pump becomes excessive, effective ventilation cannot be maintained any longer, which results in worsening hypoxaemia, hypercapnia and, most importantly, acidosis. Acidosis is particularly deleterious to muscle function. The respiratory muscles become unable to generate adequate alveolar ventilation despite large pressure swings due to the presence of severe abnormalities in respiratory mechanics (PEEPi and high inspiratory resistances) [26]. Stimulation of the respiratory centres and the large negative intrathoracic pressure swings that are created do not permit compensation for these abnormalities. Rapid shallow breathing ensues, which is associated with carbon dioxide retention and respiratory acidosis, a risk for muscular fatigue. Dyspnoea, right ventricular failure and encephalopathy characterise severe acute exacerbation. The use of NIV in this clinical situation allows the patient to take deeper breaths with less effort. NIV with pressure support and PEEP [27, 28] delivers a positive inspiratory pressure swing in synchrony with patient's inspiratory effort. A low level of PEEP counterbalances the dynamic hyperinflation, which results in a positive residual alveolar pressure at the end of expiration. The combination of inspiratory and expiratory pressure is extremely efficacious in reducing patient effort [29]. NIV has been demonstrated to reverse the clinical abnormalities related to hypoxaemia, hypercapnia and acidosis [26, 30]. A striking finding of the application of NIV in ICU setting [10–13] is a reduction in the need for mechanical ventilation, a reduced complication rate, a reduced length of time in ICU and in the hospital [27] and, most importantly, improved survival. As a result, the literature has recommended that NIV be added to standard medical therapy for patients with acute exacerbations of COPD. It is, of course, essential to monitor such patients closely in a high-dependency unit to evaluate treatment responsiveness and facilitate ETI if NIV fails.

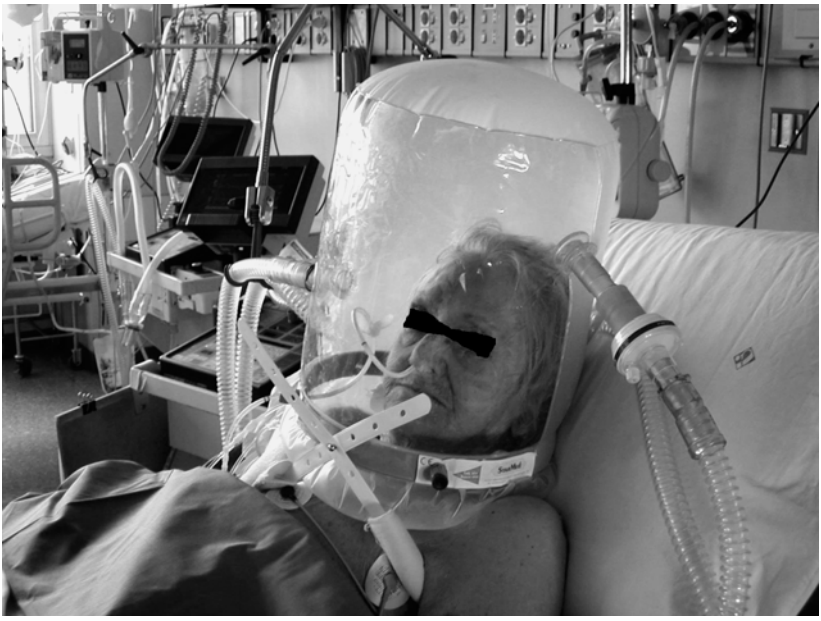

Fig. 2. Non-invasive ventilation delivered by helmet

Cardiogenic Pulmonary Oedema

Acute cardiogenic pulmonary oedema is characterised by elevated pulmonary capillary pressure, due to the presence of acute left ventricular diastolic function [31]. Interstitial and alveolar flooding ensues, decreasing respiratory system compliance and increasing the work of breathing. Muscle fatigue may be a result of increased work of breathing from both reduced lung compliance and increased airway resistance [32–34]. As a result, the inspiratory muscles have to generate large negative swings in pleural pressure, which increases left ventricular transmural pressure and afterload [35, 36]. Bronchospasm or oedema may also increase airflow resistance [37]. Hypoxic and hypercapnic acute respiratory failure frequently ensues. A concomitant reduction in cardiac output compromises oxygen delivery to the respiratory muscles and may create a vicious cycle. Efforts to maintain mean arterial pressure include sympathetic-induced tachycardia and systemic vasoconstriction. Myocardial ischaemia is potentially exacerbated by the increase in left ventricular work, by hypoxaemia and by coronary hypoperfusion. Of clin-

ical importance, respiratory distress in this situation is not directly related to hypoxaemia and, therefore, cannot be reversed with oxygen administration alone [38]. The potential benefits of NIV in acute cardiogenic pulmonary oedema are the reversal of hypoxia [39–42], decrease in flow resistance, reduction in work of breathing, and reduction in left ventricular afterload [35, 43–46]. The reversal of the adverse chronotropic and lusitropic effects of myocardial ischaemia is another potential benefit.

Immunocompromised Patient

Respiratory failure requiring ETI in a patient who is immunocompromised (due to solid organ transplantation or haematological malignancy) is a common complication and generally portends a very poor outcome [47, 48]. There is strong evidence of the efficacy of the use of NIV in these patients when acute respiratory failure, bilateral infiltrates and fever appear. The most significant trials [47, 49, 50] have demonstrated that when patients with hypoxaemic respiratory failure following immunosuppression are treated with NIV, there are increases in PaO_2/FiO_2 ratios, lower ETI rates, lower incidences of severe sepsis and shock, fewer complications and few ICU and hospital deaths, compared to conventionally treated control subjects. Although the mortality rate remained high among NIV-treated patients, the mortality rate of patients with haematological malignancies who require ETI is > 80% in some series [51–57], largely because of septic and haemorrhagic complications. Thus, the avoidance of ETI in this population of patients is a desirable outcome, and the use of NIV is justifiable in selected immunocompromised patients. In this clinical setting, authors universally stress the importance of early initiation of NIV therapy before progression to severe compromise.

Postoperative Respiratory Failure

Abdominal and thoracic surgery are characterised during the postoperative period by significant alterations in lung and respiratory volume. A statistically significant reduction in functional residual capacity, vital capacity, lung compliance, end-expiratory lung volume and an increase in pulmonary elastic recoil have been described [58, 59]. As a consequence, pulmonary collapse increases intra-pulmonary shunt and FiO_2 requirements. The resulting decrease in vital capacity, together with depression of central respiratory drive [58], may result in the retention of bronchial secretions, increased risk of basal parenchymal collapse, nosocomial pneumonia and acute respiratory failure. Some early studies reported the use of NIV in the treatment of respi-

ratory failure after surgery in hypoxaemic, hypercapnic patients or in patients with evidence of respiratory muscle fatigue [60–63]. All of these studies demonstrated that the postoperative application of NIV resulted in a prompt reduction in dyspnoea scores and respiratory complications, improvement in gas exchange and good success in avoiding ETI. Subsequent trials [64, 65] of the use of NIV in post-lung resection patients have also demonstrated significant improvement in gas exchange and pulmonary function, as well as a decreased need for ETI. Thus, there is good clinical evidence in support of the use of NIV for maintaining gas exchange and avoiding intubation in patients who undergo thoracic surgery.

Facilitation of Weaning

Failure of extubation and reintubation are not infrequent clinical problems in the ICU setting. Several uncontrolled trials [66, 67] have reported the clinical benefits of NIV in cases of failure with conventional weaning techniques. The most important controlled trials [68, 69] investigating COPD patients weaned conventionally, versus extubated and ventilated with NIV, showed a significant decrease in the period of mechanical ventilation when using the NIV approach, but data were conflicting and unable to demonstrate significant improvements in other areas. These studies present a mixed picture regarding the use of NIV in shortening the duration of invasive mechanical ventilation. Caution must be exercised when selecting patients for early extubation, reserving the technique mainly for patients with acute exacerbations of COPD who, although unable to meet standard criteria for extubation, are otherwise good candidates for NIV. Only one recent randomised controlled trial [70] has demonstrated that early extubation with NIV in patients with acute or chronic respiratory failure results in shorter mechanical ventilation and ICU/hospital stay, as well as a reduced need for tracheotomy, lower complication rates and improved survival. It remains to be seen whether NIV has a role in other patient groups and situations. In any case, the technique represents a possible addition to the therapeutic armamentarium in a group of patients who pose a significant clinical and economic challenge.

Other Applications

Several reports have described the effects of NIV in patients with acute respiratory failure who refused ETI or were poor candidates for ETI due to advanced age, debilitation (neoplastic terminal disease, chronic pathology) or due to a ‘do not resuscitate order’ [71, 72]. Some authors have argued that NIV

represents a palliative treatment and that there is little to lose with this approach because it may reverse an acute deterioration or at least afford relief from dyspnoea [73]; others have argued that it merely prolongs the process of dying and consumes resources inappropriately [74]. According to reports describing the effects of NIV, however, the overall success rate was about 60–70%, and gas exchange improved rapidly in successfully treated patients.

There are conflicting reports in the literature concerning the results of the use of NIV for the treatment of patients with acute pneumonia. Without doubt, NIV improves oxygenation in patients with diffuse pneumonia, even though they may remain hypoxic despite maximum medical treatment. Some significant studies [75, 76] have shown that, in cases of pneumonia among COPD patients, NIV reduces the need for ETI, decreases ICU length of stay and decreases mortality. In general, it makes sense to try NIV, and, indeed, its use should be routine in cases of community-acquired pneumonia.

Case series, cohort studies or anecdotal reports have reported some success with NIV in a variety of other conditions, such as asthma [77, 78], ARDS [79], trauma [80, 81], cystic fibrosis [82, 83] and restrictive lung disease [84, 85]. Data available in the literature suggest that NIV can be helpful as a rescue therapy in supporting acute respiratory deterioration, and that it may be a reasonable approach in patients who fail to respond promptly to initial standard medical therapy. Caution must be advised, however, due to the fact that acutely distressed patients can deteriorate abruptly, making the delay of ETI a substantial risk.

Conclusions

In conclusion, the success of NIV strategies requires a program that includes the availability of well-trained staff, the careful selection of patients and close patient monitoring. Current evidence supports the use of NIV to reduce the need for ETI and its attendant morbidity and mortality in selected patients with acute respiratory failure. NIV appears best suited to patients with COPD exacerbations, cardiogenic pulmonary oedema and to those who are immunosuppressed and have bilateral infiltrates. Significant evidence is accumulating to support the use of NIV for short-term applications, such as postoperative respiratory failure in patients who have just undergone lung resection, or as a means of facilitating weaning from mechanical ventilation or preventing extubation failure. NIV has also been used successfully in some 'do not resuscitate' patients, where mechanical intubation is therefore not appropriate.

There are some data in the literature that support the use of NIV in treating the numerous causes of respiratory failure resulting in hypoxic respiratory impairment, asthma, pneumonia, initial ARDS and restrictive lung disease. However, because controlled studies in support of these applications are lacking, and there is no strong evidence of clinical efficacy, the use of NIV in these populations cannot be uniformly recommended. Additional selection criteria must be considered, including moderate-to-severe respiratory distress, tachypnoea, accessory muscle use, abdominal paradox breathing, hypercapnia and moderate respiratory acidosis. If NIV is indicated, the presence factors of favouring its successful application must be determined. These include small volume of respiratory secretions, intact dentition, synchronous breathing, good initial response in terms of pH, pCO_2 and respiratory rate, low scores of APACHE II and the ability to protect the airway.

The use of NIV for patients with acute respiratory dysfunction represents a fairly narrow window of opportunity and these patients need to be sick enough for intervention, but not so severely ill as to require rapid ETI. The initial period of treatment (first 6–8 h) is resource-intensive and failure to intubate a patient who does not have a response is associated with increased mortality. The application of NIV is not without peril: adherence to defined selection and exclusion criteria is essential; and a high level of vigilance is required to identify those patients who do not have a significant clinical response. Also, the implementation should take place in an appropriate, monitored setting, usually an emergency department, with the ability to transfer patients to ICU or a step-down unit until stabilisation. To improve patient outcome in a cost-effective manner, NIV must be applied by an experienced, well-trained team using state-of-the-art technology.

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Pulmonary Effects of Acute Normovolaemic Haemodilution

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Introduction

Transfusion therapy risks have been clarified in a consistent literature for decades [1]. Transmission of infectious diseases, transfusion reactions, immunosuppression, transfusion-related acute lung injury and high costs have led to investigations regarding alternatives to allogenic red blood cell transfusion, and physiological effects of lower haemoglobin levels have been developed. Preoperative and intraoperative restrictive red cell transfusion strategies may be used individually or in combination. They include: preoperative autologous blood donation; preoperative use of erythropoietin; acute normovolaemic haemodilution; intraoperative cell salvage and pre-transfusion; pharmacological treatment (aprotinin, ε-aminocaproic acid, tranexamic acid); anaesthesia technique (normothermia, fluid replacement, hyperoxic ventilation, hypotensive anaesthesia); minimal haemoglobin levels; and transfusion algorithms based on coagulation monitoring and artificial O_2 carriers [2]. Acute normovolaemic haemodilution (ANH) has been used in an attempt to decrease the need for allogenic blood transfusion in the course of a variety of surgical procedures [3]. Many controversies exist concerning ANH, such as the target haematocrit, the most appropriate fluid to be used [4], the risks incurred [5], the real benefits [6–8], and how the anaesthetic technique may influence the compensatory mechanisms [9–11]. During haemodilution, a redistribution of cardiac output and oxygen transport occurs in favour of organs with a lower capacity to increase oxygen extraction, i.e. heart and brain. The effects on the cardiovascular and central nervous systems have been extensively studied [10, 12–14]. However, the literature is scarce concerning the pulmonary effects [15–18]. The results are controversial and the investigations frequently are not comparable for the reason that the studies were designed differently with respect to animals chosen, target haematocrit, fluid used, previous lung function, data collected and so on.

How Does Acute Normovolaemic Haemodilution Affect Pulmonary Function?

Compensatory Mechanisms in Anaemia

The major physiologic consequence of lower haemoglobin levels is the reduced oxygen-carrying capacity of the blood. Tissue hypoxia is avoided by several compensatory mechanisms, such as peripheral vascular dilation, increased blood flow, increased extraction of oxygen from the blood and increased cardiac output [19]. Actually, ANH results in reduced heterogeneity of pulmonary blood flow and an improvement in ventilation–perfusion distributions [17]. It is important to note that anaesthesia can influence and even blunt the cardiovascular response associated with acute normovolaemic haemodilution. Most anaesthetic agents decrease myocardial contractility and venous return, and, as a result, may blunt the compensatory increase in cardiac output observed during ANH [11].

Fluid Replacement in ANH and Its Pulmonary Effects

The replacement of blood with large amounts of fluids during ANH may decrease plasma colloid osmotic pressure (COP). The inverse relationship between plasma COP and transendothelial fluid flux is important to the maintenance of fluid balance in the lung, and the value of COP as an oedema protective mechanism has been clarified [20]. As expected on the basis of the Starling equation, hyperoncotic solutions reduce direct fluid flux and lung lymph flow by widening the oncotic pressure gradient in the lungs. In contrast, colloids may influence pulmonary capillary integrity independent of their oncotic effect. Cardiovascular performance impairment is an adverse condition that may emerge during ANH, mostly when large amounts of fluids are infused to reach low target haematocrit. The most appropriate plasma substitute in ANH is still under evaluation. It is important to keep in mind that throughout the ANH procedure, the maintenance of normovolaemic state is mandatory; thus, hypovolaemia episodes should not occur. Accordingly, the ischaemic reperfusion syndrome, as seen during shock and fluid resuscitation, does not take place during ANH, which makes it impossible to interchange the investigation results. Advanced Trauma Life Support (ATLS) guidelines continue to recommend early and aggressive intravenous fluid administration for the presurgical treatment of haemorrhagic shock. However, according to recent studies, the choice of the fluid used may have a significant effect on outcome. Much attention has been given to the physiologic effects of various fluids during full (normotensive) resuscitation in terms of the effects on proxy markers such as neutrophil adhesion molecule

expression, cellular apoptosis, and gene regulation; yet very little is known about the effect of these variables on whole-animal physiology or survivability from haemorrhagic shock. The current expert opinion concerning the state of this body of knowledge is that further research is needed to determine the optimal timing, duration, amount and type of intravenous fluid resuscitation after trauma [21].

Experimental Investigations

In rabbits [15], it has been demonstrated that ANH may improve the gas capability of the normal lung as shown by increased PaO_2 and lowering alveolar arterial oxygen gradient [(a-A)DO_2]. The authors hypothesised that the improvement in arterial oxygenation during isovolaemic anaemia may be explained by regional lung ventilation to perfusion ratio (VA/Q) heterogeneity reduction. Conversely, in an experimental model of acutely compromised lung, ANH resulted in a poorer gas exchange and a lowering arterial PaO_2 [16, 22]. In this situation, the decline in arterial oxygenation during ANH was attributed to an attenuation of hypoxic pulmonary vasoconstriction (HPV). HPV is a protective mechanism that diverts flow from the hypoxic pulmonary areas. During ANH, there is HPV attenuation, probably caused by a decline in nitric oxide (NO) scavengers in the presence of red blood cell reduction. Increased NO concentration at the pulmonary vascular bed may lead to inappropriate vasodilatation, blood flow redistribution and emergence of shunt areas. Deem et al. [17], in an investigation carried out in animals with normal lungs, showed an improvement in oxygen exchange associated with reduced ventilation/perfusion heterogeneity. Conversely, the same authors [22] demonstrated that atelectasis provoked by selective bronchial intubation in rabbits caused impairment in arterial oxygenation during ANH. However, contrary to all these results, Deem et al. [18] reported that ANH improved oxygen exchange in rabbits with lung injury induced by gas embolism, but they did not find a clear mechanism for this improvement.

Clinical Investigations

More recently, Szegedi et al. [14] showed impairment in gas exchange in chronic obstructive pulmonary disease (COPD) patients who were undergoing one-lung ventilation and had previously undergone mild ANH. The same effect was not observed in patients with normal lung function. There is a suspicion that in chronic injured lungs the nitric oxide mechanism involved in gas exchange amelioration during ANH may be compromised.

Experimental Setting in Our Lab

As cited above, there are many controversies regarding ANH. Our group has been studying haemodilution in experimental settings, and the ANH lung effects are one of the points addressed. The group developed an experiment to compare the pulmonary effects of ANH with those of hydroxyethyl starch and lactated Ringer's. Twenty-five pigs were randomised in Control group (n = 8), HES group (hydroxyethyl starch, n = 7) and LR group (lactated Ringer's, n = 10). Animals in groups HES and LR were submitted to ANH to reach a pre-established haematocrit around 15%. Blood was simultaneously withdrawn, and plasma expansion performed either with hydroxyethyl starch (1:1) or lactated Ringer's (3:1). Pulmonary mechanics and oxygen transport were measured before blood was withdrawn [T0], at the end of haemodilution [T1], and one and two hours after the end of the haemodilution [T2, T3]. Lung biopsies were then performed. Data were submitted for analysis of variance for repeated measures followed by the Tukey test. In regard to all parameters, there were no significant differences in the control group during the whole procedure. The LR group demonstrated a decrease in compliance and an increased in (a-A)DO_2. Hystopathological lung analysis revealed moderate-to-serious collapses, as well as basement membrane enlargement. The HES data were similar to those found in the control group. These results suggest that in severe ANH, HES preserves pulmonary structure and seems to interfere less with pulmonary mechanics and oxygenation indexes, compared with lactated Ringer's.

Conclusions

In summary, in terms of both experimental and clinical investigations, there is wide-range agreement in the literature that ANH results in gas exchange improvement in animals or patients with previous normal lung function. However, ANH can be deleterious for the patient with previously altered pulmonary function. The mechanism involved is still under investigation, but there is strong evidence that anaemia leads to reduced blood flow heterogeneity through the lungs. This is probably due to decreased blood viscosity and the attenuation of HPV. Blunting HPV turns out to be deleterious in the presence of altered lung function, probably because HPV is the major protective mechanism that diverts blood flow from nonventilated or hypoxic lung areas. The most appropriate fluid to use is also under evaluation.

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Microcirculation During Low Flow States

G. Ristagno, W. Tang, Y.-T. Chang, M.H. Weil

Microcirculation represents the ultimate determinant of the outcomes of circulatory shock states. Microcirculatory function is the prerequisite for adequate tissue oxygenation and therefore organ function. It transports oxygen and nutrients to tissue cells, ensures adequate immunological function, and, during disease, delivers therapeutic drugs to target cells. It consists of the smallest blood vessels: arterioles, capillaries and venules [1] (Fig. 1). Previous techniques for studying microcirculation (microscopes, laser Doppler and plethysmography) were able to provide only global measurements of microvascular blood flow, expressed as average values of the diameter or direction of a single vessel. Recent technological developments using orthogonal polarisation spectral (OPS) imaging techniques allow the direct visualisation and monitoring of microcirculation at the bedside [2, 3] (Fig. 2). The OPS imaging technology is a non-invasive method for directly visualising multiple conditions of the microcirculation that have clinical applications for humans. It allows the quantitative measurement of the diameter of vessels, the velocity of red blood cells and functional capillary density [4]. The technique uses a linearly polarised light to illuminate the area of interest. The light is reflected from the tissue source and forms an image of the illuminated region within the target of the video camera. The image is then captured through a polariser, which is oriented orthogonally to the plane of the illuminating light [5]. This polarisation analyser allows only depolarised photons scattered within the tissue to pass the optical probe and generate the image [6]. This optical filtration eliminates the light reflected at the surface of the tissue to produce high-contrast reflected images of the microcirculation. Red blood cells appear dark and white blood cells and platelets are sometimes visible as refringent bodies. The wavelength is chosen within the haemoglobin absorption spectrum, and both oxy- and deoxy-haemoglobin absorb equally. The vessels are visible only if they contain red blood cells. Several studies in various tissues and under a variety of conditions in both animals and humans have been per-

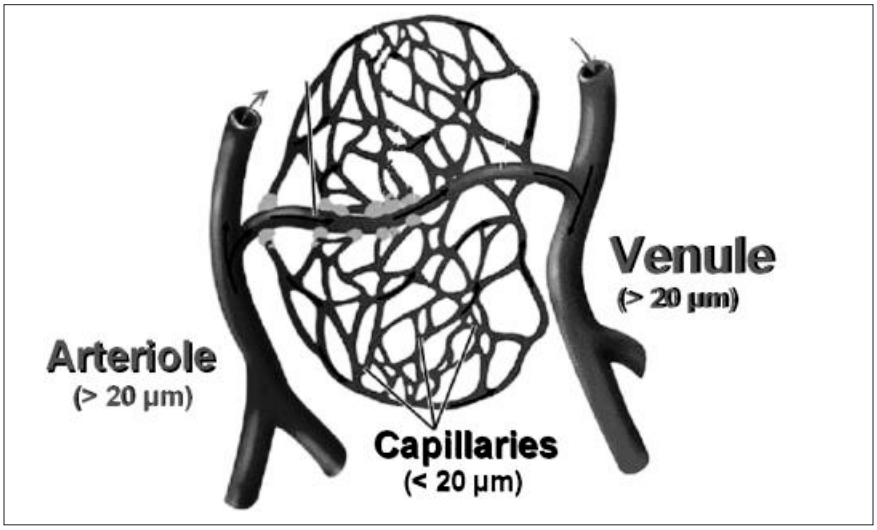

Fig. 1. Anatomy of microcirculation

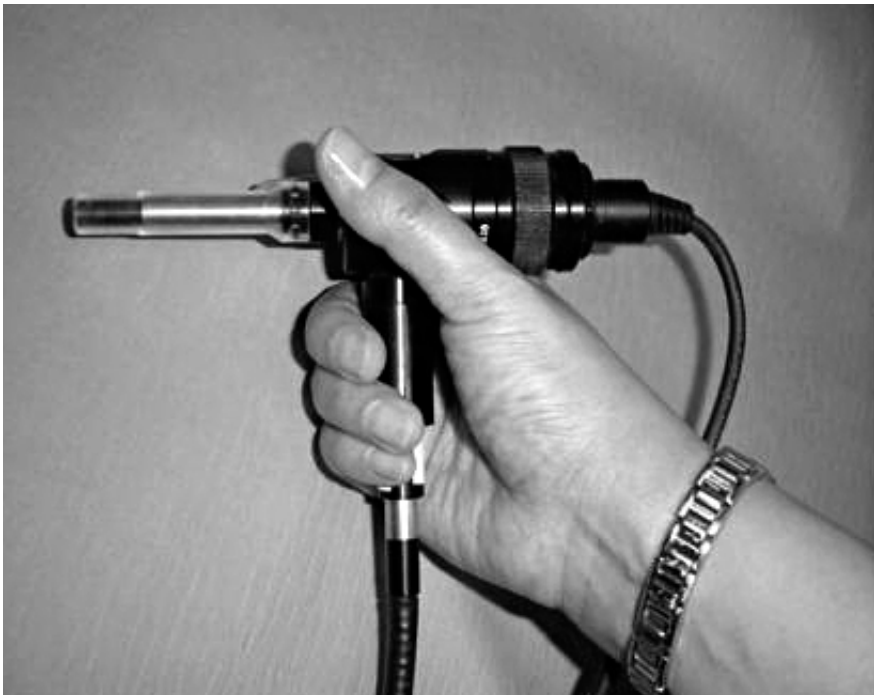

Fig. 2. Orthogonal polarisation spectral imaging camera: CYTOSCAN A/R (Cytometrics Inc., Philadelphia, PA)

formed, especially during shock [7, 8]. Recent investigations in patients with chronic cardiovascular diseases [9], as well as acute cardiocirculatory failure due to septic and cardiogenic shock, have demonstrated characteristic alterations in microcirculatory blood flow – alterations that are largely independent of the macrocirculation [10–12] – including a decrease in vessel density and an increase in the proportion of nonperfused or intermittently perfused capillaries. Flow in vessels < 20 μm has been shown to significantly decrease during septic shock, while perfusion in vessels > 20 μm is well preserved. In settings of sepsis, multiple organ failure commonly occurs, even after restoration of a stable haemodynamic state; and this appears to be related to direct impairment of cellular function or cytopathic hypoxia and/or redistribution of blood flow between and within organs at the microcirculatory level [11].

Methods previously utilised by our Institute to monitor circulatory failure were focused on the measurement of tissue carbon dioxide tension (PCO_2), identified as a universal indicator of impaired perfusion [13, 14]. Acute circulatory failure with decreased oxygen delivery to the tissues is reflected in anaerobic acid production. This excess of hydrogen ions is buffered by tissue bicarbonate and decarboxylation of metabolic intermediates resulting in increases in tissue PCO_2 [15]. We previously demonstrated a close correlation between gastric and oesophageal wall PCO_2 [16], and subsequently we established that sublingual fossa mucosa and buccal mucosa are sites that provide measurements of tissue PCO_2 comparable to those of both the stomach and oesophageal wall. Decreases in organ blood flow are highly correlated with increases in sublingual mucosal and buccal PCO_2 [16–21].

In a recent study in a rat model of sepsis and septic shock conducted by our group, we investigated simultaneous changes in gastric and buccal tissue PCO_2 and microcirculatory blood flow [22]. Sepsis was induced by ligation of cecum in its distal tract and subsequently punctured to allow the feces to be expressed into the abdominal cavity. Tissue PCO_2 was continuously measured with the aid of a miniature CO_2 electrode. Using OPS imaging, recordings of the microcirculation were taken at baseline and hourly intervals until death and compared with sham operated animals. We observed that tissue PCO_2 and blood flow in vessels smaller than 20 μm, representing predominantly capillaries, were highly correlated ($p < 0.01$). Gastric and buccal tissue PCO_2 values progressively increased after cecal ligation and puncture and terminated in death. There was an early and progressive decrease in microcirculatory blood flow in vessels smaller than 20 μm (approximately 30% at 4 h prior to death, and more than 80% 1 h prior to death), whereas blood flow in vessels larger than 20 μm was well preserved during progression of sepsis. No significant abnormalities were observed in sham control animals. This study added to the evidence that microvascular abnormalities ultimately account for the fatal course of sepsis and septic shock.

In settings of cardiac arrest and CPR, changes in macrocirculatory haemodynamics and gas exchange – especially coronary perfusion pressure (CPP) and end-tidal CO_2 – have been extensively investigated as predictors of outcome in the restoration of cardiac function [23–27]. Yet the microcirculation has had little exploration. This prompted our group to investigate changes in the microcirculation accompanying this most severe form of circulatory failure and the effects of cardiopulmonary resuscitation (CPR) [28]. In nine pigs we induced 5 min of untreated ventricular fibrillation (VF) prior to beginning closed chest cardiac compression and attempting electrical defibrillation. OPS imaging was utilised for visualisation of the sublingual microcirculation at baseline, during VF and CPR and after return of spontaneous circulation (ROSC). We observed that microvascular blood flow was highly correlated to coronary perfusion pressure during CPR ($r = 0.82$; $p < 0.01$), and that, as is the case with CCP, the magnitude of microcirculatory blood flow was indicative of the effectiveness of the resuscitation intervention and outcome. Microcirculatory blood flow decreased to less than one fourth within 0.5 min after inducing VF. In animals that were resuscitated, microvascular flow was significantly greater after 1 and 5 min of chest compression than in animals that failed resuscitation attempts ($p < 0.05$ and $p < 0.01$ respectively). After ROSC, microcirculatory blood flow returned to within 20% of baseline values within 5 min.

Recently, our attention has focused on investigating the effects of epinephrine on microcirculatory blood flow. We studied the actions of this vasopressor agent on sublingual tissue flow in a porcine model of cardiac arrest and resuscitation. In pigs that were treated with epinephrine, microcirculatory flow was significantly reduced, compared with untreated animals. These effects were present for at least five min and persisted even when ROSC was achieved (Fig. 3).

Cerebral Microcirculation

Our attention is currently focused on cerebral microcirculation and on studying its changes during cardiac arrest and CPR [29]. We performed a craniotomy on four domestic male pigs and created a window over both left and right fronto-parietal surfaces of the cortex to allow for OPS imaging (CYTOSCAN A/R, Cytometrics Inc., Philadelphia, PA) in order to record the cerebral blood flow through the surface cerebral vessels at baseline and during VF, CPR and after ROSC. Velocity of blood flow was graded from 0 (i.e. no flow) to 3 (normal velocity) on pial and penetrating vessels < 20 μm. After 3 min of untreated VF, animals were mechanically ventilated and precordial compression (PC) was performed for 4 min prior to defibrillation. Cerebral microcirculatory

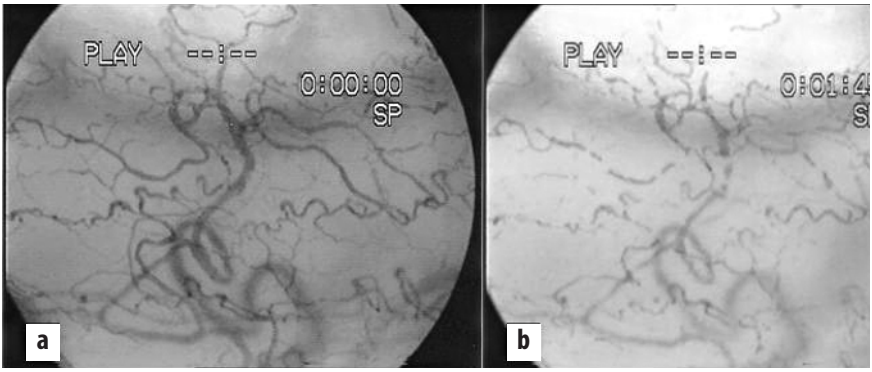

Fig. 3. Sublingual microcirculation during CPR: **(a)** before administration of epinephrine; **(b)** 1 min and 45 sec after administration of 1 mg of epinephrine

blood flow was continuously recorded. We observed that microcirculatory blood flow velocity starts to decrease, but continues during the first min of cardiac arrest ($p < 0.01$ vs BL), then is promptly (although only partially) restored by chest compression. Following ROSC, we confirmed a rapid restoration of cerebral microcirculatory blood flow to normal levels (Fig. 4).

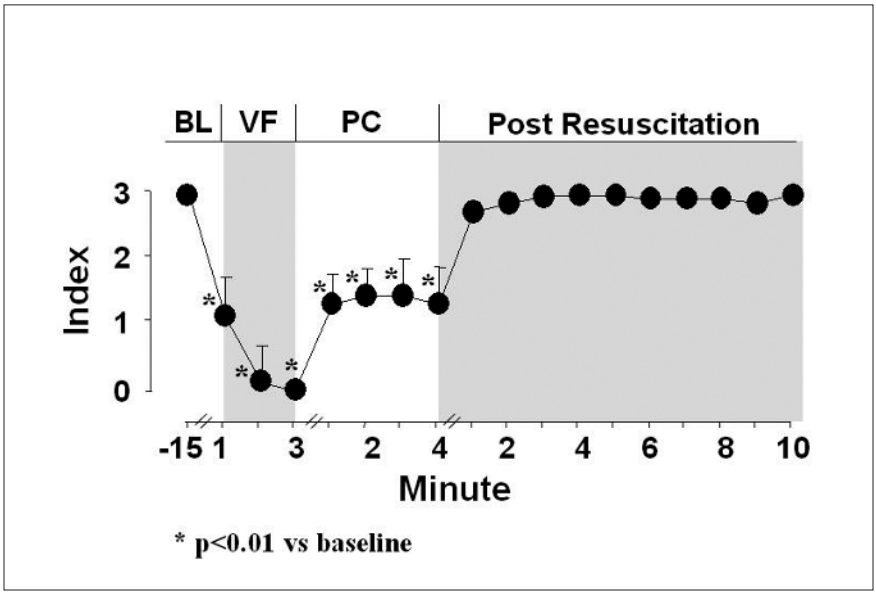

Fig. 4. Cerebral microcirculatory blood flow velocity at baseline and during ventricular fibrillation, chest compression and post-resuscitation. *BL*, baseline; *VF*, ventricular fibrillation; *PC*, precordial compression. * $p < 0.01$ vs BL

We are also examining cerebral microcirculatory blood flow in consequence of the administration of vasopressor agents, especially epinephrine, which has been the preferred adrenergic amine for the treatment of human cardiac arrest for almost 40 years [30–34]. In settings of cardiac arrest, re-establishing vital organ perfusion plays an important role in initial CPR. As a pharmacological intervention, 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 [35]. Pharmacological responses to adrenergic agents are mediated by a group of receptors classified as alpha (including $alpha_1$ and $alpha_2$) and beta (including $beta_1$, $beta_2$, and $beta_3$) [36, 37]. Primary efficacy of epinephrine in settings of CPR is due to its $alpha_1$, and $alpha_2$ adrenergic effects. This contrasts with its beta-adrenergic actions, which are inotropic, chronotropic and vasodilator. Accordingly, beta-adrenergic actions prompt increases in myocardial oxygen consumption, ectopic ventricular arrhythmias and transient hypoxaemia, due to pulmonary arteriovenous shunting. We previously demonstrated that a beta-adrenergic blocking agent, when administered during CPR, significantly improved initial cardiac resuscitation, minimised post-resuscitation myocardial dysfunction and increased the duration of postresuscitation survival [38, 39]. Both $alpha_1$- and $alpha_2$-adrenergic agonists increase peripheral vascular resistance and, therefore, myocardial and cerebral perfusion pressure and blood flows. $Alpha_1$-adrenergic receptors, which, like beta-receptors, mediate increase in both inotropic and chronotropic responses, also augment myocardial oxygen requirements and, thereby, increase the severity of global ischaemic injury [40]. When $alpha_1$-adrenergic receptors are blocked, by either a selective or non-selective alpha-adrenergic blocker, myocardial function is significantly improved after acute myocardial infarction [41]. We have shown that combining $alpha_1$- and beta-adrenergic blockade (the equivalent of selective $alpha_2$- vasopressor agonists) results in better post-resuscitation cardiac and neurological recovery [35]. In addition, $alpha_1$-adrenergic agonists may constrict coronary arteries, resulting in a reduction in myocardial function. Three subtypes of $alpha_2$ receptors are recognised, namely $alpha_{2A}$, $alpha_{2B}$ and $alpha_{2C}$ [37, 42]. $Alpha_{2A}$ plays a tonic sympatho-inhibitory function in the medulla, which results in a reduction in arterial blood pressure, myocardial contractility and heart rate. This contrasts with its peripheral vasoconstrictor effects [43]. $Alpha_{2B}$-subtype receptors, which are less abundant in brain tissue, elicit a peripheral vasoconstrictor response [44, 45]. A third $alpha_{2C}$ receptor, like $alpha_{2A}$ receptors, has predominant central nervous system effects, including stress response and locomotion but no cardiovascular action [43]. As a result, $alpha_2$-adrenoreceptor agonists have centrally acting vasodilator effects and peripherally acting vasoconstrictor effects. These selective $alpha_2$ agonists are as effective as epinephrine for initial cardiac

resuscitation but do not increase myocardial oxygen consumption and, therefore, result in strikingly better post-resuscitation myocardial function and survival [46–48]. In addition, alpha$_2$-adrenergic agonists increase endothelial nitric oxide production and, therefore, counterbalance the alpha$_2$-adrenergic vasoconstrictor effects in coronary arteries [49].

Our study, performed in an established porcine model of cardiac arrest and resuscitation, is based on 3 min of VF and 4 min of chest compression and ventilation (with a compression/ventilation ratio of 15/2) before attempting defibrillation. Our preliminary results were obtained from six domestic male pigs, weighing 40 ± 2 kg, in which we performed a craniotomy and created a window over the fronto-parietal surface of the cortex to allow for OPS imaging (CYTOSCAN A/R, Cytometrics Inc., Philadelphia, PA) in order to record cerebral blood flow through the surface cerebral vessels. Velocity of blood flow was graded from 0 (no flow) to 3 (normal velocity) on the pial and penetrating vessels < 20 μm, representing predominantly capillaries. Before we induced cardiac arrest, the animals were randomised to receive epinephrine (30 μg/kg) or saline placebo over 10 sec intervals beginning 1 min after the onset of CPR. The results were consistent with those previously obtained in the sublingual mucosa vasculature. The cortical microcirculatory blood flow was significantly reduced in pigs treated with epinephrine, compared with the saline placebo group. These effects appeared 3 min after the injection of epinephrine ($p < 0.05$) and persisted for 5 min after resuscitation ($p < 0.01$) (Figs. 5, 6).

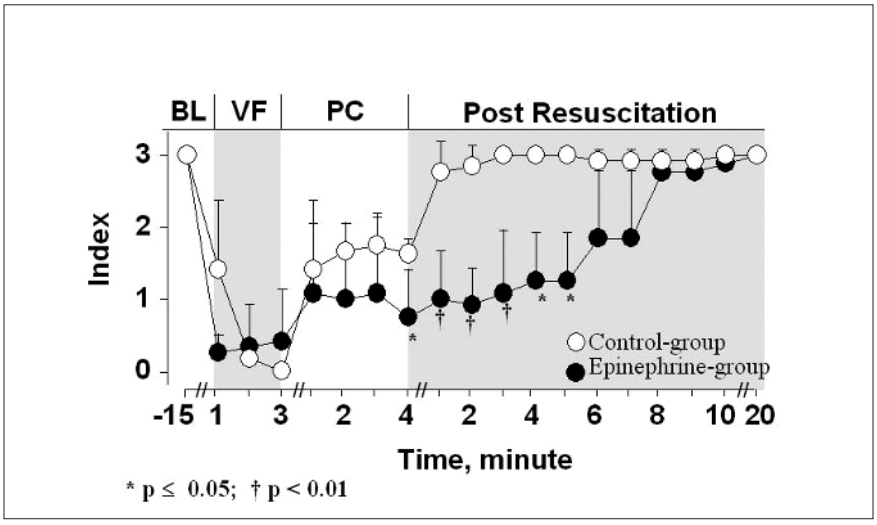

Fig. 5. Cerebral microcirculatory blood flow velocity at baseline and during ventricular fibrillation, chest compression and post-resuscitation. *BL*, baseline; *VF*, ventricular fibrillation; *PC*, precordial compression. * $p < 0.05$; † $p < 0.01$ vs saline placebo group

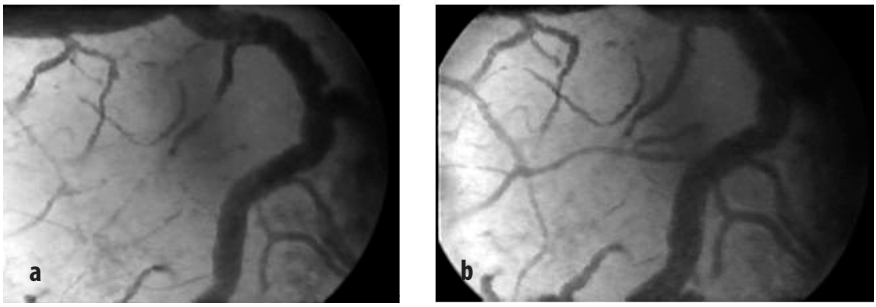

Fig. 6. Cerebral microcirculation in pigs treated with epinephrine during CPR: (**a**) 1 min after resuscitation, and (**b**) 6 min later

Although this is only a preliminary study, and additional studies are required, the results are very interesting and open new and important questions in settings of cardiopulmonary and cerebral resuscitation.

With the aid of the OPS imaging and the tissue gas sensor, we also observed that the condition of hypercarbia, produced by inducing hypoventilation in anaesthetised and mechanically ventilated pigs, causes an increase in cerebral microcirculatory blood flow and, therefore, in oxygen delivery to the brain. The microvasculature was significantly increased after 30 min of hypoventilation ($p < 0.01$ vs baseline). The cerebral tissue PCO_2 increased significantly after 5 minutes of hypoventilation ($p = 0.05$); the cerebral PO_2, instead of decreasing, showed a small increase. The present study provides anatomical confirmation of auto-regulation. For, although previous studies showing an increase in cerebral large-vessel blood flow induced by hypercarbia also showed a striking increase in microcirculatory blood flow, they demonstrated effect on cerebral oxygen tension (Fig. 7).

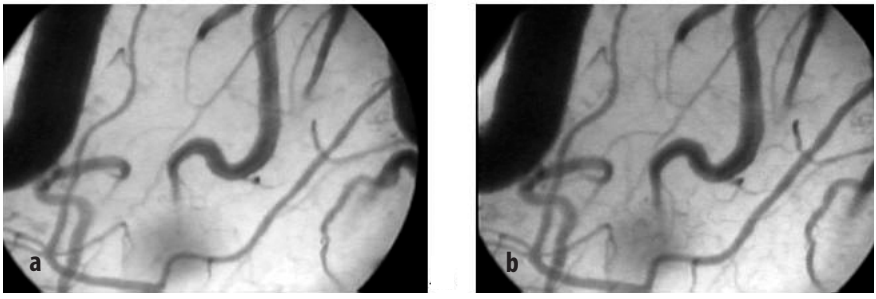

Fig. 7. Cerebral blood flow: (**a**) baseline; (**b**) 30 min of hypercarbia

In the setting of CPR, it is important to give more emphasis to the cerebral aspect. Cerebral recovery depends on numerous factors related to the arrest and CPR durations, as well as to the efficacy of the basic, advanced and prolonged life support [50]. There are still many gaps in our knowledge about optimising support for better outcomes in cerebral function, and more studies and trials are needed. We believe that the implementation of the OPS technique for the direct monitoring of organ perfusion, particularly brain perfusion, represents an exciting new development for ongoing research, one that will allow great advances, particularly in the area of resuscitation.

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The Effects of Gasping During Cardiac Arrest and Cardiopulmonary Resuscitation

Y.-T. Chang, W. Tang, G. Ristagno, M.H. Weil

Introduction

Gasping, observed commonly at the beginning and at the end of life [1–5], is a striking phenomenon characterised by fast and forceful inspirations. Gasping is especially prominent in the human newborn. In 1812, Legallois [6] described gasping in a variety of animal species and also in human patients. The Glossary Committee of the International Union of Physiologic Sciences defined a gasp as 'an abrupt, sudden transient inspiratory effort' [7].

When triggered by hypoxia, as in settings of cardiac arrest, gasping persists until the respiration centre located in the caudal portion of the medulla oblongata is disabled. This phenomenon was first demonstrated by Lumsden [8, 9] over 80 years ago. Many patients can continue breathing irregularly for several minutes after cardiac arrest. Emergency medical dispatchers offer cardiopulmonary resuscitation instruction to only a small fraction of callers in settings of suspected cardiac arrest. Agonal breathing is often confused with life-supporting respiration. The incidence of suspected agonal breathing is estimated to occur in approximately 30% of cardiac arrest patients, who, as a result, are often denied respiratory support. Agonal breathing presents as difficult or impaired breathing, gasping, occasional breathing or wheezing. Patients with a combination of unconsciousness and agonal breathing should be offered dispatcher-assisted cardiopulmonary resuscitation. This might improve survival in out-of-hospital cardiac arrest [10].

The presence of agonal breathing and gasping improves ventilation during untreated cardiac arrest, and the frequency of gasping is also predictive of the success of cardiac resuscitation. Studies demonstrate a survival rate of 27% among those with agonal breathing, compared with 9% among those without [11]. In the cardiac arrest setting, the simultaneous and persistent absence of ventricular fibrillation, gasping and light-reactive pupils was strongly associated with a poor outcome [12].

Neurophysiological Mechanisms of Gasping

In 1923, Thomas Lumsden [8, 9] systematically investigated the respiratory centre (Fig. 1) of the brain. By repeated rostrocaudal transection of the cat brain stem, Lumsden identified specific neuronal groups that determine unique breathing patterns.

A eupnoeic respiratory rhythm was preserved until the level of midpons was transected from the brain stem. This transection eliminated the inhibition of a rostral pontine 'pneumotaxic centre,' causing a breathing pattern 'apnoeusis' characterised by prolonged inspiration. Transection at the junction of the pons and medulla disabled the neurons in the lateral tegmental brain stem and caused a 'gasping' respiratory pattern. Table 1 compares the biological characteristics of eupnoeic ventilation and gasping [13–16].

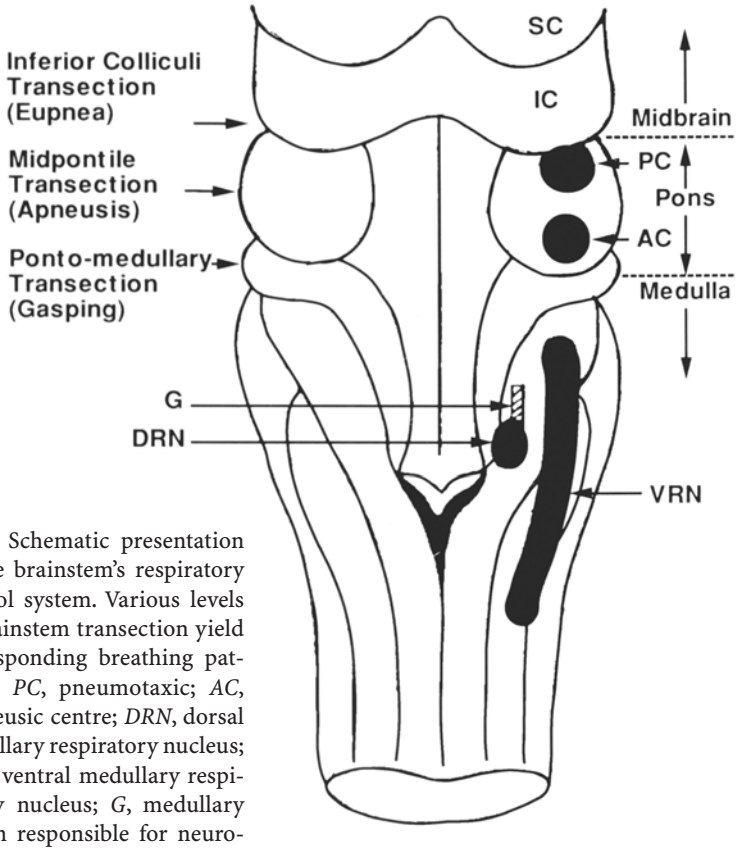

Fig. 1. Schematic presentation of the brainstem's respiratory control system. Various levels of brainstem transection yield corresponding breathing patterns. *PC*, pneumotaxic; *AC*, apnoeusic centre; *DRN*, dorsal medullary respiratory nucleus; *VRN*, ventral medullary respiratory nucleus; *G*, medullary region responsible for neurogenesis of gasping; *SC*, superior colliculus; *IC*, inferior colliculus

Table 1. Biological characteristics of eupnoeic ventilation and gasping

	Brainstem locus	Activation of inspiration	Muscle response	Ventilatory pattern
Eupnoea	Pontine penumotaxic centre, dorsal medullary nucleus, and ventral medullary nucleus	Sequential intercostal	Diaphragmatic,	Regular, rhythmic
Gasping	Lateral tegmental region	Mass discharge	Diaphragmatic, intercostal, accessory	Irregular crescendo-decrescendo

Lumsden subsequently demonstrated that asphyxia or progressive anoxia in the intact animal produced respiratory patterns similar to the patterns followed by rostrocaudal brainstem transection. Gasping emerged only after dysfunction of the pontine pneumotaxic centre and the caudal pontile 'apnoeustic centre.' With recovery of oxygen delivery by effective ventilation and oxygenation, or by reperfusion of blood flow to the brain stem, the sequence was reversed so that gasping was converted to apnoeusis and apnoeusis to eupnoea [8].

Eupnoea is generated by mechanisms within the pons and medulla. Following removal of pons or exposure to anoxia, gasping is elicited. Eupnoea and gasping are markedly different ventilatory patterns. The genesis of gasping is dependent upon rostral medullary neuronal activities. To generate the gasp, these activities should commence before the phrenic burst. In decerebrate, vagotomised, paralysed and ventilated cats, eupnoea was altered to gasping in anoxia. Rostral medullary neuronal activities had inspiratory, expiratory and phase-spanning patterns in eupnoea. During gasping, some inspiratory neuronal activities commenced before the phrenic gasp; these same neurons had commenced activities after the onset of the eupnoeic phrenic burst. Expiratory and phase-spanning neurons did not charge. Neuronal activities that play a role in the neurogenesis of gasping had very different discharge patterns in eupnoea. Results support the concept that medullary mechanisms for gasping are incorporated in the ponto-medullary circuit responsible for the neurogenesis and expression of eupnoea [17].

Effects of Gasping on Pulmonary Gas Exchange During Cardiac Arrest

Gasping promotes the entry of air into the lungs, thereby securing greater oxygen and CO_2 exchange. Studies have demonstrated that, during experimental cardiac arrest, spontaneous gasping alone augments pulmonary gas exchange [18] and improves the outcome of cardiopulmonary resuscitation [19]. Spontaneous gasping began within 1 min after the onset of ventricular fibrillation cardiac arrest induced electrically in domestic pigs. During precordial compression in the absence of positive pressure ventilation, gasping significantly increased minute volumes [20]. In the pig model of cardiac arrest, tidal volume generated by gasping was > 800 mL [18]. In the rodent cardiac arrest cardiopulmonary resuscitation model, oxygen was delivered to a hood that was loosely applied over the head of each animal at a flow rate of 1 L/min. Animals in which the airway had been protected by an oropharyngeal airway had a greater frequency of spontaneous gasping (28 ± 13/min vs 13 ± 9/min; $p < 0.05$) and significantly higher arterial oxygen saturation (77 ± 19% vs 55 ± 5%; $p < 0.05$) (Fig. 2) [21]. The frequency of spontaneous gasping in the absence of mechanical ventilation is predictive of cardiac resuscitation and associated with improved arterial oxygenation and CO_2 removal

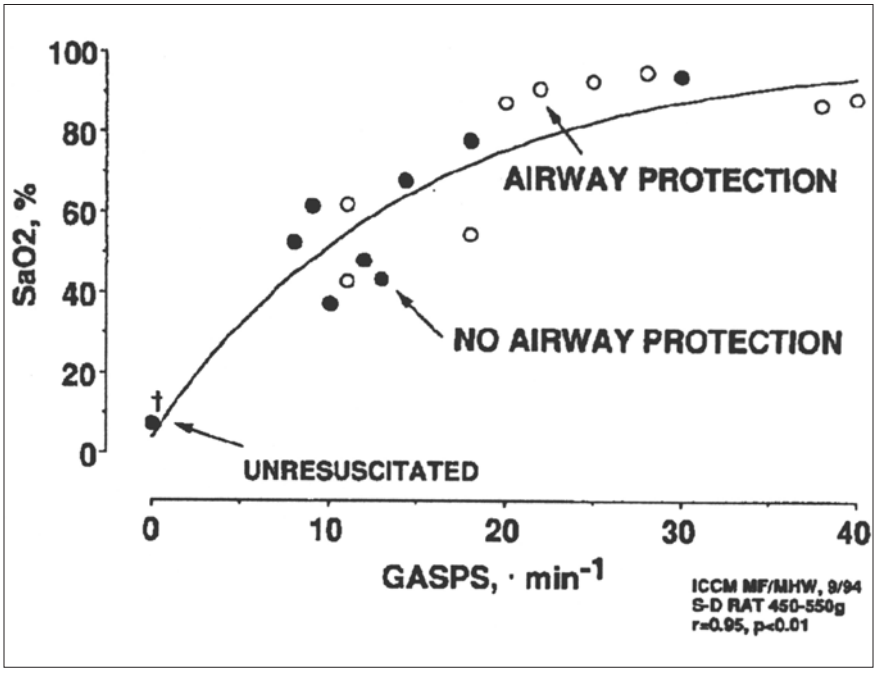

Fig. 2. Relationship between frequency of spontaneous gasping and SaO_2 prior to attempted defibrillation. $Y=100-96.1e^{-0.069X}$

[22]. Guntheroth and Kawabori [23] induced apnoea in dogs by occluding the airway or by reducing the FiO_2 to < 0.06. At the onset of apnoea, the airway was reopened. Apnoea persisted for 1–3 mins and was terminated with spontaneous gasping. Gasping increased the PaO_2 from < 5 torr (0.67 kPa) to > 30 torr (4 kPa), provided that effective circulation was maintained. Jacobi et al. [24–26] induced apnoea in mice by ventilating animals with a mixture of 97% nitrogen and 3% CO_2. Apnoea was followed by spontaneous gasping, which occurred after ~20 secs. A progressive decrease in gasp volume and abbreviation of the time interval between the first and the last gasp prognosticated a fatal course. When the FiO_2 was increased to 0.5, gasps were terminated within 30 secs, and spontaneous ventilation returned.

Our studies [27–29] related spontaneous gasping to pulmonary gas exchange and the ability to resuscitate the heart in a rodent model of cardiac arrest. After 4 mins of untreated ventricular fibrillation, precordial compression was initiated. There was no mechanical ventilation during cardiac arrest, but 100% oxygen was supplied at the port of the tracheal tube. The frequency of gasping was significantly greater ($p < 0.05$) in resuscitated animals. Sudden increase in arterial oxygen saturation and a decrease in arterial carbon dioxide tension typically followed the gasp [20, 23, 28]. More frequent gasping was associated with greater PaO_2 and lower $PaCO_2$ values. Spontaneous gasping accounted for improved capability to resuscitate, in addition to better gas exchange [30].

Effects of Gasping on Venous Return and Forward Blood Flow

During cardiac arrest in studies with both pigs and rats, spontaneous gasping is associated with both pulmonary and haemodynamic effects that aid gas exchange and promote circulation [20, 30, 31]. In a rodent model of cardiac arrest in which ten healthy Sprague–Dawley rats were mechanically ventilated, gasping typically began 1 min after induction of ventricular fibrillation [27]. Forceful contraction of inspiratory muscles during gasping decreased the intraoesophageal pressure from ~4 ± 2 to -10 ± 4 mmHg. This striking decrease in the intrathoracic pressure was associated with decreases in right atrial pressure from 8 ± 1 to 0 ± 4 mmHg. Accordingly, gasping generated a pressure gradient between the peripheral veins and the right atrium that favours venous return to the heart and thereby augments cardiac preload. During the expiration phase of gasping, an increase in intrathoracic pressure to ~10 ± 3 mmHg was associated with a 7 ± 4 mmHg increase in the aortic pressure. The resulting increase of 8 ± 4 mmHg in the pressure gradient between the aorta and right atrium favoured coronary perfusion [30].

At the onset of inspiratory gasping during untreated ventricular fibrilla-

tion, pressures in the ascending aorta and right atrium were both decreased. But the right atrium pressure exceeded the aorta pressure by an average of 6 mmHg, favouring blood flow from the right to the left heart. During the expiratory phases of gasping, the increase in aortic pressure exceeded that of the right atrial pressure and therefore accounted for increases in the coronary perfusion pressure (CPP) [30].

Our studies confirmed that preterminal gasping during ventricular fibrillation increases both ventilation and forward blood flow. We investigated a pig cardiac arrest model with ventricular fibrillation induced electrically and found that the stroke volume produced by gasping averaged 23 ± 6 mL, which represented approximately 60% of a precardiac arrest stroke volume (38 ± 8 mL, $p < 0.001$). Increases in end-tidal carbon dioxide tension coincident with each gasp were consistent with comparable increases in pulmonary blood flow and therefore stroke volumes (Fig. 3). Both were associated with increases in aortic pressure from 20 ± 3 to 33 ± 8 mmHg ($p < 0.001$) and CPP from 4 ± 3 to 13 ± 7 mmHg ($p < 0.001$). Gasps are also associated with substantial increases in $PetCO_2$. Both $PetCO_2$ and CPP were previously shown to be predictive of outcomes of cardiopulmonary resuscitation. Therefore, gasping – because it generates both respiratory gas exchange and favoured blood flow – is predictive of improved outcomes of cardiopulmonary resuscitation [31–34]. The haemodynamic effects of gasping in the pig model during untreated ventricular fibrillation are shown in Fig. 4. Both the frequency and the duration of gasping were significantly greater in resuscitated animals [30].

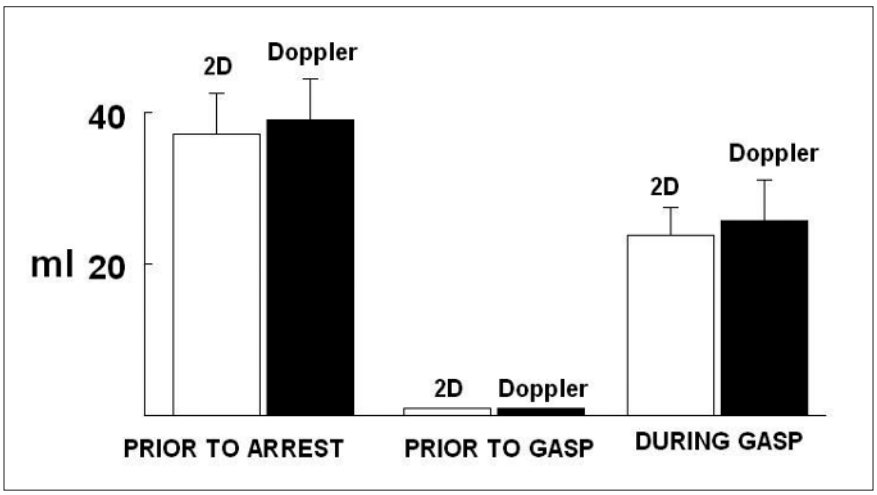

Fig. 3. Stroke volumes measured across the aortic valve compared with stroke volumes derived from the difference in ventricular volumes before the onset of cardiac arrest, before gasp and during gasping

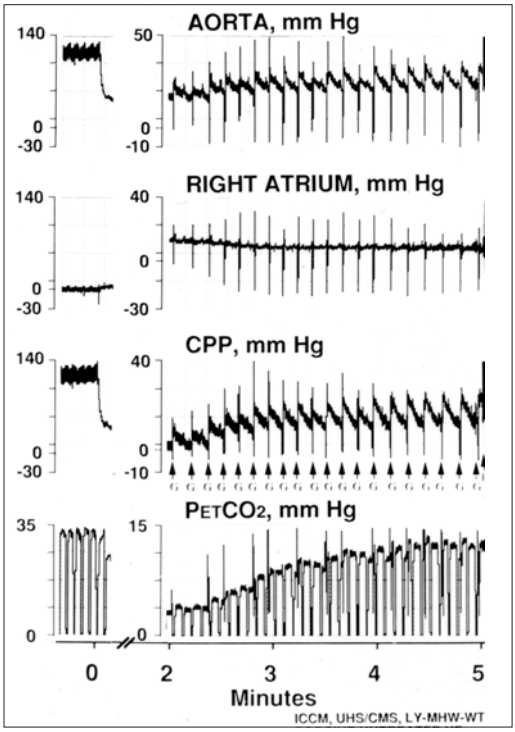

Fig. 4 A representative recording of spontaneous gasping during untreated ventricular fibrillation in pig and its effect on coronary perfusion pressure (*CPP*), end-tidal PCO_2 ($P_{ET}CO_2$). Aortic and right atrial pressures are also shown

Gasping Increases Cerebral Blood Flow During Cardiac Arrest

Previous studies demonstrated that coincident with gasping during cardiac arrest there is a prominent increase in stroke volumes in the absence of chest compression. In Bircher's study [35], sudden onset of ventricular fibrillation induced electrically during apnoea in a dog model resulted in cessation of arterial blood flow in 11 ± 3 sec and an isoelectric EEG in 26 ± 5 sec. The decay of vital parameters was delayed further when spontaneous gasping via tracheal tube against an artificial glottal closure augments airway pressure fluctuations; pulselessness occurred at 52 ± 28 sec and EEG silence at 66 ± 27 sec. Self-induced fluctuations of intrathoracic pressure generated sufficient blood flow to briefly but statistically significantly ($p < 0.001$) prolong EEG activity, compared with apnoeic controls (Fig. 5).

During our study on an established model of Sprague–Dawley rats, end-tidal carbon dioxide tension ($EtCO_2$) was continuously recorded, with the aid of an endotracheal tube and a capnometer. We performed a left craniectomy and created a window over the parieto-temporal surface of the cortex to allow for orthogonal polarisation spectral imaging (CYTOSCAN A/R, Cytometrics

Inc., Philadelphia, PA) in order to record cerebral blood flow through the surface cerebral vessels. Velocity of the blood flow was graded from 0 (no flow) to 3 (normal velocity) on the pial and penetrating vessels < 20 μm. Sudden increases in $EtCO_2$ signalled the onset and the magnitude of each gasp as previously described. Coincident with each gasp, both cerebral microcirculatory blood flow velocity and duration of flow demonstrated a strong correlation with corresponding increases in $EtCO_2$ (Fig. 6). The increases in cerebral microcirculatory blood flow velocity and duration of flow were also closely related to the magnitude of the gasp. Spontaneous gasping therefore produces not only ventilation and cardiac output but also striking increases in cerebral microcirculatory blood flow [36].

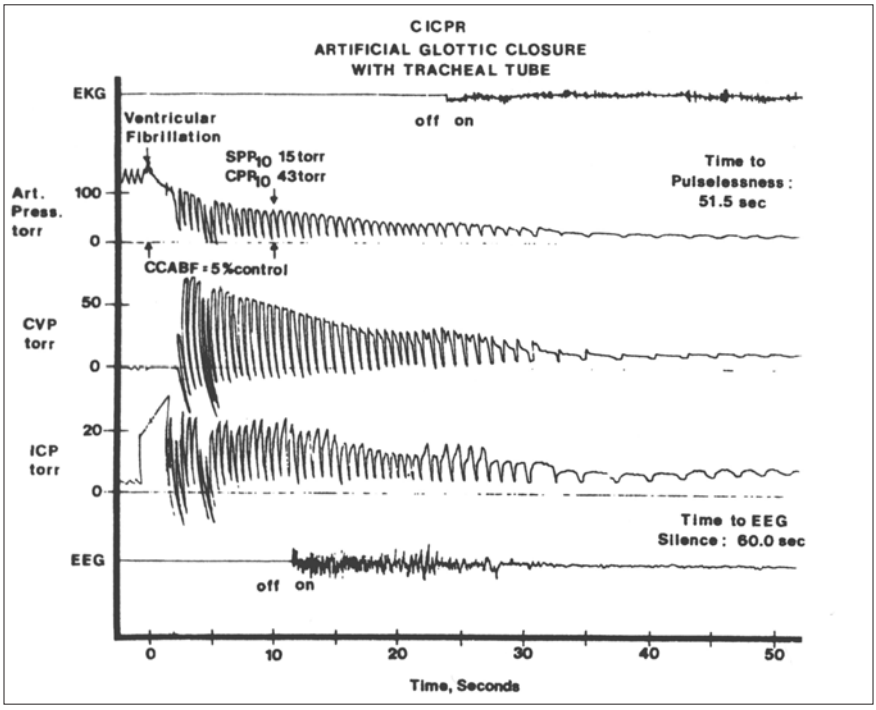

Fig. 5. Artificial cough-induced cardiopulmonary resuscitation (*CICPR*) in 1 dog. The dog was lightly anesthesised, breathing spontaneously with tracheal tube. Electrically induced ventricular fibrillation caused gasping which when augmented by artificial glottic closure (see text) sustained minimal cerebral perfusion and EEG activity for 60 sec. The ECG and EEG were briefly disconnected to protect them from the fibrillating voltage. *CCABF*, common carotid artery blood flows

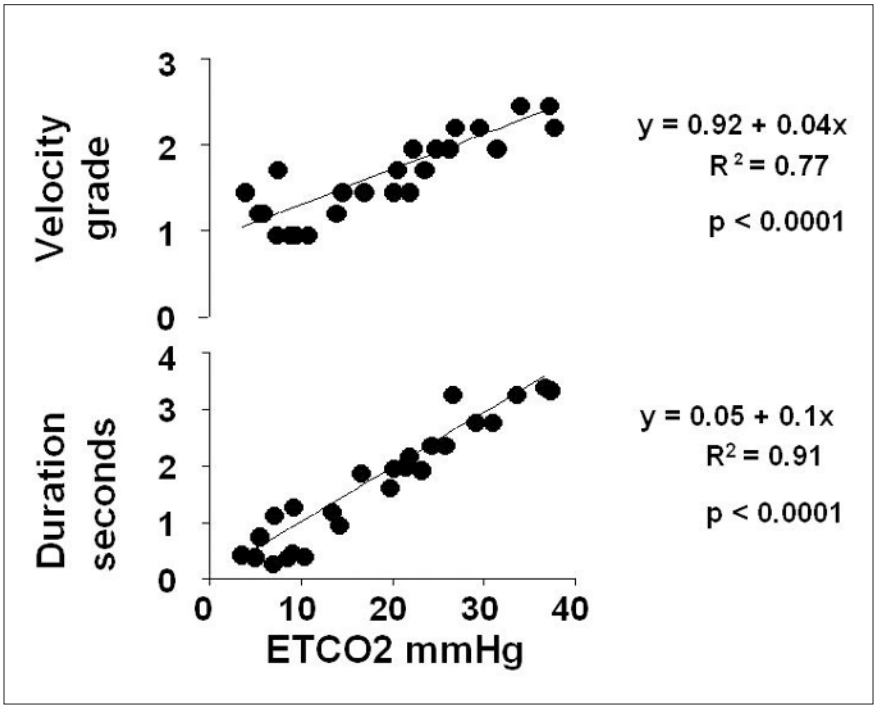

Fig. 6. Relationship between velocity and duration of cerebral microcirculatory blood flow and $ETCO_2$ during gasping in a rodent cardiac arrest model

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Perioperative Risk Assessment and Decision Making

A. Bacher, M. Zimpfer

The administration of anaesthesia is an extremely safe procedure today. Data published by the American Society of Anesthesiology tell us that the risk of anaesthesia-related death has decreased 25-fold since 1970, from 1 in 10 000 to 1 in 250 000. In the USA, this risk reduction has closely followed a second trend, namely, a doubling of the number of working anaesthesiologists. All this has occurred during a time when the youngest of premature infants in neonatal units survives intricate, lifesaving procedures and 100-year-old patients undergo and recover from major surgeries that were once thought to be impossible. Today, safety in anaesthesia is comparable to safety in aviation, i.e. the risk of an aviation accident per departure is 0.96 in 1 000 000 for scheduled passenger operations (about 145 million departures during the last 10 years) and 2.64 in 1 000 000 for other operations (charter, cargo, demonstration, etc – about 25 million departures during the last ten years) [1]. Considering the greater number of deaths involved in a passenger aircraft crash, undergoing anaesthesia is actually safer than flying!

How can safety in anaesthesia be kept as high as it is, or even improved? Apart from the above mentioned greater expertise of personnel performing anaesthesia, the development of useful monitoring techniques, and proper risk assessment, particularly before more difficult procedures in elderly patients and in patients suffering from diverse concomitant disease, may help to maintain a high safety standard even in high risk surgery.

The present article focuses on risk assessment in predominant risk populations of patients undergoing anaesthesia, and it explores possibilities for reducing anaesthesia-related mortality and complications in these high-risk populations.

Anaesthesia in the Elderly

The overall anaesthesia and surgery-related mortality rate within the 30 days following an operation is 1.2%, compared to approximately 6% in patients over 80 years [2, 3]. Clearly, age > 70-75 years is an independent factor predicting the incidence of death or myocardial infarction [4]. The risk of respiratory failure has been found to be 1.5 times higher in patients > 60 years, and 1.9 times higher in patients > 70 years [5]. One of the factors that make anaesthesia more risky in elderly patients is age-related co-morbidity, particularly with respect to the central nervous system, heart, ventilatory system and kidneys. The majority of patients over the age of 70 years have some degree of cerebral atrophy [6]. Drugs acting on the central nervous system, such as levodopa, bromocriptine, and the tricyclic antidepressive drugs, may interact with anaesthetics, causing changes in the pharmacokinetics. Hypotension may occur as a result of orthostatic dysregulation that is enforced during anaesthesia [7]. Benzodiazepines may act stronger and longer in elderly patients, thereby causing deep sedation and respiratory depression [8]. Ageing further affects cardiac function by stiffening large arteries, increasing vascular resistance and decreasing cardiac compliance [9]. These risk factors result in an increased rate of perioperative myocardial ischaemic events [4]. Similarly, pulmonary function may be disturbed by emphysema or respiratory muscle weakness, leading to a higher rate of postoperative respiratory failure, and a reduction in the glomerular filtration rate may lead to perioperative kidney dysfunction [10].

The question arises whether the anaesthesiologist can actively reduce perioperative risk in the elderly patient cohort by a specific anaesthesia management. Perhaps the primary decision that has to be made is whether general or regional anaesthesia should be applied. Two studies in patients undergoing either major general surgery or orthopaedic surgery did not allow the conclusion that regional anaesthesia was superior with regard to neurologic impairment [11, 12]. In contrast, the type of surgery has a major influence on the incidence of postoperative cognitive dysfunction, with orthopaedic and cardiac surgery showing the highest incidence (Fig. 1) [13]. Other measures have proved to be more successful in reducing the risk of postoperative cognitive dysfunction in elderly patients. Early surgery, oxygen administration, prevention of blood pressure drops, and immediate treatment of postoperative complications were able to reduce the rate of acute confusional states from 61.3% to 47.6%, and the hospital stay from 17.4 to 11.6 days [14].

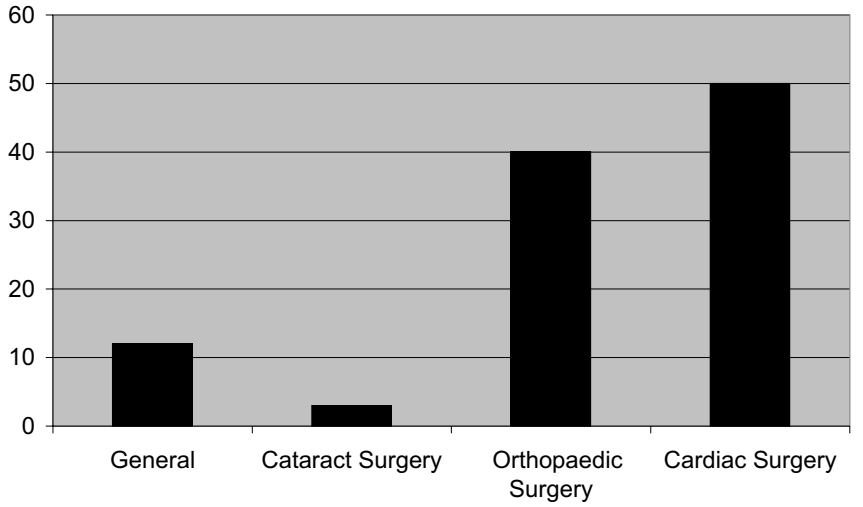

Fig. 1. Rates of postoperative cognitive dysfunction and type of surgery (adapted from [13])

Anaesthesia in Cardiac Risk Patients

The assessment of cardiac risk in anaesthesia was the subject of several early studies in the field of anesthesiology. Lee Goldman, a resident at the Massachusetts General Hospital, prospectively investigated 1001 patients over 40 years of age and identified several risk factors that independently predicted cardiac complications or mortality after surgery [15]. Among anaesthesiologists, the results of this well established study is known as the Goldman Cardiac Risk Index. Several weaknesses of this study were later addressed, such as the fact that only 18 patients in the study population had a 'high risk' index, and the fact that the sensitivity and specifity are only approximately 60%. As a result, several more studies were performed to improve the accuracy with which cardiac risk can be predicted [4, 16]. It was found that only five to six factors correlate well with cardiac complication rates or mortality in the perioperative period. In one study, these included age > 70 years, diabetes mellitus, anamnesis of myocardial infarction, angina pectoris and congestive heart failure. In another study, they included anamnesis of coronary heart disease, high-risk surgery, serum kreatinin > 2mg/dL, diabetes mellitus,

anamnesis of TIA or stroke and congestive heart failure [4, 17]. The presence of more than three risk factors was associated with a complication rate of 18% and 11%, respectively, in these two studies [4, 17]. Regardless of the fact that clinical markers are what allow us to estimate cardiac risk quite accurately, the question arises whether further cardiac diagnosis should be performed before elective surgery. A study in 878 patients revealed an algorithm to determine the status of the coronary arteries from anamnesis and clinical and laboratory findings [16]. Figure 2 shows how coronary artery disease may be predicted or excluded based on these markers [16].

Other tests for determining cardiac risk, such as stress echocardiography, bicycle ergometry or thallium scintigraphy, have been shown to have a relatively high sensitivity (80–90%), but a rather low specifity (around 70%) [18–20]. An exact diagnosis of coronary artery disease still requires coronary artery angiography. The main question that arises from all prognostic markers of cardiac risk is whether any measures can be taken to reduce this risk before the patient is scheduled for an elective surgical procedure. Today, standard treatment regimens for coronary artery disease are β-blockade, coronary angioplasty or stent implantation and coronary artery bypass graft. In several studies, β-blockade has proved to be useful in preventing perioperative ischaemic events and in reducing mortality, even in cases where relative contraindications to this therapy existed (chronic obstructive pulmonary disease, diabetes mellitus and peripheral artery occlusive disease) [18, 21–23].

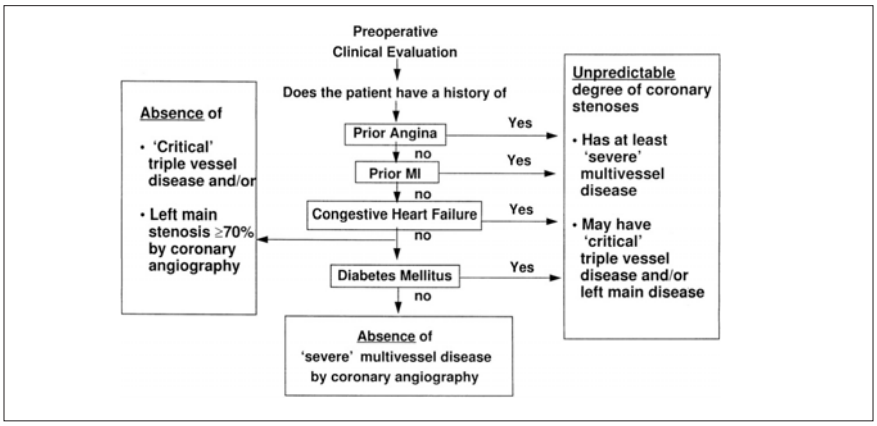

Fig. 2. For excluding critical three-vessel disease and/or left main stenosis 70%, the clinical history must exclude the first three markers. The presence of any one of these three markers makes the coronary angiogram unpredictable. For excluding severe multivessel disease, all four markers must be excluded. The presence of any of the four markers indicates a strong likelihood of severe coronary disease (adapted from [16])

For coronary artery bypass grafting, the risk reduction has only been proved for subsequent major surgery, not for other types of surgery [24]. Preoperative coronary angioplasty did not seem to be an efficient measure for reducing perioperative cardiac risk in noncardiac surgery [25]. The American Heart Association's guidelines for evaluating perioperative cardiac risk and adequate decision-making are depicted in Fig. 3.

Pulmonary Risk Factors in Anaesthesia

The assessment of pulmonary risk factors prior to surgical procedures may be performed with spirometric lung function data in combination with physical performance, blood gas analyses and pulmonary anamnesis [10, 26, 27]. Lung function may be disturbed by several mechanisms as a result of any surgery, not just pulmonary surgery:

a) Endotracheal intubation, as well as some drugs, may lead to bronchoconstriction and lack of secretion clearance.
b) Anaesthetics and analgesic drugs may alter the postoperative respiratory response of the central nervous system.
c) Residing neuromuscular blockade may reduce the force of respiratory muscles.
d) Atelectasis formation may occur.

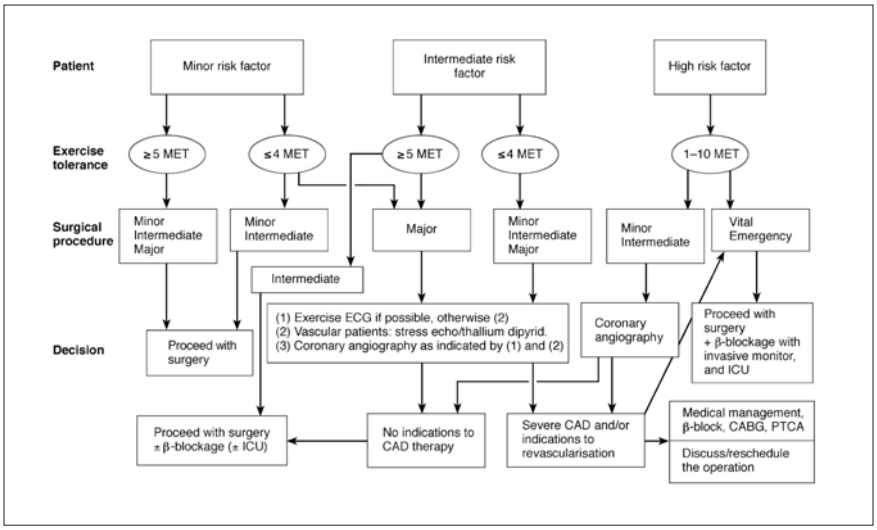

Fig. 3. The American Heart Association's guidelines for perioperative cardiac risk evaluation and decision-making

e) Surgical trauma to the chest, as well as to the abdominal wall, may lead to postoperative respiratory muscular malfunction.

In all cases, postoperative pneumonia or postoperative respiratory failure – and the accompanying need for prolonged mechanical ventilation – may worsen the surgical outcome and increase preoperative mortality. A recently published retrospective analysis of 100 patients undergoing lung tumour resection who presented with a forced expiratory volume in one second < 35%, revealed that one patient died within 30 days, one had to be put on a mechanical respirator, and three patients required mechanical ventilation and endotracheal intubation for > 48 h [27]. Additional complications included four patients with pneumonia, one patient with myocardial infarction, and eleven patients who became oxygen dependent [27]. In patients with severe chronic obstructive pulmonary disease scheduled for lung volume reduction surgery, it has been shown that preoperative dynamic intrinsic positive end-expiratory pressure was closely correlated with the postoperative benefit, as measured by postoperative dyspnoea scores and the relative improvement (40% increase from baseline value) in forced expiratory volume in one second [26]. A preoperative dynamic intrinsic positive end-expiratory pressure > 5 cm H_2O had a sensitivity of 93% and a specifity of 88% for predicting improvement following lung volume reduction surgery [26]. Forced expiratory volume in one second is an easily measurable variable that can be used for predicting pulmonary risk in pulmonary, as well as non-pulmonary, surgery [28-31]. For pneumonectomy, a cut-off value of forced expiratory volume in one second of 2 l has been found to be associated with a low perioperative risk [31]. An algorithm based on a preoperative current hypersecretion of mucus, an increase in residual volume, and a low percentage of predicted values – with respect to both forced expiratory volume in one second and transfer factor of the lung for carbon monoxide – was extremely sensitive (84%), specific (99%) and accurate (95%) for preoperative prediction of severe respiratory complications after upper abdominal surgery [28].

To avoid perioperative risk, the use of combined general and regional anaesthesia has proven very effective [32]. Apart from other factors, a pneumonia and respiratory risk reduction by 39%, and 59%, respectively, have been found in a meta-analysis that included 141 trials in 9559 patients (Fig. 4) [32].

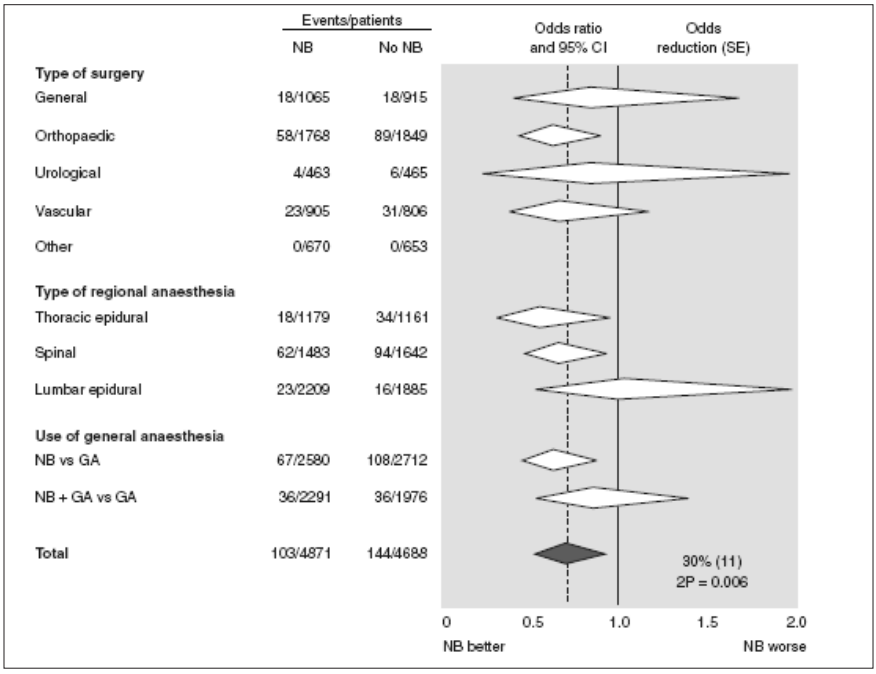

Fig. 4. Effect of neuraxial blockade (NB) on postoperative mortality by surgical group, type of NB and use of general anaesthesia (GA). Diamonds denote 95% confidence intervals for odd ratios of combined trial results. The vertical dashed line represents the overall pooled result. *c*2 test for heterogeneity between different surgical groups $p = 0.9$ (adapted from [32])

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Anaesthesia and Sedation Outside the Operating Room

J. Rupreht, J. Hofland, K. Leendertse-Verloop

Surgical theatres or operating rooms (ORs) have been changing continuously in order to enable further development of surgical procedures or to comply with the demands of anaesthesiological performance. Specialised theatres designed for particular anaesthesia and surgery now exist. The demand for anaesthesia, however, has increased and broadened. Today an anaesthesiologist must also provide safe services outside the OR, under conditions much more demanding than the classical OR [1, 2]. Anaesthesia outside the OR has developed from a facilitation of diagnostic and therapeutic procedures into an independent subspecialty. Specially trained and dedicated anaesthesia teams enable the performance of ever more invasive procedures in remote locations, and they must be able to tackle the constraints of space, technical incompatibilities in terms of machinery, dangers from irradiation, unusual logistics with respect to patient transport, and so on.

Most authors who write about anaesthesia and sedation outside the OR do so in reference to a hospital setting, and do not discuss problems of anaesthetic support during the transportation of patients, in the battle-field or in underdeveloped countries [3]. In this overview, anaesthesia outside of the general hospital will not be discussed. Exception will be made for the anaesthesiological service of the office-based dentistry and dental surgery, with an emphasis on anaesthesia in dentistry for the disabled [4].

Most textbooks of anaesthesiology contain adequate chapters on anaesthesia outside of the OR, but still within the hospital. Sedation or sedation with analgesia is usually not dealt with extensively and is often left to other medical professionals. Consequently, the practice of sedation remains a no man's territory where anaesthesiologists must maintain educational efforts and offer support to non-anaesthetists. The practice of sedation in dentistry, where it is mandatory to keep protective reflexes well functioning, is exemplary. An excellent monograph by Malamed about sedation in dentistry is available [5].

Variety of Locations for Anaesthesia Outside the OR

Diagnostic and therapeutic non-surgical procedures requiring an anaesthetist's services take place in diverse and adverse areas of a hospital with common denominators of difficulties that one does not expect within the operating and recovery room complex. The need to change sedation into general anaesthesia is always present but unpredictable and requires mature clinical judgement.

Extracorporeal shock wave lithotripsy (ESWL) and electroconvulsive treatment (ECT) are well known anaesthesiological activities outside the OR. Specific requirements apply to radiology, radiotherapy medicine, CTS or magnetic resonance imaging (MRI). Cardiologists may need anaesthesiological support for cardioversions. Endoscopic procedures all too seldom involve anaesthesiologists, although quite high mortality rates have been reported for these diagnostic activities [6]. At several surgical centres, considerably complicated procedures are performed in the intensive care unit and the anaesthesiologist may be confronted with difficulties besides the lack of space. It is advisable to treat surgical problems in the operating theatres whenever possible, and this applies in particular to procedures involving the airways and those where haemorrhage is a major risk. In intensive care medicine, the diversity of opinion as to whether the anaesthesiologist should be involved in the decision-making process is well illustrated.

Drugs for Sedation and Anaesthesia Outside the OR

In experienced hands, the choice of drugs is much less important than the knowledge of how to use them. Nevertheless, short-acting drugs and those with low solubility in the body mass are preferable. They enable quick changes in the level of sedation, and the procedure can be ended at any moment. As a rule, such drugs have a very narrow margin of safety, and a skilled professional must steer their effect to a safe end. Remifentanyl, midazolam, propofol and sevoflurane are examples of excellent drugs for sedation and analgesia, provided an experienced anaesthetist is administering them. All too often, however, midazolam is used by professionals who cannot treat an overdose promptly and adequately. There is an enormous variability in individual response, which demands not only the utmost care in titration, but also professional monitoring by experienced anaesthesia personnel [7]. Propofol is possibly an even better drug for sedation, but, at the same time, probably even more dangerous. Most non-anaesthesiologists do not use it for sedation now, as it has become quite clear that administration of propofol requires the undivided attention of an anaesthesiologist [8]. Nitrous oxide

(N_2O) has been a cornerstone for sedation and analgesia in dental practice, in delivery rooms and during transportation of some patients in pain. Although there is no good substitute for N_2O in these medical fields, the gas has come under unfair scrutiny by many anaesthesiologists and work hygienists. Perfectly safe self-administration is a remarkable feature of the patented mixture Entonox (British Oxygen Corporation; $N_2O:O_2$ = 1:1). Some volatile drugs may not be used in areas with insufficient ventilation and the pollution with other gases must be regularly monitored during procedures.

Principles of Safety During Non-OR Sedation or Anaesthesia

Most anaesthesiological societies have issued guidelines for the practice of safe sedation by non-anaesthetists. The British guidelines for sedation [9] were issued in 1993, the Americans approved their guidelines [10] in 1995 (latest update 2001) and the Dutch followed in 1999 [11]. The Dutch booklet, called the 'National consensus for sedation,' has become a respected standard of care for non-anaesthetists involved in sedation and analgesia. Its guidelines help non-anaesthetists safeguard against the over-application of treatment, resulting in anaesthesia. These guidelines provide useful definitions for anxiolysis, analgesia, sedation and amnesia, and they propose a scoring system for sedation. Nearly twenty medical societies have worked on the joint guidelines for sedation in the Netherlands. The process was initiated and coordinated by anaesthesiologists. The recommended standards for personnel, equipment, monitoring and selection of patients have resulted in much safer practice of sedation by non-anaesthetists. The chapter on inhalation-sedation in dentistry for the handicapped and phobic patients is particularly interesting.

Procedural Safety for Sedation or Anaesthesia Outside the OR

Each practitioner of sedation should write protocols and update them regularly. Continuous venous access must be established. Monitoring of patient response to verbal commands should be routine, except in patients who are unable to respond appropriately, or during procedures where movement could be detrimental. During procedures where a verbal response is not possible, the ability to give a 'thumbs up' should be considered. Continuous monitoring must include pulse oximetry, ECG and blood pressure. Monitoring exhaled CO_2 should be considered for all patients receiving deep sedation, as well as for patients whose ventilation cannot be directly observed during moderate sedation. Resuscitation equipment, including a defibrillator, must be available and

functioning. The anaesthesia machine used must meet the same standards as in a normal OR. Special equipment must be purchased if necessary, an example being a magnetic resonance imaging-compatible apparatus. It is recommended that an individual with advanced life support skills be immediately available (within 5 min) for moderate sedation and in the procedure room for deep sedation. In case of a mishap, further intensive care treatment must be feasible. At all times suction and oxygen must be available. All standard resuscitation drugs, the required anaesthesia agents and common antagonist drugs must be in the space of non-OR anaesthesia activity. A reasonably easy transportation to the recovery room must be possible. Preferably, an anaesthesia team member should transfer the patient to the recovery. Following sedation/analgesia, patients should be observed in an appropriately staffed and equipped area until they are near their baseline level of consciousness and no longer at risk for cardio-respiratory depression or aspiration. Education and updates on knowledge about sedation are good safeguards against the unsafe practice of sedation outside the OR. Possibly the most important lesson involves how to select eligible patients for safe sedation, and when to involve the anaesthesiologist during sedation planning.

Anaesthesiologists involved in sedation and anaesthesia outside the OR are usually senior professionals with special interest in procedures requiring their presence. Such individuals can cope better with unexpected adversities requiring a change from sedation to anaesthesia or the prompt initiation of resuscitation. They usually can better instruct the personnel who are less familiar with anaesthetised patients and associated problems. All necessary equipment for sedation, anaesthesia or resuscitation should be in working order and checked before and after each working session. Updating protocols should be the foremost activity of senior medical officers performing anaesthesia outside the OR. In the long term, attention to quality control pays off by enabling practioners to prevent or correct potential pitfalls [12]. Opinions differ regarding how safe sedation and anaesthesia outside the OR can be. Although it is thought that an anaesthesiologist guarantees the same degree of safety as in the OR [13], the patients, procedures and aftercare are not comparable. As noted above, it is probable that a non-anaesthesia professional can safely provide sedation to a patient who remains conscious, provided the person administering the sedation is not operating on the patient at the same time [10, 14]. As it is impossible for anaesthesiologists to administer all the sedations that are required, it is critical that non-anaesthetists understand that sedation should not result in a loss of consciousness, and that, at the level of conscious sedation, the patient is capable of responding when addressed [15]. It is highly questionable whether general anaesthesia outside the OR could ever be equally safe as in an area where there are several anaesthesiologists and surgeons present.

Some Common Problems Related to Anaesthesia Outside the OR

Besides the restraints in space and the unfamiliarity of the location, there is difficulty in meeting OR-safety standards outside the OR [15]. Fluid overload may result from hypertonic contrast media, and allergic or anaphylactic reactions should be anticipated, prevented or promptly treated. Hypothermia of patients, closely related to morbidity after surgery [16], is also a problem outside the OR [17, 18], as is the possible lack of a recovery facility. Cardiovascular reactions to electroconvulsive treatment in psychiatric patients remain a considerable difficulty during anaesthesia for this treatment, and they are probably related more to the patient's condition than to the outside-OR location. The logistics outside the OR require a capable anaesthesiologist-organizer, due to the fact that providing anaesthesia in a non-OR setting involves many surprises. There are few data on morbidity and mortality associated with anaesthesia in non-OR settings [19], but it appears that the choice of anaesthetic or sedation technique is probably not associated with the outcome [20].

Inadequate ventilation in some non-OR settings may preclude use of N_2O for sedation, even though this agent has repeatedly been found to be the most suitable agent for procedural sedation in children [21] or, for example, in urology, where it has been suggested to be the analgesic of choice for prostate biopsy [22]. Nitrous oxide is excellent in well-indicated settings, and in one study, only two out of 150 children who received N_2O became nauseated and vomited [23].

Some Remarks on Sedation and Sedation-Analgesia Performed by Non-Anaesthetists

The demand for sedation or sedation combined with analgesia has been steadily increasing within and outside of the hospital, and there is no practical, logistic or economic way to have an anaesthesiologist present under all circumstances. Therefore, doctors who have had no surgical or anaesthesiological training should be trained in the basic aspects of safe sedation, selection of the appropriate patients and after-care. They should be educated about the minimally required monitoring apparatus and how to use it. All such medical practitioners should be discouraged from acting as operator and 'sedationist' simultaneously. The undivided attention for sedation and controlling a patient's vital signs should be the responsibility of an adequately trained assistant.

Anaesthesiologists should share responsibilities to educate and train other medical professionals to practice sedation safely and efficiently. In

some places, anaesthesiologists object to the use of nitrous oxide by dentists, which is a rather outmoded point of view. The use of nitrous oxide sedation in dentistry is an excellent example of a situation in which non-anaesthetists can be trained to use specific sedation-analgesic techniques safely.

In the Netherlands, an official diploma exists for dentists who receive special training in N_2O sedation [15]. In some Scandinavian countries and in the United Kingdom, dentists learn nitrous oxide sedation during the normal curriculum. As the general medical development of a country advances, the curriculum for students of dentistry should include reliable education in safe sedation and analgesia. This would make the practices they employ safe, provided that they are taught when – and when not – to proceed without an anaesthetist. Other medical professionals, as well, should be taught to safe sedation procedures. The Dutch Quality Institute of Health issued Guidelines for sedation and sedation–analgesia by non-anaesthesiologists [11]. Since these guidelines were issued in 1999, the practice of sedation in the Netherlands by non-anaesthetists, not unexpectedly, seems to have improved.

Anaesthesia in the Non-Hospital Setting

Many health procedures can be safely performed outside of hospitals; of these, however, many still require sedation or anaesthesia. Dental procedures for extremely phobic or handicapped patients are an example, but there are also pregnancy-termination clinics and office-based environments where surgical activities take place. Administering anaesthesia away from a general hospital can be done, of course, but expert and senior professionals should patiently develop the specialist approach, write protocols, determine the patient-selection and educate other non-anaesthesia team members in how to provide competent and reliable help. Surgery at locations away from a hospital may have many advantages, but it also demands high predictability in the administration of the anaesthesia. In Dutch dental practice, only anaesthesiologists are permitted to administer and titrate intravenous agents, either for sedation or general anaesthesia. Special attention should be paid to the social background of patients in order to guarantee proper after-care following discharge. It must be possible to hospitalise a patient in a nearby hospital in the event of an untoward course of events [2]. A trend away from office-based anaesthesia for dentistry is being seen in the United Kingdom. The reason is that non-anaesthetists do not provide the same standard of care as professional anaesthetists. As a result, more dental healthcare requiring anaesthesia is being performed in British hospitals on day-care basis.

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Anaesthesia for Endovascular Repair of Abdominal and Descending Thoracic Aortic Aneurysm

B. Drenger

Aortic aneurysm surgery is a formidable burden for every patient, as it carries substantial risks of serious complications. Thoracic aortic repair carries even higher risks for postoperative morbidity and mortality, and they have diminished only slightly in recent years in spite of significant advances in perioperative care and surgical techniques. The death rates from aortic aneurysm increases with age, from 6.1 per 100 000 per year for those 55-64 years of age, to 22.0 for those 65-74 years of age, 48.9 for those 75-84 years of age, and 79.9 for those 85 years or older. The introduction of stent-grafts (which are less invasive and potentially safer) into clinical practice as an alternative to operation led to new perspectives in the treatment of aneurysms and aortic dissections. Endovascular graft insertion has the distinct advantage of being a much less traumatic technique than conventional arterial reconstruction, owing to the unique ability to insert the graft through a small incision from remote arterial access sites. In patients with cardiac, renal and pulmonary comorbidities, avoiding the need for extensive periaortic dissection, prolonged aortic occlusion, significant fluid shift and substantial blood loss and thoracoabdominal incision, have even greater significance in patient outcome. Proper placement of the endovascular stent may reduce the incidence of aortic rupture, and, in cases of dissection, will seal the intimal tear, decompress the false lumen and may replace conventional medical therapy of the condition. Two recent multicentre, randomised trials, one from the Netherlands and the other from the U.S., advocate the use of endovascular repair over the open surgical approach, particularly if the aneurysm size is greater than 5 cm, there are significant cardiopulmonary or renal comorbidities, or there is a poor preoperative functional status [1, 2]. In the Dutch multi-centre study, Prinssen et al. [1] showed improved mortality outcome in the endovascular patient group, 1.2% compared to 4.6% in the open repair group, and severe morbidity was 3.5% compared to 10.9%, respectively.

The current indications for endovascular treatment of thoracic and abdominal aorta are no longer limited to patients who are unfit for open surgical repair due to older age and severe systemic concomitant diseases. Most aortic aneurysms and type B aortic dissections can be treated by an endovascular procedure as long as they meet the technical criteria for safe advancement and deployment of the stent. In younger patients with minimal or no medical comorbidities, an open surgical repair should be considered, because of the uncertainty of long-term outcome and the established track record with low complications. At present, the long-term durability of aortic stent grafts is not known, and the indications for using the technique in special disease states, such as type B dissection, or complicated aneurysms, are not clearly defined. A patient is a candidate for stent graft procedure if the major prerequisites are met:

a) The morphology of the aneurysm is appropriate. Special attention must be given to the 'lending zone,' where the graft is anchored. A minimum of 20 mm of normal aortic wall is required for safe stent deployment, secure anchoring and for avoiding the obstruction of major branch-artery ostia. Aberrant vessels, such as an indispensable inferior mesenteric artery or an accessory renal artery, must not be present in the segment of the aorta to be excluded from the circulation. The accessory renal artery is not a concern, if it supplies less than a third of the blood supply to one kidney and the other kidney functions normally.
b) There is a distal vascular access of sufficient size. Severe stenosis or occlusion of the abdominal aorta or the iliac arteries may prevent the passage of the endograft delivery system. The common and external iliac arteries should be of sufficient calibre to allow passage of the introducer sheath, or they must be amenable to balloon dilatation to facilitate passage.
c) A limited tortuosity of the aorta. Substantial kinking may result in arterial dissection after insertion of the vascular sheath [3].

Thoracic aneurysms are considered for repair in cases of pain or a maximum diameter of more than 5 cm. In case of aortic dissection, continuing pain despite 'optimal' medical treatment, suspicion of end organ, or lower extremity ischaemia and acute aneurysmal expansion of the false lumen, are indicative of the need for endovascular intervention. Aortic transection from blunt trauma and acute ruptured aortas are emerging as additional indications.

Surgical Technique

The patient is usually prepared from the lower chest to the thighs to allow for the possibility of an urgent laparotomy for an open repair. During endovascular aortic repair, a remote arterial site such as the femoral artery is exposed

and isolated through a small groin incision. More aggressive retroperitoneal dissections may become necessary to expose the external iliac artery if the femoral artery is small, stenotic or severely calcified. The aortic anatomy is defined using fluoroscopy, with particular attention to the selection of appropriate 'landing zones' for the endovascular stent-graft. Depending on the device used, a large endovascular stent-graft delivery system may be introduced after heparinisation (5000 IU) into the remote artery over a stiff guide wire. This would then be advanced under fluoroscopic guidance to the diseased aortic segment. When the final position of the stent-graft is achieved, confirming the patency of important branch-arteries, the delivery device is withdrawn, and the endograft is deployed within the aorta. Modes of deployment are basically two-fold, either self-expanding or balloon expandable. In either case, the deployment involves gradual removal of the sheath that is constraining the collapsed stent graft device. After deployment, fluoroscopic and possibly transoesophageal echocardiografy (TEE) – for thoracic aortic lesions – is performed to confirm that the endovascular stent-graft has successfully excluded the lesion from central aortic flow. The angiography confirms that no portion of the graft covers the renal arteries and there is no sign of blood leakage around any of the attachment sites.

Special caution in aortic arch pathology and in descending thoracic dissections is necessary to exclude the initial intimal tear. Excluding the intimal tear with a short endoluminal stent is usually followed by rapid thrombosis of the false lumen, but as the long-term sealing of the secondary lumen is less certain, longer grafts are usually needed. By inhibiting the continued flow of blood into the false lumen, end-organ ischaemia, infarction and the risk of rupture are prevented, and future aneurysm formation is retarded. In the case of aortic arch pathology, additional surgical interventions might be needed to preserve carotid flow (carotid-to-carotid bypass), or to re-establish perfusion to the arm (carotid-to-subclavian bypass) or distal organs (femoroaxillary bypass) [4].

Intraoperative Complications and Patient Outcome

As in open abdominal aortic aneurysm (AAA) surgery, the primary goal of perioperative evaluation and management is to get the most accurate estimate of the patient's condition and preserve organ function. The patient's comorbidities are the same as in those scheduled for endovascular stent insertion, and often their general health is even poorer. The same anaesthetic considerations should be taken, both in the preoperative evaluation and in monitoring selection during the procedure. Both procedures should be classified as high-risk according to the American College of Cardiology (ACC)/American

Heart Association (AHA) guidelines on preoperative cardiac evaluation. For such high-risk surgery, preoperative non-invasive or invasive cardiac testing is indicated if the patient has major or intermediate clinical predictors of cardiac risk. An endovascular repair of AAA carries a variable risk of sudden conversion to a laparotomy for rupture. High-risk patients consist of more than 50% of the patients scheduled for endovascular procedure, and their 30-day mortality rate exceeds 10% [5]. Thus, appropriate anaesthetic monitoring should be considered. Large-bore intravenous catheters should be placed for volume replacement, and an arterial line should be placed for continuous monitoring of blood pressure and sampling of blood. A large-bore central venous line is mandatory, and a pulmonary artery catheter for volume monitoring may also be indicated, based on the perceived institutional risk of conversion to an open repair, as well as on patient comorbidities. With an average blood loss of more than 500 ml and fluid requirements of about 3000 ml, the use of invasive monitoring in selected patients is indicated even when monitored anaesthesia care (MAC) or regional anaesthesia are used.

Although there may be two small incisions in the groin only, the patient is usually prepared from the nipple line to the knees, because of the possible need to extend the incisions. Additional incisions may be needed, not only for a sudden conversion to a laparotomy, but also occasionally for a femorofemoral or axillofemoral graft along with an endovascular stent. With such a wide preparation and exposure, temperature monitoring and maintenance are crucial. Forced warm air blankets may be used over the upper torso and the head.

With multiple angiograms to position the prosthesis and check blood flow and exclude endoleaks, approximately 250-300 cc of contrast will be administered during the procedure. Contrast-induced renal failure is a serious consideration, particularly in those with chronic underlying renovascular disease due to arteriosclerosis and/or diabetes mellitus. After successful exclusion of the aneurysm by the stent graft, there will be aneurysm sac thrombosis with subsequent haemolysis. In addition, myoglobinuria may occur in cases of ischaemia and reperfusion injury. All of these factors add to the risk of renal complications. The incidence of renal complications following endovascular repair of AAA can be 4% or higher [6]. Adequate hydration should be ensured and urine output closely monitored during the procedure. The intravenously injected contrast material can induce diuresis and give a false sense of adequate hydration and urine output, if one relies solely on urine output as a measure of adequacy of hydration. Central venous pressure monitoring may be a useful adjunct.

Another consequence of multiple angiograms is the increased radiation exposure for all personnel involved. In one review of 47 cases over a year, the average fluoroscopy time was about 40 minutes per case [7]. Lead aprons

attenuate > 85% of the radiation dose and thus, whenever possible, the anaesthesiologist should keep himself or herself a proper distance away from the radiation tube. The average exposure of an anaesthesiologist who observed this cautions was 0 mSv over a 6-month period at one institution [6].

Blood loss can be steady and considerable, yet remain hidden during endovascular repair of AAA. Most blood loss occurs when the introducer sheaths and stent grafts are passed into and out of the femoral arteries and may be hidden in the surgical drapes. One group of authors reported an average blood loss of 550 ml, but the actual blood loss will depend on the amount of catheter manipulation and on the duration of procedure. A sudden, unexplained decrease in blood pressure should alert the anaesthesiologist to the possibility of a vascular catastrophe such as rupture, perforation, or evulsion of the aorta or another large artery. An aortic rupture, recognised in a timely manner, may sometimes be amenable to treatment with intraluminal balloon tamponade and subsequent deployment of the device beyond the area of rupture, but an emergent laparotomy is often necessary.

Aortic arch and descending thoracic aortic reconstruction using transluminally placed endovascular branched stent grafts have additional intraoperative risks, such as cerebrovascular accident (CVA), paraplegia and massive micro-embolisation, endoleaks and graft migration [3].

Anaesthetic Techniques

Different anaesthetic techniques have been described for aortic stent graft placement, including local anaesthesia, regional anaesthesia and general anaesthesia. With increasing physician experience, as well as the development of more sophisticated devices, regional anaesthetics (including epidural, spinal, spinal-epidural and continuous spinal anaesthetics), as well as local anaesthetics supplemented by sedation, may be utilised. Choice of anaesthetic technique is dependent on the planned surgical interventions and the patient's comorbid conditions. The need for extensive inguinal exploration and dissection, or for the construction of a femoral artery to femoral arterial conduit, may favour either regional or general anaesthesia. When conversion to open surgery is more likely, as in the event of complicated anatomy of the iliac arteries or the aorta, general anaesthesia should be considered. If surgical dissection is extended into the retroperitoneum, a higher level of regional anaesthesia or general anaesthesia will be necessary. If the patient is undergoing local anaesthesia with MAC or regional anaesthesia, adequate intravenous sedation is necessary due to the agitation that is secondary to the restlessness and pain from lying in one position for a prolonged period of time. The disadvantage in high epidural anaesthesia is related to the difficulty in

precisely controlling the anaesthetic level, as well as to the concern for possible intercostal muscle weakness need to support ventilation. For patients with severe co-existing diseases, the spinal/epidural technique or continuous spinal anaesthesia are likely to be better options. The latter may offer haemodynamic stability and accurate control of the anaesthetic level [8].

Proximal Graft Deployment

Distal migration of the device occurring during proximal endograft deployment may result in inadequate exclusion of the aneurysm sack with resultant endoleak. Device malposition secondary to inadvertent migration may result in either occlusion of major arterial branches or incomplete aneurysm exclusion. The use of induced hypotension, by sodium nitroprusside or nitroglycerin, during device deployment has been successfully used by some centres to assist in proximal endovascular stent graft placement and may reduce the magnitude of migration. In theory, the risk of malposition may be further decreased by ventricular quiescence, which can be achieved by the pharmacological induction of sino-atrial and atrio-ventricular nodal inhibition with high dose adenosine [9].

TEE monitoring

With the rapid evolution of TEE technology and with the oesophagus in close proximity to the aorta, TEE has become an excellent tool for diagnosing pathology of the distal aortic arch, the descending thoracic aorta and the proximal abdominal aorta. TEE can provide instantaneous views of the location of the guide-wires and estimation of endograft sizing and location prior to deployment in relation to the normal and diseased thoracic aorta. TEE appears to have distinct advantages over perioperative angiography, as it provides exact vessel and lesion sizing and localisation, which is difficult to obtain during single-plane angiography. In contrast to angiography, both endograft leakage as well as iatrogenic dissections may be diagnosed by TEE. Although not imaged in all patients, large intercostal arteries have been imaged, thus avoiding inadvertent obstruction by the aortic stent-graft; however, consistent visualisation of intercostal arteries may not be assured in all patients. After stent-graft placement, exclusion of flow from the aorta into the aneurysm, thrombosis of the false lumen, or, alternatively, the existence of residual endoleaks, can be confirmed using colour Doppler flow imaging most of the time. TEE might be very decisive in choosing the stent-lending zone, and in identifying (B mode) incomplete obliteration of the false lumen,

which necessitates additional balloon expansions of the stent. Initial thrombosis of the false lumen is picked up as 'smoke' by the TEE [10].

Spinal Cord Ischaemia

The reported incidence of neurological injuries in the postoperative period after endovascular thoracic aortic reconstruction is similar to that in open thoracic aortic repair. With descending aortic reconstruction, intercostal arteries that supply the anterior spinal cord may be sacrificed, resulting in spinal cord injury. The anterior spinal cord enjoys little if any reserve of blood supply. The major collateral joining the anterior spinal artery is the arteria radicularis magna of Adamkiewicz, which, in most patients, originates from an intercostal artery between T8 and Ll level. If this critical branch is patent and emerges from the aneurysmal wall, a significant ischaemic risk to the spinal cord can occur if excluded by the endoluminal stent. Additional supply to the distal cord comes from the iliolumbar arteries and the lateral sacral arteries, branches of the hypogastric arteries. Several reports have demonstrated an increased incidence of post-stent paralysis in patients whose abdominal aorta was previously operated on. It seems that during such operations several tributaries to the cord are sacrificed, a fact that becomes crucial later, when additional endograft repair is performed. In case of significant disease of the common iliac arteries and stent graft manoeuvring in both internal iliac arteries, signs and symptoms of pelvic ischaemia may appear, from non-limiting claudication to new onset impotence, buttock rest pain and even colon ischaemia. Intraoperative or postoperative acidosis or other signs of deterioration following intentional occlusion of the internal iliac artery should raise concern of colon ischaemia. Colon infarction may then lead to cardiovascular collapse [11].

Long-segment thoracic endovascular repair or consecutive endograft segments connected in a row also pose a significant risk factor for spinal cord ischaemia [12, 13]. Application of short endografts and avoidance of placing stent grafts between T8 and L2 is therefore recommended to prevent spinal cord ischaemia.

The successful use of cerebrospinal fluid (CSF) drainage during endovascular aortic repair has been described anecdotally in several case reports of patients who underwent thoracoabdominal aortic aneurysm (TAAA) repair [14, 15]. Clinical symptoms of paralysis were resolved, although the primary CSF pressure upon catheter insertion was not always high. Possible explanation for the increase in CSF pressure after stent graft deployment might be attributed to sympathetic spinal stimulation or to the local acidosis that occurs in the presence of inadequate spinal cord perfusion [16]. The CSF

drainage should be continued for 48-72 h, and strict control of the haemodynamic status maintained to prevent hypotension. Recently, following sporadic reports of the occurrence of intracranial haemorrhage while spinal catheters were still in place, CSF drainage has been suggested as a possible explanation for the cerebral bleeding. To be on the safe side, during the postoperative period modulation of CSF pressure should be used only as a secondary method in maintaining spinal perfusion pressure, and the CSF drained whenever the pressure exceeds the normal value of 15 mmHg. The practice of 'free drainage' of CSF in the postoperative period should be re-examined in light of the current reports of possible neurological haemorrhagic complications.

Postoperative Care

In the postoperative period, after successful exclusion of the aortic aneurysm, thrombosis will occur in the excluded aneurysmal sac. Platelet count invariably decreases due to thrombosis, and this may sometimes result in clinically significant thrombocytopenia and fever and, rarely, in consumptive coagulopathy. It is hypothesised that this post-implantation syndrome may be attributed to a significant inflammatory response, resulting in endothelial and macrophage cell activation from intra-aneurysmal device manipulation. We should keep in mind that the high-risk group of patients have a comorbidity similar to that of patients operated on for aortic aneurysm resection. Thus, close monitoring for 24 h is recommended.

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Postoperative Pain Management: Organisation and Audits

D. Caristi

Introduction

Pain relief after surgical procedures continues to be a major medical challenge. The alleviation of pain is given a high priority by the medical profession and health authorities, who recognise that improvements in perioperative analgesia are not only desirable for humanitarian reasons, but essential for reducing postoperative morbidity and mortality [1, 2]. The guidelines for acute pain management established by the Agency for Health Care Policy and Research highlight the fact that appropriate pain management in postoperative patients contributes to earlier mobilisation, shorter hospital stay and lower costs. Pain relief per se does not significantly improve the postoperative outcome, with the exception of patient satisfaction and pulmonary complications. Postoperative morbidity and the length of hospital stay are dependent on many factors, including preoperative information, quality of analgesia and existing programs for postoperative care and rehabilitation, including orders for mobilisation, oral nutrition and discharge criteria [3]. In recent years, the techniques for pain management in patients undergoing surgery have substantially improved. The choice of analgesic and the route and technique of administration can be tailored to individual need to optimise pain control and to avoid postoperative discomfort and suffering. However, although there is no reason why a patient should not receive appropriate analgesia, recent surveys have revealed that the incidence of moderate or even severe postoperative pain may be as high as 30–70% [4, 5]. Most patients, physicians, surgeons and nurses still consider moderate-to-severe pain an acceptable consequence of surgical interventions. Undertreatment of pain has been determined to have a negative impact on short-term recovery and may even have a detrimental long-term effect on health. Three reasons for the undertreatment of pain relate to fear of narcotic addiction, poor communication among staff and perceptions by patients that medications for pain are neither necessary

nor good. The recognition that unrelieved pain contributes to preoperative morbidity and mortality has inspired many institutions to develop an Acute Pain Service (APS) in an attempt to provide effective postoperative relief. Immediate and sustained formal support, as well as authoritative recommendations from various medical and health care organisations, have promoted the widespread introduction of APS [6–16]. This in turn has led to the successful and safe implementation of multi-modal pain management strategies in surgical wards [17]. It has also led to an increase in the use of specialised pain relief methods, such as Patient Controlled Analgesia (PCA) and epidural infusions of local anaesthetics/opioid mixtures. Implementation of these methods may represent real advances both in improving patient well-being and in reducing postoperative morbidity [18].

Studies have shown that pain is a particularly important determinant of patient satisfaction. It is now recognised that many patients have been greatly under-treated for their postoperative pain in the past. In spite of this fact, however, studies that include the assessment of patient satisfaction with postoperative pain management have repeatedly indicated that most patients seem satisfied with their postoperative care. Satisfaction is a subjective appraisal of personal care, and a number of factors seem to influence satisfaction with hospital care. Thorough information about the predictability and controllability of the painful stimulus is a major influence in pain expectation; however, most patients do not receive any information on pain and its possible methods of treatment. Providing patients with accurate preparatory information regarding the onset, duration, intensity and sensory qualities of the stressful events has been shown to minimise the distress of patients undergoing invasive medical procedures [19, 20]. To ensure that patients have all the information they need, it is important to have annual audits of the postoperative pain unit; the audits should include an investigation of the quality of analgesia (the efficacy and safety of pain management), the amount and quality of patient information, patient satisfaction and the costs of treatment.

Acute Pain Service

The importance of establishing an organisation for the management of postoperative pain relief, with special attention to a team approach, was proposed more than 40 years ago. Although some editorials [21] from 1976 through 1980 again advocated the introduction of an analgesia team to supervise and administer pain relief and to take responsibility for teaching and training hospital staff in postoperative pain management, almost a decade passed before a specialised in-hospital pain service emerged. Thus, in 1985, the fist

acute pain service was introduced in the United States [22], and in Germany [23]. In Europe, only a few other countries (Sweden, Holland, and United Kingdom) developed an acute pain service in their hospitals. One document explicitly stated that all major hospitals in the UK should have an APS. Similar recommendations were made by the Agency for Health Care Policy and Research in the United States, as well as the National Health and Medical Research Council in Australia. In the United States today, as many as 63% of all hospitals have an APS; and, in Australia and New Zealand, the provision of an APS is a prerequisite for accreditation for training by the Royal College of Anaesthetists and the Australian and New Zealand College of Anaesthetists. Financial concerns remain a major impediment to the implementation of an APS in many hospitals, especially smaller ones.

There is international debate about the best APS model: the anaesthesiologist-based model of Ready, the cheaper nurse-based, anaesthesiologist-supervised model of Rawal [16] or other models widely used in Australia or in the UK, which are nurse or resident-based and anaesthesiologist-supervised. The APS has the responsibility for day-to-day postoperative pain and ensuring the safety of the treatment. Thus, it should provide an organisational framework for an appropriate level of care and monitoring, adjusted to the clinical conditions of the patient. It should also address the techniques to be used, and establish programs for the identification and management of complications. Evidence-based practices for pain management ensure that patients receive compassionate care, including the timely recognition and assessment of pain. Research utilisation provides a way to standardise initiatives for improving clinical outcomes through evidence-based findings. Crafting evidence-based practice standards for pain management is an important step toward ensuring that patients receive quality healthcare with optimal outcomes. It is generally assumed that the APS should be overseen by an anaesthesiologist [24]. Furthermore, APS is committed to audits and clinical research in order to determine the efficacy and outcomes of existing and new methods of treatment. Although 24-h coverage has been recommended, a Canadian survey showed that only three quarters of the services actually provide such coverage.

Regular assessment and documentation of pain is one of the most important objectives of an APS. Available data indicate that implementation of APS is associated with a significant decrease in patients' postoperative pain ratings. However, there are several issues that remain to be investigated – for example, the contribution of increased awareness and the importance of postoperative analgesia, the introduction of more effective regimens (i.e. epidural analgesia) and the placebo or undefined effects of the twice-a-day visits of the APS.

In-service education and training is another important aspect of the APS

role. Improving the competency of the healthcare team when attending to patient pain is a major component of this process. Myths, often held by healthcare providers as well as patients (for example, that the use of opioids for pain control leads to addiction) can be dispelled by increasing the understanding of physical dependence and tolerance. Because the attitudes and beliefs of healthcare providers influence their actions and intervention, as well as patient responses to pain, it is important that the entire team receive evidence-based education, and that this replace old patterns of care related to pharmacology, scheduling and dosing and adjunctive treatments. Protocols encourage consistent standards of safe and effective care and should be used as a framework for individualising treatment. The introduction of an APS into a hospital leads to improved knowledge and understanding of pain assessment and greater control for staff and patients.

Joint Commission pain standards [25–27] can have a powerful impact on the quality of pain management. The standards require accredited healthcare facilities to recognise the patient's right to the appropriate assessment and management of pain; to this end, they require healthcare facilities to assess pain in all patients and to record the assessment in a way that facilitates regular reassessment and follow-up. The standards also require accredited healthcare facilities to educate patients, families and providers, to establish policies that support appropriate prescription or ordering of pain medicines, to include patient needs for symptom control in discharge planning and to collect data and monitor the appropriateness and effectiveness of pain management.

Patient Information

Educating the patient and family during the pre-anaesthesia evaluation is pivotal in facilitating optimal care; it is important that patients be fully informed preoperatively about the range of treatments available and their possible adverse effects [19]. Patient ignorance with regard to postoperative pain and its control can increase both patient dissatisfaction and the degree of pain experienced during the postoperative period. Some patients, of course, may not wish to be faced with options and may welcome more guidance on the best form of pain control. For patients who wish to receive information, however, the discussion should include what pain to expect, what treatment options are available – both for pain and nausea (or vomiting) – and what the risks and side effects are. Patient awareness of pain and the ability to control pain are important components of pain assessment.

The Association of Anaesthetists guidance on risk management [20] recommends the provision of information leaflets or videos describing the

process of anaesthesia. It may be argued that this should also include advice on postoperative pain and emetic control.

Assessment of Pain

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. Making pain visible actually has become a central theme in many settings, leading to the genesis of the now familiar 'pain as the fifth vital sign' campaign. While this slogan was never literally intended to make pain intensity a vital sign (similar to temperature, pulse, blood pressure and respiratory rate), it has heightened awareness of the need to document pain in a prominent place. This place could be the vital signs section of a patient's chart to alert clinicians to the problem and elicit a prompt response.

Monitoring the management of postoperative pain is important to ensure its safety and effectiveness. There is solid consensus [28] that the 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 with the other postoperative vital signs. An educational programme dedicated to nurses strongly increases the use of regular pain assessment and may contribute to an improvement in postoperative analgesia [29].

Anaesthesiologists in collaboration with others should use pain assessment instruments to facilitate the regular evaluation and documentation of pain and the effects (as well as side effects) of pain 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 operation and severity of the pain; and 3) with each new report of pain. It is important that the team immediately evaluate each instance of unexpected intense pain, particularly if it is sudden or associated with oliguria or altered vital signs (such as hypotension, tachycardia or fever), and, in this event, it is important that the team consider new diagnoses such as wound dehiscence, infection or deep venous thrombosis.

Not all observations need be undertaken at the same frequency, and no consensus exists with regard to the optimal frequency of observations. It will be higher at first and decrease as time goes by. It is necessary to have hospital guidelines for the type and frequency of observations to be performed and documented. The target for best practice should be that fewer than 7% of

postoperative patients experience a failure of analgesia during the first 24 h. In the absence of a nationally agreed upon pain scoring system, a score above 50% on the pain scale at 2–4 hourly intervals during the first 24 h constitutes a failure of analgesia [30].

Postoperative pain is usually characterised 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 patient's pre-existing disease, its location, and the type of surgery, but also and sometimes mainly, on factors resulting from the pain/tissue injury ratio, which can be associated to some degree 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 [31]. 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 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 report of his or her own 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. Neither behaviour nor vital signs can substitute for a self-report.

Self-assessment using unidimensional methods, that 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 through the use of rating scales. These scales, which incorporate either words or numbers, are simple and can be readily understood. The visual analogue scale (VAS) is considered the gold standard for postoperative pain assessment. It consists of a line, most often 100 mm long, with two descriptors representing the 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 of the mark from the 'no pain' end of the line. This 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, the method may not be reliable [32]. The visual analogue scale is not easy to use in the immediate postoperative period because of residual anaesthesia, blurred vision or nausea, and several patients require additional instructions to complete the VAS. When using the VAS for making treatment decisions, or for measuring of the effects of pharmacological interventions, it is important to be aware that it has an imprecision of about ± 20 mm. The numerical rating scale (NRS) consists of a series of numbers ranging from 0 (or 'no pain') to 10 or 100 ('the worst imaginable pain'); and 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 then 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 gradations, clinicians should request the patient's self-report, not only while at rest but also during routine activities such as coughing, deep breathing or moving (e.g. turning in bed). Pain on movement, because it responds to different types of treatment, may be recorded separately from pain at rest. 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 behaviour and depression. 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 [33]. A patient's score on the unidimensional pain intensity scale reflects the emotional qualities of pain much more than its sensory intensity or other qualities. Accordingly, such scales may be poor indicators of the analgesic requirement, and the patient's postoperative anxiety and depression may be inadequately treated.

Another issue concerns the clinical significance of VAS change scores. How much of a decrease is necessary before it is noticeable by patients? How much of a decrease is necessary for it to be deemed significant and meaningful by patients? Unfortunately, relatively little research has examined the question of the 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 perspective [34]. Occasionally, apparent discrepancies between behaviours and patient self-reports of pain may occur. For example, patients may describe pain as an 8 out of 10 on a pain scale, while smiling and walking freely, or as a 2 out of 10, while experiencing tachycardia, splinting and sweating. Discrepancies between behaviour and patient self-reports may result from excellent coping skills. The patient who uses distraction and relaxation techniques may be engaging 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.

Patients unable to communicate effectively with staff – e.g., neonates and children, developmentally delayed persons, psychotic patients, patients with dementia and foreign patients – require special considerations for pain assessment. Children and cognitively impaired patients require simpler or modified pain measurement scales and assessment approaches. 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 to determine a convenient way to assess pain.

It has been reported that, in general, the management of pain in children is still inadequate. It is now well established that the failure to manage pain may have immediate deleterious physiological, biochemical and behavioural effects, as well as longer-term consequences. Several attempts have been made to develop observational scales that are useful for assessing pain in children. The Facial Pain Scale (Smiley Analogue Scale) is a self-evaluation, unidimensional test available for children more than five years old. 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 younger than five because self-evaluation is usually impossible to perform. Children's Hospital of Eastern Ontario Postoperative Scale (CHEOPS) is the most popular. Physiological scales help to assess pain intensity and the effect of rescue therapy in releasing pain, by monitoring vital signs, such as respiratory rate, heart

rate and blood pressure. The various pain assessment options are summarised in Table 2.

Table 2. Pain assessment in infants

Children < 3 yrs	OPS, CHEOPS, parent report, nurse report, physiologic measures, NFCS
Children 3–6 yrs	Faces Pain Scale, Oucher Scale, Poker Hip Tool, VAS, observation tools, parent report, nurse report
Children > 6–7yrs	Self report (VAS, NRS), observation scales, parent report, nurse report

Pain severity measurement scales are not the only form of discomfort assessment in postoperative analgesic care. Studies consistently report the overall incidence of postoperative nausea and vomiting (PONV) as 36%. PONV can lead to medical problems such as aspiration, electrolyte imbalance, wound dehiscence and impairment of the oral absorption of drugs and nutrition, all of which can result in a delayed recovery. Furthermore, it has been shown that the patient's memory of PONV is greater than that of the pain experienced after surgery [35]. Research 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.

Patient Satisfaction

Patient satisfaction is one of the most important endpoints in clinical practice and quality assurance [36]. A number of factors seem to influence satisfaction with hospital care. With difficulty, the patient can isolate the different factors that are involved in pain management; this is particularly evident during the provision of a questionnaire when patient gives suggestions or comments

about the analgesia received. Different studies have shown that female sex, high pre-operative pain intensity, high anxiety about postoperative risks and problems, as well as relatively young age and willingness to report pain, correlated with low satisfaction; younger patients and females need a different and more efficient pain management regimen to experience the same level of satisfaction experienced by elderly patients and males [37]. A couple of questions concerning the clinical importance of the predictive relationship of expectancies of pain to the experience of postoperative pain are important. One is, how much do patient expectations regarding pain and symptoms influence the subsequent reporting of pain and symptoms? The other question concerns the manipulation of expectancies (by providing information regarding the intensity, pattern and duration of the pain and symptoms). Does this reduce patient experience of trauma, or does it sensitise patients to the negative aspects of surgery?' According to De Groot et al. [38], patients who expect to feel pain will report greater pain intensity than patients who do not hold these expectations. As a rule, the greater the discrepancy between expected and actual pain, the greater the experience of postoperative distress. Those patients who expect pain to be more intense than it actually is will report being less distressed [39]. The positive correlations between expected and reported pain and emotional variables suggest that the manipulation of patient emotional responses may be as effective as manipulating pain expectancies in controlling the pain and the distress of surgery. This finding stresses the importance of pre-operative intervention strategies aiming at diminishing the stress prior to surgical procedures. A preliminary assessment by APS staff of the patient's capacity to cope, as well as how much analgesia is wanted, might also be expected to lead to greater satisfaction, as would a cognitive–behavioural reduction of anxiety. Some studies suggest that a more accurate picture of treatment can be communicated if patients receive not only information about the procedure, but also sensory and temporal information, i.e. about the physical impact of the procedure. This idea is supported by the finding that patients who receive accurate preparatory information about their surgery, in contrast to those who have no additional information, report lower pain intensity even though there is no difference with respect to expected pain intensity before the operation. Other authors have shown that patients who receive preparatory information report lower pain intensity, as well as lower expected pain intensity, and that patients who expect more pain have less transient anxiety after surgery [40].

Another consideration that needs to be addressed when utilising data from a patient satisfaction survey on pain management is how an organisation determines the overall quality of its pain management services. In reviewing our data, several deficiencies were noted, including moderate-to-severe postoperative pain intensity scores. If one were to examine only the

patient satisfaction scores from this survey, however, one might conclude erroneously that there were no problems with pain management within our hospital.

Costs of Pain Management

Studies of healthcare costs attempt to analyse the benefit of intervention and to provide well defined and relevant outcome measurements [41, 42]. Cost analysis of acute pain management is impeded by the lack of a well-defined baseline or outcome assessment. There is no valid method for assigning financial cost to differing levels of analgesia. Attempts at cost–benefits analyses that incorporate complication and outcome measures have been advocated, but a few studies involving APS have been conducted. It is important that cost-efficacy analyses consider the costs of analgesics, devices and nursing time, as well as the duration of stay in PACU/ICU/surgical wards. The survival of APS may be threatened because of the present economic constraints in healthcare and the requirements for cost-effective therapeutic interventions. This makes it especially important in the context of improved pain relief and outcome that there be well-defined quality criteria for provided service and an APS that is integrated in the multimodal rehabilitation program.

Pain Management Organisation and Audits at Cattinara Hospital in Trieste

Without an organised process by which pain is recognised, documented, assessed and reassessed on a regular basis, staff efforts to treat pain may become sporadic and ineffectual. For this reason, the APS at Cattinara Hospital in Trieste (Italy) provides 24-h coverage of postoperative pain management. Since 1998, our APS has followed up over 7500 surgical patients.

This model is nurse and resident anaesthesiologist-based, anaesthesiologist on duty-supervised. It is a variation of the nurse-based, low cost model of Rawal [43]. It provides postoperative pain management for general, orthopaedic, vascular, urological, thoracic, ear-nose-throat, plastic and neurosurgical patients after elective and acute interventions. During the preoperative anaesthesiologist's visit, patients receive routine verbal information and extensive written information about postoperative pain management. The routine postoperative analgesia, based on standard protocols, is commenced with intravenous boluses or continuous intravenous infusions of opioids, combined in some cases with anti-inflammatory drugs (NSAID), or continuous epidural infusions of opioids and local anaesthetics. The section anaesthetist selects the modality of analgesia among standard protocols, tak-

ing into account the type of surgery, the severity of postoperative pain and patient 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, as well as other side-effects, are assessed and recorded on a postoperative chart by specially trained, acute pain nurses every hour during the first three hours, then three–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).

Periodic evaluation studies should be conducted to monitor the effectiveness of the pain assessment and management procedures. In 2004, our APS followed up 1504 surgical patients with expected moderate-to-severe pain. The patients received intravenous (90.5 %) or epidural (9.5%) analgesia. The overall pain assessment scores made by the nurse and anaesthetist were 16 598. A rescue dose of analgesic drug was necessary in 14.48 % of patients. Side effects were present in 11.4 %, more frequently hypotension (4.45%), nausea or vomiting (3.59%), followed by confusion, hallucinations and itching. The overall trend of VAS, both at rest and on movement, was always below 3 (Fig. 1).

The studies of Jamison et al. [39] indicate that low pain intensity ratings can be a good predictor of satisfaction with pain management and the helpfulness of treatment. For this reason, at the end of analgesic postoperative treatment, but before discharge from hospital, a sample of consecutive patients were administered a satisfaction questionnaire containing 17 items about areas of importance in pain management. In addition to patient information,

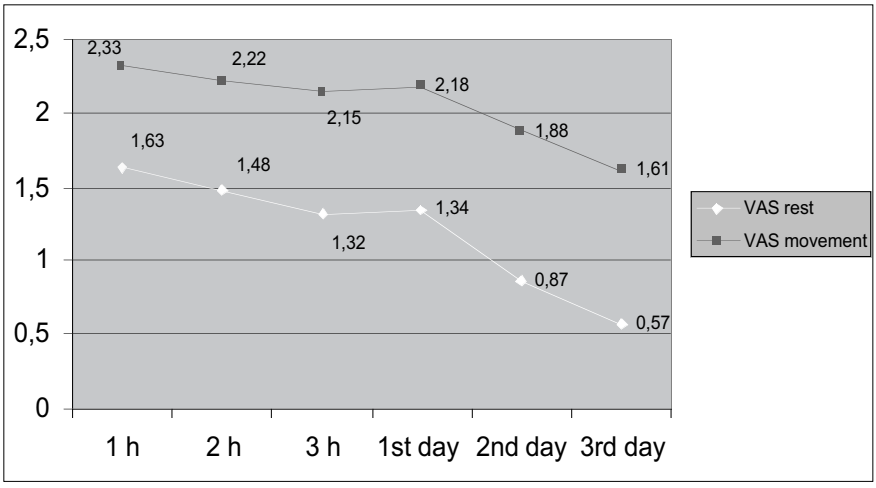

Fig. 1. The trend of VAS in 2004

the areas included the quality of analgesia (including the adequacy of pain relief provided and side effects), the actual pain experienced (intensity and frequency of pain perceived), patient preoperative expectation, patient satisfaction and, finally, suggestions. To decrease the risk that the patients would not respond honestly to the questions, the questionnaire was administered orally, by a specifically trained interviewer who was not directly involved in the care or pain treatment of the patient. This precaution, of course, did not completely eliminate the possibility of a 'staff pleasing-factor.' No patient refused to complete the questionnaire. Four items were included in the patient information portion of the questionnaire (informed or not, when informed, informed by whom and patient understanding of the information). Six items concerning the quality of analgesia were included (helpfulness of preoperative information with respect to asking for medications, length of wait for pain medication once requested, side effects such as itching, numbness, sedation or nausea (and vomiting). Four items pertained to pain intensity (the worst and the least pain experienced on a 0–10 pain scale, the frequency of peaks of moderate-to-severe pain, and the preoperative expectation of pain on a verbal rating scale). Finally, the last three items explored the overall satisfaction with the given pain management routine in the postoperative phase, based on a 5-category scale (very satisfied, satisfied, slightly satisfied, slightly dissatisfied and very dissatisfied), the patient's agreement with the analgesic management routine and suggestions on how to improve analgesic management. The satisfaction level was high: 91% of patients were very satisfied, 7% were satisfied and only 2% were slightly satisfied (Fig. 2).

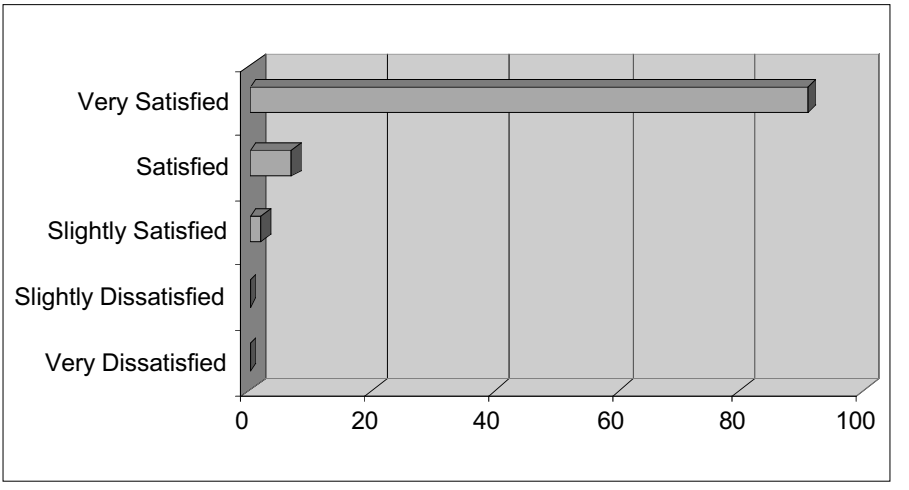

Fig. 2. Patient satisfaction with postoperative pain management

The majority of patients reported that, if they should require surgery again, they would like to be treated in the same manner (93%). Furthermore, when asked what they would like to change in their pain management, 29% reported that they would like to receive more information about available analgesic methods, 5% reported that they would like a better analgesia and 66% reported that they would not change anything (Fig. 3). Because most patients claimed to have experienced moderate-to-severe pain during the postoperative period (Fig. 4), it is surprising that most patients were satisfied

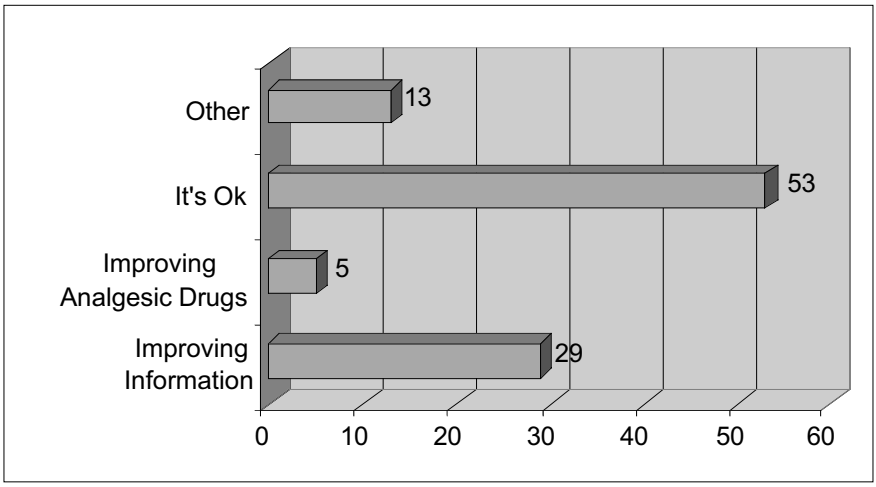

Fig. 3. Patient suggestions (on how to improve postoperative pain management)

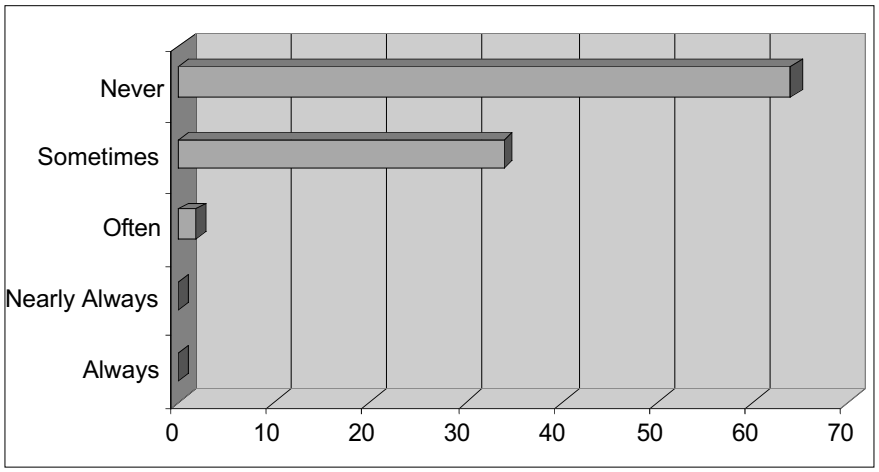

Fig. 4. Frequency of peaks of moderate to severe pain experienced

with the pain management provided. Interestingly, it has been noted in a retrospective report [44] that there seems to be no relationship between the severity of the incidence of pain and the satisfaction score. Nevertheless, a number of organisations have suggested that measures of patient satisfaction be included in quality of outcome assessments for pain management. It is possible that the pattern of pain relief, rather than pain severity in itself, is a critical determinant of satisfaction [45]. In that case, the observed discrepancy between pain actually experienced and patient satisfaction might not be as poor as pain intensity measurements suggest. It is also possible that patient satisfaction depends more on the quality of communication with the physician(s) than on analgesic efficacy. In any case, patient ratings of satisfaction, as a measure of APS efficacy, have to be evaluated cautiously [46].

Conclusions

Pain relief after surgical procedures continues to be a major medical challenge. The introduction of the Acute Pain Services has led to a successful and safe implementation of multi-modal pain management strategies and an increase in the use of specialised pain relief methods. The APS has the responsibility for day-to-day postoperative pain, and it plays an important role in ensuring safe treatment and improving the knowledge and understanding of pain assessment in staff and patients. A key point 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 pain treatment.

There has been growing interest in the assessment of patient satisfaction with healthcare. Studies have shown that pain is a particularly important determinant of patient satisfaction; low pain intensity might be a good predictor of patient satisfaction. An awareness of the importance of controlling postoperative pain and the awareness of the options for effective postoperative pain relief (due to accurate preoperative information regarding the strategies presently available) should have a positive influence on patient satisfaction, despite postoperative experience with pain severity. Good communication between APS staff and patients appears to be as important as analgesic efficacy in determining patient satisfaction. Furthermore, the exchange of information between patients and hospital staff members seems essential for a more individualised and optimal pain relief treatment plan. An APS in the hospital can improve both the knowledge of pain treatment and patient satisfaction; indeed, despite the fact that they may experience high levels of pain, most patients are satisfied with the efforts that nurses and physicians make to manage pain.

Our experience suggests that a satisfaction questionnaire provides useful baseline data for evaluating the quality of an institution's overall pain management program, and, furthermore, that the information it provides can be used to develop a plan for improving pain management. However, by itself, a satisfaction questionnaire is not the solution, even when repeated at regular intervals to determine APS progress. Indeed, if used in isolation from other data, satisfaction ratings can lead to the erroneous belief that pain management practices are optimal.

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Introduction to Trauma Care and Improving Performance

F. Della Corte, G.L. Vignazia, C. Olivieri

Traumatic injury and trauma deaths have been worldwide considered a major health problem [1]. The World Health Organization estimates that 16 000 people die everyday from trauma injuries, and for every person who dies, several thousands more are injured, many of them with permanent sequelae. Injury accounts for 16% of the global burden of disease [2].

In 1966, the National Academy of Science called for the Institution of Trauma Systems in the United States [3]. Only a few countries have established permanent Trauma Registries (TR). Almost all the evidence concerning the effectiveness of improvements in trauma care services comes from developed countries, and primarily from two related activities: (1) verification of trauma services through hospital inspections; and (2) planning trauma management procedures. Verification applies to a review of individual facilities and their ability to provide a variety of items, including human resources (e.g. availability of personnel with specific qualifications), hospital resources (equipment and supplies) and administrative and organisational functions, such as quality evaluation and improvement. There is considerable evidence that political jurisdictions that improve the organisation of trauma services benefit from reduced trauma mortality, compared with similarly resourced jurisdictions that do not. Such evidence comes from panel reviews of preventable deaths, hospital trauma registry studies and population-based studies [4–6].

Most studies confirm a reduction in mortality with an improved organisation provided by a system for trauma management. In one of the best series of studies done on this topic, Nathens et al. [7, 8] used population-based data to examine the effects of planning such systems for trauma management in all 50 states of the United States. They looked at mortality rates, adjusting for several potential confounding variables, including traffic laws and other safety measures. They demonstrated an 8% reduction in mortality for those states where a system for a direct referral to a defined Trauma Centre had been established. It should be mentioned that this figure represents overall trauma

mortality, including persons dead at the scene, before any chance of medical treatment. In comparison, the larger reductions in mortality mentioned above reflect the changes in mortality for patients surviving the trasport to the hospital. In the Nathens' study, it is especially notable that, in most cases, the effect of a system for trauma management was not evident until 10 years after its initial enhancement and reached its maximum at 16 years [7, 8].

Jurkovich et al. systematically reviewed the published literature on assessing the effectiveness of trauma systems using registry-based data. There was evidence of a 15–20% reduction in the risk of death in trauma system outcomes, compared with Major Trauma Outcome Study (MTOS) rms [9].

In England, Wales and Northern Ireland, severe injury remains a common cause of death and disability in all age groups. Of particular concern is the high incidence of trauma leading to death and disability in people under 40 years of age. Some 450 children are known to die every year as a result of accidents, and 10 000 are permanently disabled [10]. The incidence of severe trauma defined by an Injury Severity Score greater than 15 (ISS > 15) is estimated to be four per million per week [11] – a lower prevalence than in the US, where penetrating trauma is more common.

The MTOS report of 1992 [12] showed that the initial management of major trauma remained unsatisfactory. There were delays in providing experienced staff and timely operations. Mortality varied between hospitals, but the incidence of death due to blunt trauma was higher in the UK than in the US, a trend that has been continuing since then [13].

In Italy, we have far to go to establish a national TR that allows us to accurately describe the dimensions of the problem in this country. No data about outcome are currently available. Comprehensive collections of data on traumatic injuries have been undertaken in the past, but only regionally [14]. In the regional study, Di Bartolomeo et al. found the incidence of severe trauma (defined by an ISS > 15) to be 522 cases per million per year. The overall mortality was 45.6% or 238 per million per year, and 43.6% of the fatalities were found dead on the scene.

Trauma care starts from the scene of the accident and finishes with rehabilitative therapy. In a study of 1088 injured patients, 430 died prior to arriving at the hospital and another 309 following treatment. Subsequent evaluation showed that 46 of these 309 hospital deaths might have been prevented [10]. Chiara et al., in a retrospective study in a Milan urban area, found that 53% of all hospital deaths were preventable [15].

Audits are crucial for improving trauma care. Fortunately, there is an increasing awareness of the importance of measuring the effectiveness of the 'process' of trauma care as an aid to developing optimal systems. Trauma scores are widely used in countries with a systematic epidemiologic approach to the problem. In Italy, trauma scores are used only in local registries. All

current trauma-auditing systems use death or survival alone. These systems do not assess the effects of treatment on the quality of life or the functional outcome in survivors. The target population is young, and many severe disabilities are known to persist. Even temporary disability has important social and economical effects.

For intensive care unit (ICU) or severely injured patients, a multicentric, epidemiological, observational study has been started at three second-level hospitals in three different regions of Italy [16]. Thus far, only preliminary data has been published. An evaluation of the outcome, to be prepared at six months from the onset of the study, will be of great interest.

A multicentric, prospective, observational, web-based study of a population of 810 000 inhabitants of the Eastern Piedmont district began in March 2004 [17]. All consecutive trauma patients admitted to one of the ICU facilities at the six hospitals in the district were enrolled in the study. Patients with self-inflicted injuries and patients who arrived dead at the first hospital were excluded from the study. The data form consisted of 102 variables exploring demographics, mechanism of injury and type of injury, as well as on-scene team leader, pre-hospital clinical data, procedures and pre-hospital timing. In-hospital data consisted of vital parameters at the first hospital, early emergency room procedure, time intervals for diagnostic procedures, types of surgical intervention, ICU complications and time/cause for secondary transfer, in accord with Utstein-style recommendations for uniform data reporting on major trauma [18].

If trauma registry and data audit are key elements in the improvement of the care of the trauma patient as far as the organisational aspects are concerned, what are the key elements or questions that should be asked for evaluating and improving trauma care on a clinical basis? Certainly, it is important to examine how severely injured patients should be treated and triaged, what is needed during the first hours of the hospital stay and what should be avoided. In the following sections, we will focus on the main issues relevant to severely injured patients and identify the goals of the early in-hospital care for the most typical lesions that occur in multiple-injury patients.

Major Head Injuries

Major head injury is a frequent component in multiple-injury patients and often the major determinant of outcome. Worsening of a primary brain injury can be minimised by preventing hypotension and hypoxia. Recognising the potential for the neurosurgical and neuro-intensive care of secondary intracranial complications and haemorrhage must be a priority for ICUs receiving such patients. An appreciation of the critical timing and indications

for computed tomography (CT) scanning in the immediate assessment of these patients is essential; however, the majority of hospitals will not have on-site neurosurgical support. Early consultation and image transfer to the neurosurgical unit is fundamental to the rapid and safe transfer of those patients requiring management by neurosurgeons. Continuing neurosurgical advice on treatment and further scan interpretation are also components of the system of care for the brain-injured patient. The clinical management of patients with head injuries must be in accordance with the guidelines for the management of severe traumatic brain injury [19]. There must be a 24-h capability to secure an airway and provide mechanical ventilation in every receiving hospital. All receiving hospitals must have direct access to 24-h CT scanning, with at least on-call radiologists. An effective image transfer facility must be available between the receiving hospital and the neurosurgical unit. Patients with severe head injuries or focal signs should be transferred to the care of neurosurgery units regardless of whether they need surgical intervention.

Cardiothoracic Injuries

Twenty percent of severely injured patients admitted to the hospital have chest injuries. The majority of chest injuries are not fatal and their management will frequently rest with a surgeon whose specialty and interests do not regularly involve chest surgery. This clinical issue, combined with the potential for occult or progressive cardiopulmonary problems, poses a significant risk of under-diagnosis and avoidable compromise. Due attention must be paid to the history of the injury and, in the case of blunt trauma, to the magnitude of energy dissipated, which should alert the clinician to the severity of the intrathoracic damage. The inherent difficulties of chest assessment and sub-optimal resuscitation room radiographs should be recognised. Early diagnosis of lung contusion, pneumothorax and haemothorax is essential. An understanding of the potential for blunt or penetrating injury, cardiac tamponade, oesophageal rupture and aortic rupture comes from the mechanism of injury. Urgent specialist investigation and advice is mandatory. Penetrating chest trauma is infrequent in Italy, compared with most European countries, but 20% of such injuries require thoracotomy. Examination of the chest is a fundamental component of the cardiopulmonary assessment of the seriously injured, and it requires supervision by the most experienced clinician. Urgent referral to a specialist in thoracic or cardiothoracic surgery is required for major chest injury, massive or continuing intra-thoracic haemorrhage, major or persistent air leaks, suspected aortic tears and oesophageal ruptures. Interhospital transfer is frequently required for angiography and thoracic surgery, and it is also frequently required for access to cardiopulmonary facilities.

Abdominal Injuries

The reliability of clinical examination can be limited by the presence of altered consciousness, distracting pain from skeletal injuries, spinal cord injury, and the minimal peritonism caused by free abdominal blood. The detection of abdominal visceral injury is vital if mortality is to be minimised and other trauma salvage and reconstructive surgery undertaken safely. Emergency laparotomy for trauma is surgically demanding when the nature and extent of injury are unknown. The indications for immediate laparotomy include penetrating trauma with haemodynamic instability, ballistic injury, free air, diaphragmatic rupture, intraperitoneal bladder rupture and haemodynamic shock that is unexplained by other injury sites. All patients considered to be at risk for abdominal injury who cannot be continuously assessed must be investigated after the resuscitation phase and before definitive non-emergency treatment by the receiving unit's preferred method. The preference for CT, ultrasound screening, diagnostic peritoneal lavage and laparoscopy will depend on the stability of the patient and on the local 24-h availability of expertise and facilities.

Soft Tissue and Skeletal Injuries

The early management of severe open fractures, especially of the tibia, requires combined plastic and orthopaedic assessment. The severity of open fractures is frequently under-estimated. The significance of fracture fragmentation, closed or multi-layer degloving and the degree of contamination are pitfalls for the inexperienced surgeon. The fear of creating unmanageable wounds, inadequate wound excision, inappropriately sited extensions, insufficient skeletal immobilisation and delayed transfer have tested and undermined the efforts of reconstructing plastic and orthopaedic surgeons for years. The opportunity for salvage and optimal soft tissue cover – by the early transfer of microvascular tissue, local flap or acute shortening and bone transport – is frequently missed, despite published evidence to the contrary. A full wound excision and irrigation should be performed within 6 h of injury. Reduction and stabilisation of the fracture, with internal or external fixation (as appropriate), should also be performed at this time.

The initial assessment and management of pelvic high-energy complex fractures may be extremely difficult. Prompt and appropriate surgical reconstruction in the majority of cases will substantially improve outcome. The most demanding, but fortunately rare, type of injury consists of a haemodynamically and mechanically unstable pelvic disruption. This type of injury often exceeds a hospital's expertise and available facilities. The immediate application of a pelvic external fixator is indicated for the combination of

haemodynamic and mechanical instability relating to pelvic fracture/dislocation. This may be required in the resuscitation room. Pelvic fracture management demands an awareness of the urological components of the injury.

Many patients with pelvic (and acetabular) fractures have other and more pressing injuries, but the window for performing pelvic reconstruction is limited. Delay in transfer compounds the difficulty of surgery, increases the complication rate and worsens the outcome. Protracted ICU stays in district general hospitals are a common failing.

Spinal Injuries

Spinal injury patients are managed in general hospitals and in special units for orthopaedic or neurosurgical and spinal injuries. The latter are dedicated to the total management and rehabilitation of patients with spinal cord injury. Patterns of referral are well established, but often not supported by agreed upon standards or protocols. The infrequency of these injuries and the poor experience of the initial receiving staff are the weakest links in the process. Injuries at more than one level in the spine are not uncommon. For the best outcome, very early consultant involvement and discussion with specialists in spinal injury is required.

A full spinal protection, handling and nursing protocol must be in place for all at-risk patients. This must be maintained throughout the care and investigation of a patient identified to be at risk of a spinal injury. For all patients with unstable injuries a referral must be made within 12 h. Immediate care, transfer advice and prioritisation of patients are the advantages of this early contact. Imaging studies (plain radiographs and CT scans) must be completed on an emergency basis for patients with neurological deficits, and on an urgent basis (within 12 h) for other unstable injuries. CT scans must include the first normal vertebra above and below the fracture to allow surgical planning.

Vascular Injuries

Severe vascular injuries are a rare component of major blunt injuries. Penetrating injuries carry a much higher risk but are presently uncommon in Italy. Blunt or penetrating vascular injuries may frequently present a threat to life or limb, and the prompt recognition and rapid access to vascular surgical expertise is required for a favourable outcome. Vascular trauma emergencies may be complex and test the skills of the specialists in a vascular unit. There should be a full vascular radiology service. The balance between accessing

surgical proficiency and the potential ischaemic interval must be explicit and addressed in the emergency service planning for all receiving hospitals. Delays can be avoided by the vigilance of senior clinicians and by the establishment of preagreed upon transfer arrangements to a vascular surgical unit. Patients with vascular injuries should be accorded the same priority as neurosurgical transfers. All patients with significant blunt injuries and those with penetrating wounds require full documentation of the distal neurological and vascular status. Particular reference should be made to pulse volume and simmetry, skin capillary perfusion, temperature and sensation. Doppler pressure measurement should be recorded whenever possible.

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Fluid Resuscitation in Trauma

G. Berlot

Introduction

Trauma is a complex and multiphasic disorder, with a precisely known initial time, an advanced phase characterised by a wide array of neurohormonal and immunological changes [1] and latter phases during which the deranged functions recover to a greater or lesser extent. These latter phases can last weeks or months and the passage from one to another is ill defined. There is a certain amount of evidence indicating that besides the severity of injures, the appropriateness of the initial approach heavily influences the clinical course and possibly the long term consequences of trauma [2–4]. There is also evidence that the inflammatory response can eventually lead to the development of Multiple Organ Dysfunction Syndrome (MODS) if primed by factors immediately after the trauma [5]. This has led to the concept of the 'golden hour,' a theoretical timeframe during which the biological response to trauma is triggered. During this critical period, every effort should be made to restore perfusion and tissue oxygenation in order to prevent the activation of mechanisms ultimately leading to widespread tissue inflammation and apoptosis [6, 7].

Along with the maintenance of oxygenation, fluid resuscitation is the cornerstone of the treatment of injured patients. However, behind this apparently obvious statement, a number of open questions exist despite decades of investigations and thousands of papers focused on the topic. First, is it safer to initiate a fluid resuscitation in the field or to rush the patient(s) to the most appropriate hospital? Second, which is the best fluid, if any, to infuse? Third, what are the endpoints of treatment? This last question is of particular relevance, because both under and over-treatment can worsen the outcome and cause avoidable deaths. In other words, it is a matter of choosing the right strategy for the right patient, or providing correct answers to some critical questions.

Indications for Fluid Resuscitation

Critical Question: Which Patient Should I Aggressively Resuscitate in the Pre-hospital Phase?

Everyone involved in the pre-hospital treatment of trauma patients recognises that the 'golden hour' hardly can be used as intended. What the concept really means is, 'the sooner, the better.' In real life, a 'silver day,' intended as an interval for correcting tissue hypoxia, seems a more realistic goal [8].

A number of circumstances contribute to delays in restoring perfusion, including a prolonged extrication time, difficulties in securing an intravenous line, environmental factors etc (Fig. 1). There are two mutually exclusive lines of thinking on this subject, each with its own rationale, and advocates and detractors. The 'scoop and run' policy basically aims to avoid further time gaps between the rescue and the prompt treatment of surgically-amenable injuries. Accordingly, only life-saving procedures that cannot be delayed are performed, including securing the airways and decompressing tension pneumothoraces by means of needle puncture or field thoracostomy. This approach is the opposite of the 'stay and play' strategy, which mandates a full stabilisation (i.e. restoration of acceptable blood arterial pressure values) before transportation. In the early 1990s Bickell et al. [9] demonstrated that patients with penetrating torso injuries (mostly caused by fire arms and stab wounds) who underwent an aggressive fluid resuscitation in the pre-hospital phase had a worse prognosis, compared with patients who were rapidly rushed to the hospital. The authors attributed these results to various factors, including the greater lapse of time between the injury and the definitive surgical repair of bleeding injuries, the dilution of the coagulation factors by the resuscitation fluids, and a higher arterial pressure resulting in a greater escape of blood through torn blood vessels. Other authors have also demonstrated a worse outcome in patients who were fluid-resuscitated in the field, although some attribute this finding primarily to the longer time spent attempting to establish an intravenous line than to the counterproductive effects of fluid resuscitation [10]. Due to the lack of clinical trials compatible with the Evidence Based Medicine (EBM) criteria, in 2001 the Cochrane Group stated that, at that time, there was insufficient data to conclude that the early and/or large volume administration of fluid is of any benefit in uncontrolled haemorrhage [11]. Today, the situation remains the same; however, if taken to its extreme – i.e. by delaying the restoration of volaemia until the diagnostic work-up is complete, the practice could increase the already elevated rate of potentially avoidable deaths of trauma patients, most of which are caused by untreatable hypotension – either the result of advanced hypovolaemia alone, or in association with hypoxaemia [2, 12]. Moreover, there are circumstances in which an aggressive fluid resuscitation and/or the use of

Fig. 1. A typical scene after a car crash. The patient is still trapped; the positioning of an intravenous line is difficult and time consuming. Under these circumstances the concept of the 'golden hour' is naïve and purely indicative of the urgent need of restoring blood flow as soon as possible. In addition to these difficulties, it is not yet clear whether the patient will benefit more from a 'scoop and run' strategy or a 'stay and play' approach

vasopressors is warranted, as in the case of a coexisting head trauma, where a prolonged hypotension sets the stage for the occurrence of secondary brain injuries, which carry devastating consequences, or in patients with extensive burns and massive musculoskeletal injuries [13, 14]. Thus, although it is apparent that, in the absence of the clinical indications noted above, the administration of large volumes of fluids is not advisable until active bleeding focuses have been excluded, nevertheless there are situations in which the restoration of volaemia is critical. It can be concluded that (a) the positioning of multiple large-bore IV lines is mandatory, provided this manoeuvre does not cause a substantial delay in transportation; (b) in the presence of penetrating injuries of the torso or other clearly exsanguinating injuries (i.e. major vessel injuries) the time spent on the scene cannot be justified by the obtainment of 'normal' arterial pressure values; and, finally, (c) fluid resuscitation, as well as the concomitant use of vasopressors, should be titrated more on the clinical conditions and on a therapeutic target, rather than on algorithms which do not take into account the minute-by-minute changes of perfusion (this will be discussed at greater length below).

The Choice of Fluid for Resuscitation

Critical Question: Which Fluid Should I Give?

Despite the fact that most trauma patients present the signs and symptoms of hypovolaemia due to moderate-to-severe blood loss [15], packed red cells (PRC) and blood derivates are uncommonly transfused on the scene of the accident. It is important to carefully scrutinise the pros and cons associated with their use even in more advanced phases [16, 17]. Today, many different classes of fluids (other than blood and blood-derivates) are available [18, 19], and their actions are best understood by examining the relationships between the fluids used in the resuscitation of trauma victims and the body's water compartments (Fig. 2).

Crystalloids are a broad family of water solutions composed of inorganic ions and small organic molecules. Depending on their concentration, they may be iso-, hyper- or hypotonic to plasma. Due to their volume of distribution (VD), which encompasses the whole extracellular volume (intravascular + interstitial), they must be administered in consistent amounts in order to obtain a sustained increase in volaemia. Their half-life is limited, due 1) to the fact that they partly escape from the intravascular space into the tissues, especially when the capillary permeability is increased or in the presence of hypoalbuminaemia, and 2) to the fact that they are eliminated from the kid-

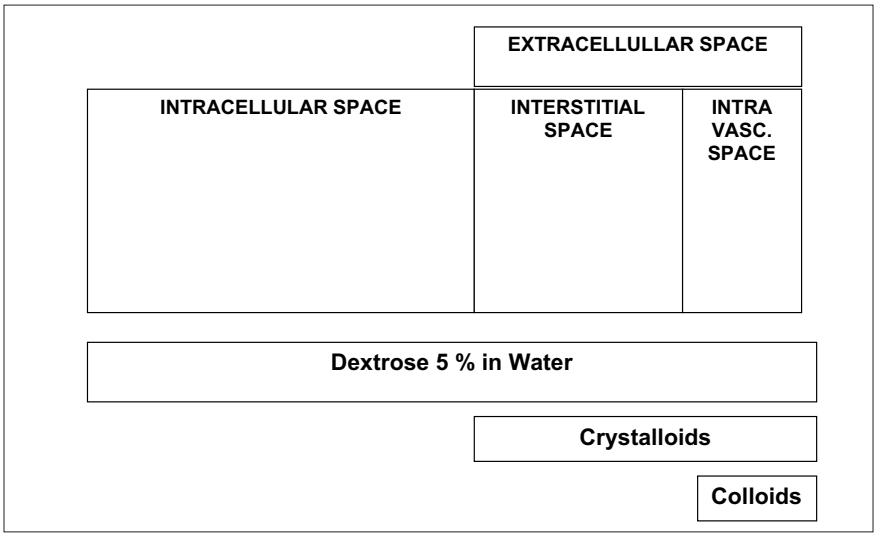

Fig. 2. Distribution of body water and resuscitation fluids. Dextrose 5% in water freely permeates the whole water distribution space, whereas crystalloids and colloids have access only to the extracellular and intravascular spaces, respectively

neys. A simple rule of thumb based on their pharmacokinetic properties is that 3–3.5 volumes of crystalloids replaces 1 volume of lost blood. There are several drawbacks to a full crystalloid-based resuscitation; these are mainly dose-related and include the occurrence of fluid overload, the dilution of albumin and the associated reduction in plasma colloid oncotic pressure (COP), the dilution of blood bases and concomitant hyperchloremic acidosis and tissue oedema. To overcome these drawbacks, hypertonic saline (HS) solutions (whose concentrations range from 5.4 to 7.5%) are extensively used, either alone or in combination with colloids. The rationale behind their use is based mainly on their elevated hypertonicity, which causes an increase in COP and subsequent refilling of the intravascular space by water from the interstitial space [18]. The use of HS is associated with a series of consequences. First, there is a substantial increase in volaemia, which reduces the risk of fluid overload. Second, the escape of water from the tissues helps reduce brain oedema, making HS suitable for the treatment of elevated intracranial pressure; this, however, is somewhat controversial in view of the results from some trials [20–23], despite radiologically documented decreases in brain extracellular fluid [24]. Third, the use of HS has been associated with a modulation of the immunologic response, whose clinical value has not yet been established [25]. Last but not least, because less volume is needed, packages of HS are lighter and smaller than those of other crystalloids, making them suitable for on-scene use and mass casualties. The side effects of HS are related to their action, and include hypernatraemia, hyperchloremic metabolic acidosis and the risk of pulmonary oedema, especially in patients with limited cardiac reserve. Another theoretical risk derives from an excessive increase of the volaemia and/or arterial pressure, which could enhance bleeding [18]. Because it is eliminated by the kidneys, HS has a time-limited effect. To increase its length of action, colloids have been added to the HS preparation. This not only extends the polemic effect, it also enhances the HS-induced elevation of COP.

Colloids are the other class of substances commonly used in fluid resuscitation. Although extremely heterogeneous as far as their origin (natural vs synthetic), molecular weight (MW), chemical structure (amino acids vs sugars) and T/2 are concerned, colloids nevertheless share some common features, including the VD, which is limited to the intravascular space, provided that capillary permeability is normal, an elevated size and high MW, which causes the COP to increase and eventually prompts the transcapillary escape of water from the tissues [18, 19]. However, as far as this latter point is concerned, it should be noted that colloid solutions, with the exception of albumin, are polidisperse, as they consist of molecules with different MW (the final value is influenced by the most represented one). Based on these features, the effects on volaemia are derived both from the volume administered

and the water-retaining capabilities of each agent [26]. Such characteristics justify the collective definition of 'plasma expanders' attributed to the colloids. All these agents have been associated with side effects; some of them are expected and, as with the crystalloids, dose-related. Anaphylactic reactions, although not common, can also occur and be life-threatening.

- Albumin represents the prototype of this class of volume expanders. It is synthesised by the liver and released into the bloodstream. Its elevated MW (69KD) is the main determinant of COP. Clinically available albumin derives from pooled human plasma, heated and sterilised by ultrafiltration and prepared in various concentrations, ranging from 2.5 to 20%. In 1998, a systematic review (SR) performed by the Cochrane Group of 30 randomised, controlled trials (RCT) comparing albumin vs crystalloid-based fluid resuscitation in the treatment of 1149 patients with burns, hypotension or hypoalbuminaemia, concluded that the odds ratio of mortality was significantly increased in patients given albumin [27]. Although this result was not confirmed in another SR [28], some authors have proposed banning or at least limiting the use of albumin in critically ill patients, pending the results of other RCTs [29, 32]. Two recent RCTs failed to confirm the results of the Cochrane Group [27]. Despite these findings and the properties of albumin, it is not commonly suited as a plasma expander in volume resuscitation, mainly due to its high cost and the ready availability of other molecules.
- Dextrans are glucose polymers available in two different MWs – 70 KD and 40 KD. The first (D70) has been extensively used as a plasma expander, and the infusion of 1000 ml of D 70 is associated with an increase in plasma water of 600–800 ml [18]. The use of D70 has been limited by the occurrence of harmful side effects, including coagulative abnormalities and the occurrence of severe hypersensitivity reactions.
- Gelatins are modified beef collagens with a relatively low MW (35–40 KD), which makes them relatively short-lived (T/2 of ± 2 h) and not very effective in terms of plasma expansion (70% of infused dose). On the positive side, there is no dose limitation and the gelatins have a lower rate of hypersensitivity reactions, compared with D70 [18, 19].
- Hydroxyethil starches (HES) are the most recent and probably the most widely used colloids. The molecules of HES derive from the amylopectin extracted by maize or sorghum and conjugated with ethylene oxide. Several HES solutions are available and can be subdivided mainly according to their relationship between the native molecule and the ethylene oxide radical (Table 1). The majority of substitutions occur in the C2 position of the glucose ring, and the rest in the C3 and C6 positions. The C2/C6 ratio is related with the T/2, the enzymatic degradation of HES being slower in the presence of an elevated C2/C6 ratio. The degree of substitution

Table 1. Characteristics of different HES solutions

	LMW			IMW		HMW
	70/05	130/0.4	200/0.5	200/.05 200/0.62 (Pentastarch)	200/0.62	450/07 (Hetastarch)
Concentration	6	6	6	10	6	6
Volume efficacy (%)	80–90	100	100	130–150	100	100
Duration (h)	1–2	3–4	3–4	3–4	5–6	5–6
Mean MW	70	130	200	200	200	450
Degree of MS	0.5	0.4	0.5	0.5	0.62	0.7
C2/C6 ratio	4:1	9:1	6:1	6:1	9:1	4.6:1
Max dose (ml/kg)	33	33-50	33	20	33	20

LMW, low molecular weight; *IMW*, intermediate molecular weight; *HMW*, high molecular weight

(DS), ranging from 0 to 1, indicates the proportion of glucose molecules which have been substituted. HES with a DS close to 1 have a greater resistance to enzymatic hydrolysis than those with a lower value. The final step in the preparation of HES consists in the cleavage of the starch into fragments of the required MW; however, all HES are polidisperse. They are removed from the blood via two main mechanisms: (a) renal excretion; and (b) redistribution in the tissues, particularly in the reticulo-endothelial system. Among the HES solutions, Pentastarch is thought to exert more anti-inflammatory effects and to be the most efficient in terms of the retention of fluids within the intravascular space. The side effects of HES are similar to those of D70, namely, anaphylactic reaction and coagulation disturbances [33]. High MW HES have been associated with the occurrence of acute renal failure in septic patients [34].

Knowing the pharmacology of resuscitation fluids makes it possible to draw some conclusions. It is clear that all the above listed agents are effective in restoring blood volume. The main differences are: (a) their efficacy, which is maximal with HS, intermediate with colloids (high MW HES > D70 > gelatins) and lowest with crystalloids; (b) their duration of action is greatest in high-MW HES, but longer in gelatins than in crystalloids (high MW HES > D70, and gelatins > crystalloids); and (c) the rate and severity of unanticipated side effects, which are absent with crystalloids and more frequent with HES, D70 and gelatins. On the basis of these considerations, and in the

absence of contraindication, it appears appropriate to start an infusion of crystalloids and to shift to HS colloids if no response or an insufficient one is recognised.

The Endpoints of Volume Resuscitation

Critical Question: How Much Fluid Is Enough?

As is true with all pathological states, if one decides to start fluid resuscitation, some clues are needed to up or down-regulate the volume administered. This point is vital, given that severe clinical consequences can result from an inappropriate administration of fluids. Unfortunately, the most common markers of hypovolaemia and/or hypoperfusion monitored in the pre-hospital phase are also the least reliable for driving the therapy, namely, the arterial pressure (AP) and the heart rate (HR) [15, 36]. Moreover, these signs can also be influenced by factors other than trauma, including the effect of drugs and alcohol, the presence of medullary injuries, the presence of intoxication, etc. Under-resuscitation can result in a poor outcome through two different pathways. In the first case, hypoperfusion is severe and acute, ultimately leading to the irreversible damage of the brain and/or to death. This scenario appears to be relatively common, as a considerable rate of in-hospital preventable deaths still occur in the early post-admission phase due to hypovolaemia [12, 35]. In the second case, a less severe but long lasting hypoperfusion is present, leading to a gradual deterioration of organ function until full-blown MODS occurs [37]. A hypoxia-driven translocation of germs and/or germ-derived substances from the gut lumen to the bloodstream likely plays a major role in the initiation and worsening of this condition [5].

Unfortunately, the diagnostic tools for investigating the presence and extent of hypovolaemia in the pre-hospital setting are rather limited. If the necessary diagnostic tools were available, one could recognise alterations that are commonly observed in some of the haemodynamic variables, including AP, HR and the presence of peripheral cyanosis – all of which can also be caused by factors different from hypovolaemia, including pneumothorax, pain and hypothermia. Keeping in mind these limitations, two approaches are possible [38–40]. The first involves the assumption that every severely injured patient is hypovolaemic, the rationale being that it is better to err on the side of overtreatment and start an aggressive volume infusion immediately. The infusion should be continued until the diagnostic investigation either confirms or excludes a source of bleeding. The pros and cons of this extended 'stay and play' attitude have been described earlier. (The continuation of the volume resuscitation en route to the hospital might be said to constitute a third approach, namely 'run and play.') The second approach is based on the

gross evaluation of clinical conditions: in the case of a disturbance of consciousness, it is safer to obtain a relatively elevated arterial pressure (systolic arterial pressure 120–130 mmHg) in order to prevent the occurrence of a secondary brain injury. Lower values (systolic arterial pressure 90 mmHg) are tolerated in trauma patients without any neurological injury, provided that the arrival to the destination hospital does not exceed 30–40 minutes. This second strategy, which in essence consists of hypotensive resuscitation, closely resembles the time-honoured anaesthesiologic practice of 'controlled hypotension,' currently used in neurosurgery and in other situations requiring a blood-free surgical field. As a matter of fact, despite the development of a number of diagnostic tools designed to detect both the efficacy of fluid resuscitation and tissue hypoperfusion in critically ill patients, their application in the pre-hospital phase appears limited. This is due either to (hopefully) the short time elapsing between the rescue and the admission, or to the technical limitations associated with the various techniques [41]. Moreover, it should be strongly emphasised that in critically ill patients, time trends of biological variables are more valuable than absolute values; and that the use of point-of-care diagnostic technologies on the scene of trauma could supply, at best, a panel of initial markers (i.e. blood lactate, base excess etc.) whose variations should be monitored during a more advanced phase of treatment. With these limitations in mind, capnometry appears to be the only monitoring tool easily suitable in the pre-hospital phase, as it can supply real-time information both on the haemodynamic and the pulmonary function in tracheally intubated and mechanically ventilated patients [41–43].

Conclusions

Fluid management in severely injured patients is a complicated issue, and there are no high-ranked RCTs that can help clarify the situation. Nevertheless, some conclusions can be drawn from the existing studies. First, patients are more important than protocols, and fluid resuscitation should be tailored to the condition of the patient's, i.e. as this can be ascertained with the limited diagnostic tools suitable for on the scene and/or in the immediate post-admission phase. Adjustments of the flow rate and/or type of agent administered must be done once more information becomes available. Second, even if there is no evidence of the superiority of one preparation over another, differences in the side effects of blood coagulation indeed exist, and these differences should be taken into account when deciding which preparation to use. Finally, whatever fluid, regimen or strategy is adopted, organ perfusion should be restored as soon as possible.

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Ongoing Challenges in Sepsis and Organ Dysfunction

A.E. Baue

The challenges we face in treating patients with sepsis leading to organ dysfunction and failure are overwhelming. Their descriptions and dilemmas could fill a number of books. I will focus on several challenges, including:

- Polymorphisms
- The problems of blood transfusions
- Harbingers or predictors of doom
- Neutrophils
- The lungs and multiple organ dysfunction syndrome (MODS)
- Control of hyperglycaemia (is scoring futile?)
- The problem of lumping of all infections as sepsis.

Polymorphisms

Wang writes about polymorphisms saying, 'at the same time it is well known that the response to infection varies significantly between individuals and that genetic factors contribute to this variation' [1]. He goes on to define single nucleotide polymorphisms (SNPs) as 'allelic variations in a single base pair (insertion, deletion or substitution) with a frequency of less than 1% compared with the normal allelic variant. SNPs are found in exons and introns or in the promoter region of a gene, and they are most frequent in introns and promoters where they do not alter protein function.' Sutherland et al., found an association of specific SNPs in the pathogen recognition receptor CD14, mannose-binding lectins and Toll-like receptor 2 with infections and increased intensive care unti (ICU) mortality [2]. Watanabe et al., found extremely high interleukin (IL)-6 blood levels in critically ill patients to be associated with tumour necrosis factor (TNF) and IL-1-related gene polymorphisms [3]. Polymorphisms have also been reported in haemostatic genes – prothrombin, fibrinogen, factor V, tissue factor, endothelial protein C receptor and plasminogen activator inhibitor 1 genes [4]. Such studies of

polymorphisms may help our understanding of the development of sepsis and in the future identify patients at risk of developing and dying of infections and thus anticipate disease and therapy [5].

Blood Transfusions

Problems with blood transfusions in critically ill and injured patients have now become facts with increased experience. Blood can be lifesaving, but an early report by Moore et al., in 1997, described blood transfusion as an independent risk factor for post-injury multiple organ failure (MOF) [6]. Transfusion has also been demonstrated to increase the risk of infection and MODS in ICU patients. This was dose-related [7]. Other studies have shown transfusion to be an independent predictor of mortality and poor outcome of trauma admissions, even after controlling for injury severity [8, 9].

Why is blood transfusion a risk factor? Blood transfusions may adversely affect outcome by their well-documented effect on immunologic and inflammatory responses. Storage of blood lowers adenosine triphosphate (ATP) and temporarily decreases 2, 3 DPG levels, interfering with the ability of red blood cells (RBC) to unload oxygen and impairing RBC deformability [10]. Leukocyte reduced blood is used more commonly in Europe and Canada than in the United States, and it may be protective. A small beneficial affect has been found [11]. Fresh blood also seems better [12]. The age of the blood correlates with risk. Blood conservation programs may help. Phlebotomy losses in ICU patients can be large (phlebotomy anaemia) [13]. Elimination of unneeded testing, large-volume collection tubes and wastage of diluted blood drawn from catheters will help decrease the need for transfusions [14]. Three-way stopcocks will help minimise blood loss [15]. Anaemia in ICU patients is common. The threshold for transfusion (transfusion trigger) of a haemoglobin level of 10 g/dl and a haematocrit of 30% should be abandoned in favour of blood transfusion for a defined physiological need [16]. Blood substitutes are still being evaluated and are not ready for general use [17]. Recombinant human erythropoietin has not been found to be an efficient use of limited resources to avoid transfusion in critically ill patients [18].

Harbingers of Doom

The explosion of knowledge about injury, inflammation and infection has identified a large number of mediators and biologic functions or activities. The complexities and interrelationships of these mediators make it difficult to define an organised, sequential response in the experimental animal or

patient exposed to such insults. In fact, some believe that there is no such coordinated system, but rather multiple overlapping responses that easily get out of control. Given our present state of knowledge, one wonders whether such indicators are 'harbingers of doom and/or gloom,' i.e. mediators and activities whose level or performance indicates an unfavourable outcome such as death, MOF, acute respiratory distress syndrome (ARDS) or another untoward event [19]. The question remains: are these *true* mediators of unfavourable outcome, or just markers of impending disaster?

A frequent exercise in the ICU is to look for measurements, laboratory tests or pathophysiologic states that predict big trouble, a fatal outcome or both. Many mediator levels, laboratory measurements and other phenomena have been used to suggest a bad outcome. There are many examples of this, such as a high IL-6 level, a low anti-thrombin III level or an increased soluble TNF receptors (sTNFR). None of these scores or tests of levels is accurate enough to warrant discontinuing therapy in an individual patient. It is important to give the patient the benefit of the doubt in trying for survival even though the odds are bad. Seemingly miraculous recoveries do occur. There are few absolutes in human biology. The Harvard law of experimentation states that: 'under controlled conditions, animal and people behave as they damn well please.' There are few conditions that are definitive, one being (as my friend, Father Kevin O'Rourke, pointed out, 'If your brain is dead, you are dead.') Short of that, however, caring for an ICU patient is always worth a shot. I rely on the progression of events to advise families, friends and the clergy. Progressive deterioration in organ function over a period of days, with no response to therapy or evident remedial course of action is the best indication that the situation is becoming irreversible.

All of these measures have been interesting and led to innumerable publications, international conferences and clinical studies. Most of the findings have been retrospective. Thus, 'these harbingers or predictors of doom and disaster' couldn't help the patients. Some identify mechanisms of disease severity, development of infection or complications. Others may have little or no relevance to what seems to be happening to the patient. Scoring systems, while often predicting disaster or mortality, may be used in certain circumstances to improve care in general. I divide scoring systems into those for:

- Operations and surgical patients
- Trauma
- Patients in ICU's (adult or paediatric)
- Predictions of the development of sepsis (infection).

  There may be others.

The question remains, is there any value in listing, describing or reviewing factors that suggest a poor outcome? Can we do anything for the patient with this information? Does it help patients? I don't think so. The levels or factors

may have nothing to do with the outcome; these are simply markers of severe illness. I believe that there is value in such a review in that it helps define the pathophysiological events and limits in human disease. From this may come an idea, a therapy, or a research project which will increase our understanding. Some factors predict specific abnormalities, such as ARDS, and may suggest earlier or alternative therapies. The real question then is – are they markers or mediators or both? Further understanding of these agents is necessary. Examples of a few are shown in Table 1. There are many more.

Table 1. Harbingers of doom

Measurement	Predicts
Systemic neuropeptide	Lethal outcome
Decreased cytokine expression	Worse prognosis
Increased $sPLA_2$	Increased hypoxamia
High serum IL-18	Lethal outcome
Increased brain natriuretic peptide	Poor outcome
Low lipid and lipoprotein	Poor outcome
Low exogenous lactate clearance	Increased mortality
High macrophage migration inhibitory factor (MIF)	Bad trauma
Early lymphocyte apoptosis	Poor outcome
High IL-6	Decreased survival
Pre-op B-type Natriuretic peptide	Trouble after coronary artery bypass graft (CABG)
Low ICU-antithrombin activity	Adverse outcome
Intra-abdominal hypertension	Worse outcome
Coagulopathy with sepsis	Increased mortality
Elevated $sPLA_2$ (secretory phospholipid A_2)	Lung problems
Diminished blood cell pro- and anti-inflammatory cytokines	Worse prognosis
Calcitonin gene-related peptide (CGRP) and substance P with sepsis	Increased lethal outcome

Neutrophils

Neutrophils are known to be necessary to fight infection, but they also produce problems when a septic process is activated. At the Society of Critical Care Medicine Congress in 2003, Abraham reported on neutrophil activation beginning with phosphoinositide 3 kinase (Pl3-K0 to AKT) [20]. Patients with greater neutrophil activation of AKT did poorly. Downey reported that 'neu-

trophils are a major mechanism whereby the lung is injured with sepsis' [20]. Slutsky cites mechanical ventilation as a problem leading to MODS by stimulating the release of cytokines and margination of neutrophils [20].

Hyperglycaemia

Tighter control of blood glucose is known to be important in reducing complications of diabetes, such as diabetic retinopathy, nephropathy and neuropathy. It is now believed to be important also in critically ill patients. Hyperglycaemia has been found to be associated with poor outcomes. It affects immune function and promotes dehydration and inflammation, and it may contribute to wound infections. Van den Berghe et al., as reported by Hashmi and Rogers [21], showed that blood glucose control significantly reduced mortality in critically ill patients, and also decreased septic episodes.

Scoring

Another favourite pastime in ICU's is the development of scores – scores that predict disaster or show the severity of trauma or illness. There are many such scores. For trauma or injury, I have found more than 25 scores. For ICU scoring and sepsis there are over 45 scores. There are cell injury scores, scores for operations (surgery), infection probability scores, futility scores, paediatric scores, an injured extremity score, and burn scores. Some scores are organ-specific, such as the Glasgow Coma Score. You name it, and there is a score for it. Examples are shown in Table 2.

Perhaps we can predict outcomes from scoring or suspect a bad result from key measurements, but can we do anything about it? I would prefer having a measurement or a score that would help me treat the patient differently, in

Table 2. Examples of Scoring Systems

Trauma	ISS – Injury Severity Score
	AIS – Abbreviated Injury Score
	TS – Trauma Score
	PEBI – Penetrating and Blunt Injury Score
Severity of illness scores	
	APACHE – Acute Physiology and Chronic Health Evaluation
	SAPS – Simplified acute physiology Score
	TISS – Therapeutic Intervention Scoring System
	MPM – Mortality Probability Model

order to turn things around and prevent a disaster. I suspect that there are times in the ICU or operating room (OR) when things seem bad for a patient but we don't seem to be able to do anything about it. Instead of just wringing our hands, we take measurements or calculate a score. It doesn't help the patient, but it makes us feel as if we are doing something. The development of scores has been a full time career for many in science. They have meetings and conferences and international get-togethers to review, debate and fine-tune scoring. Some measurements that predict disaster may suggest ways the abnormality developed. This could lead to a better therapy. Angus wrote about scoring system fatigue, and urges evaluations of ICU's, not just scores [22].

What Is Sepsis?

A major challenge is to stop talking, writing and trying to treat sepsis, and begin separating individual infections. We can't treat sepsis – it is not a disease. It is not even a syndrome, it is a lumping together of patients who have infections or inflammation from any source, region or cause. You can't treat sepsis. Why do some authors like to lump everything together as sepsis? Is it because it is catchy – it's modern – it's what everyone is writing or talking about? Some of the gurus of sepsis have suggested this, including the late Roger Bone [23]. Hong et al. [24], wrote about the influence of infection on sepsis. According to them, the nature of infection in surgical ICU patients has no influence on the outcome of sepsis. This seems rather remarkable. Martin et al., called sepsis a disease [25]. Hundreds of thousands of articles and studies have been written about sepsis – its definitions, epidemiology, pathophysiology and treatment. Now, there is the 'surviving sepsis' contingent.

The question remains, however, how do you evaluate and treat an empyema of the lung, acute hemorrhagic pancreatitis, perforated diverticulitis and appendicitis, compared with *Staphylococcus aureus* pneumonia and *E. coli* enteritis? The Canadian Sepsis Treatment and Response Registry (STAR) concluded that severe sepsis is a complication to recognise, monitor and manage [25]. Matot and Sprung use Rackow's definition of sepsis as 'the systemic inflammatory response to infection' [26]. Thus, shouldn't we call it an infection (where is it, what kind?) with sepsis. To treat so-called 'sepsis,' we culture, give antibiotics and support the circulation, ventilation, the kidneys, liver, gastro-intestinal tract, endocrine system and central nervous system. When do we drain, explore, tap, catheterise, irrigate, excise, amputate or monitor? Is viral flu/Asian flu sepsis? Let's be specific – where is the infection or inflammation and what is it doing to the patient? Only when we have answered these questions can we treat it specifically, have better measurements and compare results [27].

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Microdialysis Monitoring of Organ Chemistry in the Intensive Care Unit

U. Ungerstedt

Introduction

Microdialysis is a technique for sampling the chemistry of the interstitial fluid of tissues and organs in animals and man. It is minimally invasive and relatively simple to perform in a clinical setting. The lactate/pyruvate ratio in the dialysate from the tissue is a well-known marker of changes in the redox state of cells caused by ischaemia/hypoxia. Loss of energy due to ischaemia eventually leads to an influx of calcium and a decomposition of cell membranes, which liberates glycerol into the interstitial fluid. Thus the lactate/pyruvate ratio and glycerol have become the most important markers of ischaemia and cell membrane damage.

In neurointensive care, the primary insult at the site of the accident is beyond our control; however, secondary insults during intensive care should be avoided by all means. The single most important finding from our microdialysis studies in man is the dramatic difference in the vulnerability of the penumbra surrounding a lesion, compared with normal brain tissue. As a consequence, cerebral perfusion pressure that is perfectly adequate for the normal brain may be totally inappropriate for the vulnerable penumbra and eventually result in a severe secondary insult.

Microdialysis monitoring has recently been applied to peripheral organs – for example, graft monitoring after liver transplantation, monitoring the intraperitoneal chemistry after abdominal surgery and monitoring flaps after reconstructive surgery. The technique has proven to be highly sensitive for the detection of local ischaemia using the same markers as in the brain.

Perhaps the most important aspect of microdialysis monitoring of organ chemistry is the fact that changes in organ chemistry often precede clinical symptoms, offering intensivists a 'window of opportunity' for starting treatment several hours or days earlier than is possible when relying solely on non-chemical symptoms.

The Microdialysis Technique

Microdialysis is a technique for sampling the chemistry of the interstitial fluid of tissues and organs in animal and man [1]. It is minimally invasive and relatively simple to perform in a clinical setting. It has become a standard technique in physiological and pharmacological investigations on animals with over 9000 published papers. During the past 10 years, it has developed into a clinically useful technique, with more than 500 papers published in several different clinical fields.

The idea of inserting a dialysis membrane into the tissue where a continuous flow of physiological fluid inside equilibrates with the interstitial fluid outside was conceived 30 years ago by Delgado et al. [2] and Ungerstedt et al. [3]. Simply put, samples of the tissue chemistry are transported out of the body for analysis in contrast to the traditional biosensor, where the analysis takes place inside the body. The availability of modern analytical techniques has made microdialysis a 'universal' biosensor capable of monitoring essentially every small molecular compound in the interstitial fluid of endogenous as well as exogenous origin. The original microdialysis 'probes' for animal use have been developed into flexible and sterile microdialysis 'catheters' (CMA Microdialysis, Stockholm), which are CE labeled and FDA approved for the use in human brain and peripheral tissues.

The dialysis membrane at the distal end of a microdialysis catheter functions like a blood capillary. Chemical substances from the interstitial fluid diffuse across the membrane into the perfusion fluid inside the catheter. The recovery of a particular substance is defined as the concentration in the dialysate, expressed as percent of the concentration in the interstitial fluid.

A low perfusion flow and a long dialysis membrane give a high recovery. If the membrane is long enough and the flow slow enough, the concentration in the dialysate will approach the concentration in the interstitial fluid, i.e. recovery will be close to 100%. In the case of brain catheters and perfusion pumps available for clinical use, the standard perfusion flow is 0.3 µl/min and the length of the membrane is 10 mm, allowing exact positioning in relation to a lesion in the brain. Under these conditions, recovery has been estimated to be approximately 70% [4]. In peripheral tissues, using 30 mm membranes, the recovery is close to 100%

It is important to realise that the concentration in the dialysate not only depends upon the flow and the length of the membrane, but also upon the supply of substances from blood capillaries as well as uptake and release from cells. For example, the supply of glucose to the microdialysis catheter may decrease due to a decrease in the capillary blood flow and/or due to an increase in the cell uptake of glucose.

Biochemical Markers of Ischaemia and Cell Damage

The interstitial fluid is the 'cross road' of all substances passing between cells and blood capillaries. By monitoring this compartment in the brain and peripheral tissues, it is possible to get crucial information about the biochemistry regarding how seriously cells are affected by, for example, ischaemia, hyperaemia, trauma, hemorrhage or vasospasm, as well as various physiological, pharmacological and surgical interventions during intensive care.

Although microdialysis samples essentially all small molecular substances present in the interstitial fluid, the use of microdialysis in intensive care has focused on markers of ischaemia and cell damage. The reason is that they are of obvious importance for the survival of the tissue, in addition to being well understood from a biochemical point of view and easy to interpret in the clinical setting of intensive care.

Microdialysis tells us how cells react to an increase or decrease in the supply of oxygen and glucose. However, while normal tissue may not suffer from a moderate decrease in oxygen and glucose, vulnerable cells may simply not survive. In this way, severe secondary damage to brain tissue may pass unnoticed if microdialysis is not performed in the most vulnerable tissue of the brain and peripheral tissues (see below).

Lactate/Pyruvate Ratio

The lactate/pyruvate ratio is a well-known marker of changes in the redox state of cells that are caused by e.g. ischaemia [5]. Pyruvate is formed from glucose in the anaerobic phase of glycolysis, generating two molecules of ATP. It enters the citric acid cycle, provided that oxygen is available. The citric acid cycle is the dominant producer of energy, yielding 32 molecules of ATP. If the tissue is exposed to ischaemia (a decrease in blood flow causing an inadequate supply of oxygen and glucose) the production of ATP decreases.

The cells attempt to compensate for the decrease in ATP production by increasing the turnover of glucose in the anaerobic part of glycolysis. During this process it is necessary to regenerate NADH from NAD^+, by converting pyruvate to lactate, which causes an increase in lactate and the lactate/pyruvate ratio.

The decrease in glucose delivery from blood capillaries causes a fall in the glucose concentration in the interstitial fluid. This leads to a decreased production of pyruvate, due to lack of glucose. In the dialysate this is seen as a fall in pyruvate and a further increase in the lactate/pyruvate ratio, i.e. a worsening of the ischaemia.

Expressing the two analytes as a ratio has the advantage of abolishing the influence of changes in catheter recovery, as such changes will influence lactate and pyruvate to a similar degree. Therefore, the lactate/pyruvate ratio may be used to compare the redox state of different tissues in one individual as well as in different individuals. The ratio is essentially the same in all tissues, i.e. 15–20. We consider a ratio above 25 as a sign of tissue ischaemia.

Lactate alone is not as good a marker of the redox state of the cells, as an increase in lactate may be due to hypoxia or ischaemia, as well as hypermetabolism [6].

Glycerol

Glycerol is an integral component of cell membranes. Loss of energy due to ischaemia leads to an influx of calcium into cells, activation of phospholipases and, eventually, decomposition of cell membranes, which liberates glycerol into the interstitial fluid [7].

Considering the rapid increase and decrease of glycerol in vulnerable peri-contusional brain tissue, it seems highly likely that cells may react by 'leaking' more or less glycerol due to the severity of the ischaemia. The normal glycerol concentration in the dialysate from the brain when using a 10 mm dialysis membrane and a perfusion flow of 0.3 μl/min is approximately 50–100 μM [8].

In subcutaneous adipose tissue, in contrast, glycerol originates from the splitting of fat (triglycerides) into free fatty acids and glycerol. This process is controlled by the local sympathetic noradrenalin nerve terminals. Glycerol in subcutaneous tissue is therefore an indirect marker of sympathetic tone in the dermatome where the catheter is inserted [9].

During intensive care, a subcutaneous catheter may be inserted in the periumbilical region monitoring glycerol as an indicator of sympathetic 'stress' and glucose as an indicator of the systemic blood glucose levels [10]. The normal glycerol concentration in the dialysate from subcutaneous tissue of a sedated patient when using a microdialysis catheter with a 30 mm dialysis membrane and a perfusion flow of 0.3 μl/min is approximately 200 μM.

Implanting and Positioning of Microdialysis Catheters

Microdialysis monitors the local chemistry of an area roughly corresponding to a diameter of a few mm and the length of the catheter membrane. The interpretation of microdialysis data therefore depends upon the position of the catheter in relation to the existing pathology. The first clinical microdialysis catheters appearing on the market were not visible on computed tomography (CT). Several clinical studies in the literature are therefore difficult to

interpret, as we do not know if the microdialysis catheters ended up in normal tissue, penumbra tissue surrounding a contusion or in damaged or dead tissue.

Catheters available today are easily visible due to their gold tip. It is of great importance for the interpretation of bedside microdialysis data that the position of a catheter in the brain can be determined from CT [11]. Only then is it possible to use microdialysis data effectively 1) to provide an early warning of secondary insults and 2) to evaluate the result of various clinical interventions aimed at improving the condition of brain tissue during neurointensive care.

It is important to adopt a consistent strategy with respect to placement of the catheters – for example, in the penumbra surrounding a mass lesion in the brain, in the region most likely to be affected by vasospasm after subarachnoid haemorrhage and/or in 'normal' brain tissue.

In the intensive care unit (ICU) it is often convenient to place catheters through cranial bolts, thus avoiding the need to bring the patient into the operating room. However, it is difficult to position the catheter in a select region of the brain when using bolts, as there is no provision for changing the depth or angle of the catheter. Therefore, catheters are often tunnelated and placed through burr holes by a neurosurgeon in the ICU, making it possible to aim for a predefined region of the brain.

In situations where the patient is subjected to a craniotomy, it is easy to place the catheter under visual inspection into the peri-contusional penumbra of a lesion or in the territory of the parent vessel of an aneurysm. The catheter is tunnelated under the scalp and a small incision is made through the dura, subarachnoidea and pia. The dialysis membrane is positioned in the penumbra, usually 1 cm from the border of the lesion or in the region most likely to be affected by vasospasm after haemorrhage. In our own experience, we have seen no consistent difference in the chemistry if the catheter is placed in white or gray matter. However, it is to be expected that the levels of neurotransmitters will vary depending upon the position. When a large craniotomy is performed in order to relieve pressure, it is also easy to place the catheter in brain tissue after opening a small hole in the meninges. In this case, microdialysis may serve as an important 'replacement' for intracranial pressure (ICP) monitoring, which is less relevant after the craniotomy.

In the liver and in microsurgical flaps, the positioning of the catheter is not as crucial as in the brain, due to the fact that ischaemia is liable to affect an entire liver lobe or a surgical flap. However, in the peritoneal cavity, the detection of ischaemia is liable to be delayed if the catheter is positioned far away from the ischaemic area. It is therefore wise to place the catheter close to the intestinal anastomosis. In case of complete mesenteric ischaemia, it will be detected regardless of the placement of the catheter.

Interpreting Microdialysis Data

During intensive care, organ chemistry often changes profoundly in the patient. At our present state of knowledge, it is impossible to interpret every change; however, major pathological states manifest themselves as dramatic increases or decreases of the chemical markers. Although many such changes cannot be interpreted in retrospect, they are easily related to clinical events when observed bedside.

The first hours of microdialysis data give an indication of how severe the condition of the tissue is in the affected region, compared with normal tissue, as monitored by a correctly placed reference catheter. This information gives the starting point for intensive care and reference values for determining whether the tissue physiology is improving or deteriorating.

The range from normal to pathological levels of different analytes is well known from normal brain tissue in patients with posterior fossa tumours [8] and from damaged as well as 'normal' brain tissue in traumatic brain injury (TBI) and subarachnoid haemorrhage (SAH) patients.

Detecting Secondary Insults and Evaluating the Success of Therapeutic Interventions

While the primary insult at the site of an accident is beyond our control, it is critical that secondary insults during intensive care be avoided. Therefore, the single most important finding from microdialysis studies of traumatic brain injury is the dramatic difference in the vulnerability of the penumbra surrounding a lesion, compared with normal brain tissue at the site of the 'reference' catheter.

The introduction of the new gold tip catheter, which is visible on CT, represents a quantum leap in the diagnostic power of microdialysis. Microdialysis chemistry can now be directly related to known regions of the brain; and the focus of treatment can be to avoid secondary insults in the vulnerable part of the brain, while restoring normal physiology of brain tissue.

Clinical Studies

Microdialysis of the human brain was first performed in 1987 at the Karolinska institute in a Parkinson patient subject to thalamic lesion for alleviating tremor [12]. The catheter was introduced stereotaxically, and samples were collected every 10 min and analysed for a large number of neurotransmitters and metabolites. We found that baseline levels of the various analytes were much higher than in animals, due to the possibility of using a much larg-

er dialysis membrane. Even more important, baseline levels were reached much faster, probably due to the small implantation trauma in relation to the size of the human brain.

We performed the first study on brain ischaemia in Uppsala, monitoring the brain chemistry in tissue resected during tumour surgery [13]. This led to a first paper on microdialysis during neurointensive care of TBI and SAH, which described changes in (especially) lactate, pyruvate and glutamate [14].

The experience from Karolinska and Uppsala, and from the subsequent neurosurgery in Lund, led to the development of flexible catheters more suitable for implantation in human brain and peripheral organs and microdialysis analysers (CMA Microdialysis, Stockholm) designed for bedside use.

Traumatic Brain Injury

Persson and Hillered [14] made the first microdialysis studies of the human brain after traumatic brain injury. They found that microdialysis can be used for long-term studies of energy-related metabolites and amino acids, e.g. glutamate, and that the fluctuation of these substances corresponded to various clinical events 'presumably involving hypoxia/ischaemia.' They used the lactate/pyruvate ratio as a marker for energy disturbance in the brain. This ratio is known to reflect the redox potential of the tissue and thereby the severity of ischaemia. A basal lactate/pyruvate ratio of 23 was found by us in normal brains of patients operated for posterior fossa tumours [8].

Bullock et al. made the important observation that when placing the microdialysis catheter next to a cerebral contusion, sustained cerebral blood flow reductions caused massive release of excitatory amino acids, while in patients without secondary ischaemic complications or focal contusions, post traumatic glutamate release appears to be only transient [15]. They concluded that sustained high ICP and poor outcome were significantly correlated to high levels of glutamate ($> 20\ \mu M$) [16].

In 1995, CE-labelled microdialysis catheters intended for human use and an instrument for bedside analysis of glucose, lactate, pyruvate, glycerol and glutamate became available on the market (CMA Microdialysis, Stockholm). This enabled us to start routine monitoring of all patients with severe head injuries in Lund, and a few years later, in Stockholm and Linköping. In our first report on normal brain, we established baseline values for the energy-related metabolites [8].

In view of previous findings, we routinely placed one catheter in pericontusional, penumbra tissue and a second catheter in normal tissue, usually through a second burr hole in front of the intraventricular ICP catheter. We found that microdialysis could be performed on a routine basis by the regular staff in an ICU, and that the data could be used for detecting global as well as local complications [17].

Our most important observations were:
- The metabolites measured give information that is of direct clinical importance.
- There is a great difference in the energy metabolism of the pericontusional tissue, compared with that of normal tissue in the same patients.
- The biochemical consequences of severe anaemic hypoxia are observable several hours before the deterioration can be detected by conventional methods (ICP–CPP).

Graft Monitoring After Liver Transplantation

Hepatic failure as a result of a malfunctioning graft is a life-threatening complication during the post-transplantation period. Early detection of impaired graft function due to arterial or portal vein thrombosis is especially important, as this may enable surgical intervention at a point when complications may still be reversible. Various techniques have been used to monitor early hepatic metabolism, as well as vascular complications and liver ischaemia, after the operation. Apart from bile secretion studies, however, none of these methods has been able to monitor liver metabolism continuously. Microdialysis provides the opportunity for the simple, continuous monitoring of metabolic changes in the tissue before they are detected in peripheral blood chemistry [18].

In summary, the metabolic profiles seen during microdialysis detect a recovery of the liver graft from ischaemia/reperfusion injury. Changes observed in patients with complications indicate that the complications can be identified several hours before biochemical changes in blood or the onset of clinical symptoms, which gives the surgeon time to act in order to save the graft.

Intra-Peritoneal Microdialysis

Animal studies have shown that it is possible to detect intestinal ischaemia using microdialysis by placing a microdialysis catheter intraperitoneally. The catheter is perfused with a Ringer solution, which equilibrates with molecules in the intraperitoneal fluid. The technique has also been extensively tested in humans.

A normal postoperative course results in a decrease in the lactate/pyruvate ratio. Complications such as peritonitis, bowel ischaemia, anastomosis leakage and urinary fistula were preceded by 2–4 days of increasing lactate/pyruvate ratio as an early marker of intraperitoneal ischaemia, which precedes surgical complications. Visceral ischaemia is an early step in the development of shock and multiorgan failure. Intraperitoneal microdialysis is a sensitive and safe method for the detection of local visceral ischaemia [19, 20].

Reconstructive Surgery

Animal studies, as well as clinical studies, have demonstrated that microdialysis is a highly reliable technique for the early detection of ischaemia in surgical flaps.

In a study of TRAM flap failure, due to the fact that arterial anastomosis thrombosis was clearly demonstrated by the samples from the microdialysis, 1) the concentration of glucose fell to an immeasurable level, 2) the concentration of lactate increased for a period before it stopped, due to lack of glucose, and 3) the concentration of glycerol increased to a very high level, probably because ischaemia caused damage to the cell membranes of which glycerol is an important part. The authors concluded that microdialysis is able to detect ischaemia in free flaps at an early stage, making early surgical intervention possible [21].

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Ethical Dilemmas in Surgical Critical Care

A.E. Baue

There are some specific ethical issues related to surgery as an operative discipline. However, in surgical critical care or intensive care the ethical issues are quite similar to other medical specialties. First, I will review some general ethical principles in patient care, going back to Aristotle and Hippocrates, and proceed to the problems of the modern era, i.e. since during World War II.

My wife, Rosemary, has written about ethics in a chapter, 'The patient as a person: Ethical considerations of patients with multiple organ failure' [1]. We have also written together, 'Clinics, technology, ethics and human patient physician relationships in critical care (monitoring, diagnosis, intervention strategies)' [2] and 'Medical Decision Making' [3]. Both of these have been presented and published in books from Anaesthesia, Pain, Intensive Care and Emergency Medicine (APICE) proceedings.

The Hippocratic oath is taken by all graduating medical students in the United States at the time of their commencement. It states, 'I will come for the benefit of the sick, remaining free of intentional injustice, free of all mischief.' Thus, the message – First, do no harm. The Nuremberg Code developed after World War II reinforces the Hippocratic oath to prevent the heinous medical crimes that occurred during World War II. The Declaration of Helsinki was developed by the World Medical Association to deal with medical research ethics. This began in 1964. There were revisions in 1975, 1983, 1989, 1996 and 2000. The fifth revision in 2000 remains controversial. The reason for this is that the revision discourages placebos and mandates that researchers provide the best-proven therapy to participants in a trial. This makes it very difficult to have a randomised, placebo-controlled trial of a medication or a therapy in order to determine its efficacy. Aristotle, in the Nicomachean Ethics, Book I, said, 'Every craft and every investigation, and likewise every action and decision, seem to aim at some good; hence, the good has been well described as that at which everything aims.' Medical practice has evolved from the beneficent physician to the near absolute right of patients to control the means and manner of their healthcare [4].

Principles of ethics were developed by the American Medical Association in 1980 and are state that, 'As a member of this profession, a physician must recognise responsibility not only to patients, but also to society, to other health professionals and to self.' The French have a wonderful saying, 'Guerir quelquefois, soulager souvent, consoler toujours' (to cure occasionally, to relieve often, to comfort always) [5].

Some specifics about surgical ethics include the following. Should a surgeon refer a patient to another surgeon who has better results? There is a great push in the United States now for patients to be referred to high volume centres with the belief that the results are better. Certainly, it is true that a surgeon must do a certain number of operations every year to maintain competence. This, however, represents an ethical dilemma. Should a surgeon who does not have comparably good results not perform an operation?

Another aspect of surgical ethics is the problem of a placebo control. If an operation is being done and evaluated, should controls undergo an operation that has the appearance of therapy but omits the essential therapeutic intervention? This is a serious ethical problem and most of us believe that sham operations should not be done. There was an example of this happening a long time ago before coronary artery bypass grafting was developed. It was thought that bilateral internal mammary artery ligation improved angina pectoris. Someone then did a controlled trial in which some patients received a sham operation: the incisions were made, and the internal mammary arteries were exposed but not ligated. The results were compared with those of patients in which the arteries were ligated. Obviously, there was no difference in the two and the operations were stopped. In surgical ethics, there must be 1) truth telling, 2) development of the capacity for informed consent, 3) full disclosure to the patient of what is being done, 4) substitute decision making if the individual is unable to make a decision and there is an emergency, 5) the need for confidentiality, 6) prevention of conflict of interest, 7) surgical competence – a surgeon should only do operations that he/she can do well, 8) a consideration of end-of-life issues, 9) a consideration of resource allocation, and 10) research ethics that are similar in all specialties. When we were residents, we were taught that if we performed an operation on a patient we must do everything in our power to ensure that the patient survived. Given, sometimes, that survival alone may not be in the patient's best interests, this, too, must be reconsidered.

In the intensive care unit (ICU), there are a number of potential ethical problems. The ICU patient is often wired, ventilated, irrigated, restrained, sedated and has tubes in three or four orifices. There are bright lights, beeping monitors, constant television, large ticking clocks, constant ministrations and conversations about the patient. As a result, members of the hospital staff often forget to talk to the patient. This can be irritating for patients, prevent-

ing them from resting, and some believe that it can limit or jeopardise recovery. Principles of ethics in intensive care, both medical and surgical, are: 1) primacy of the individual, 2) privacy of the individual, 3) dignity of the individual and 4) the right to die peacefully with one's loved ones close at hand in the event that the patient doesn't survive. The question has been asked, who monitors in the ICU? Who oversees the patient's privacy and dignity, and even the patient's willingness to be in the ICU at all? ICU decisions can be categorised in terms of three decision-making groups. The primary decision makers are the patient, the patient's family and the physician. Helpful secondary agents in the process can be the ICU staff, nurses, chaplains, relevant religious traditions and an ethics committee of the hospital. I will discuss ethics committees later. One should try to avoid the courts, which are the third decision-making agent. Litigation resulting in the courts making decisions about ICU patients presents considerable difficulty. Medications are necessary, and they may be supportive, palliative, experimental, or necessary in order to control or restrain a patient. All of these factors have ethical problems. Various orders that can be left or given in an intensive care unit include living wills, 'do not resuscitate' (DNR) orders and advanced directives. Again, the physician and the family should be directly involved, and the courts should be avoided whenever possible. Informed consent in intensive care has been written about extensively. One of the best articles in my judgment is that by Nyman and Sprung, 'Informed consent in intensive care' [6].

The question must be asked, 'When is intensive care futile, unnecessary, unqualitative, not productive, unwise, or experimental?' It is not uncommon for there to be difficulty in deciding which of these questions is appropriate in a certain circumstance. Certainly, if a situation is futile for the patient, this has direct implications on how the patient is to be cared for, and it is important to discuss this with the family. The difficulty is in determining, 'what is futility?' How do we know that something is futile? I have developed a futility score – namely, any fatal illness with a life expectancy of six months or less, which would include 1) immune failure – AIDS, 2) severe single-organ failure not easily supportable, 3) chronic obstructive pulmonary disease (COPD) that requires increasing O_2 at rest when the patient is not an operable candidate, 4) congestive heart failure that is recurrent, 5) cardiomyopathy in a patient who is not a transplant candidate, 6) metastatic malignancy, as well as non-resectable, multiple lesions in the brain, lung, liver, or bone (post irradiation therapy), and 7) mental status unresponsiveness or disorientation with respect to time, place and person. Also in this futility score would be 8) cerebrovascular disease – a dense stroke with inability to care for oneself but not brain dead, 9) hepatic failure, 10) progressive multiple organ failure, 11) severe sepsis with any of the preceding, 12) end-stage metabolic muscular disease, 13) a status of DNR – no code, 14) patients incapable of independent

living with any of the preceding, 15) possibly Alzheimer's disease; however this is not clearcut, and 16) persistent vegetative state – a decision must be made regarding how long should this be allowed continue.

A serious ethical question concerns the physician's responsibility to provide care that he or she believes is unreasonable or futile when the patient and/or family insist upon it? I have had this happen a number of times. It usually occurs with a distant relative or a child of the patient who has not had any contact with the patient for years and wants to do something to help now that the patient is seriously ill and dying. In other words, it is often a guilt reaction.

A major development in medical care in recent years has been the belief that rights of patients include autonomy. They must be able to make their own decisions and not simply follow the doctor's orders. In the United States, this has led to a number of programs – advanced instructive directives such as living wills, proxy directives, surrogates appointed with durable power of attorney for health care to follow these directives if the patient is no longer competent, and medical directives, which is a new comprehensive advanced care directive. This raises the question about what is autonomy in the clearly non-autonomous patient – i.e. the pleasantly demented patient.

Research in the ICU presents a particular problem. Informed consent is needed, but is it possible in critically ill patients? Do they or can they understand? Family involvement is important for surrogate decision-making. Sometimes waiver of consent in emergencies is used but only for an emergency. This usually does not qualify for research. Research in the emergency ward is similar where there are needs for study for things such as fluids for resuscitation, intubation, ventilatory practices and other therapy. How does one obtain consent from an emergency ward patient who may or may not be able to understand? Should there be waiver of consent in such a circumstance? Should there be surrogate consent? Each circumstance is different, depending upon whether the study is potentially life saving. As for informed consent in the intensive care unit, surrogate decision making for clinical care is very common because the patient may be so sick that only the family can help in the decision. Surrogate decision making for research is not satisfactory unless there is a chance for direct benefit to that patient with minimal risk [7].

In the United States, Institutional Review Boards (IRBs) are now required in all hospitals. The membership – a comprehensive group of all who are interested in the welfare of the patient – includes ethicists, physicians, lawyers and lay people. The review board must review the patient's records and study and approve all research involving patients. The primary purpose of the board is to determine how informed consent should be obtained, whether it's appropriate and what should be done with it. The patients are not identified. The review boards can be quite rigorous and demand that appropriate stan-

dards for informed consent be obtained. Waiver of consent has been used for research and emergencies. An example is the well-known Gerinf 05 study of the use of low-dose steroids in severe septic shock. The study clearly demonstrated that many patients in severe septic shock had adrenal insufficiency and that low dose steroids were life saving [8].

There are two ethical danger points in intensive care and emergency wards: 1) what is experimentation versus treatment? (Sometimes they seem very similar); and 2) what are hopeless versus heroic measures? Although an heroic measure may be good for the patient and even help the patient, it should not be done in a hopeless situation.

A status of DNR is important to consider, and many patients want that to be honoured if their situation is hopeless. Some families want it. DNR status is used to prevent unwarranted intervention. It is also used as a vehicle to withdraw life support. The question is, why isn't this done on admission to the intensive care unit? I have had the experience of an elderly patient who comes in with an emergency problem that could be treated by an operation. The operation is carried out and immediately afterward the family gives a DNR order. Why didn't they let the patient go peacefully beforehand? Why perform a big operation on an elderly person who the family does not think should or will survive anyway?

Advanced directives and living wills have been used, and have been urged, in the United States. The question is raised, 'Do they really help?' They are not used as frequently as some had hoped they would be. The problem is, where are they kept? In the doctor's office? In a safe at home? They may not be available at the hospital when the patient is emitted with an emergency. The problem that I have with advanced directives or living wills is that someone may say that they do not want to be admitted to an intensive care unit or that they do not want to be resuscitated or whatever, but they may have a recoverable illness. For example, a patient may say, 'I never want to be intubated and put on a ventilator.' However, what if they have pneumonia from which they may recover after a period of ventilatory support? It is very difficult to spell out in an advanced directive exactly what should be done in every circumstance. Practical concerns include: 1) incomplete information about future risk versus benefits, 2) the importance of communicating with physicians may seem unnecessary, 3) problems concerning when the directive takes effect – when the patient is terminal, incurable, seriously ill, has an incapacitating illness? – and, finally, 4) problems that, on occasion, arise as a result of aggressive or unscrupulous physicians. Tonelli writes about this in an article entitled 'Pulling the plug on living wills' [9]. He performed a critical analysis of advanced directives and found many problems associated with them.

Another ethical consideration is with physician-assisted suicide. This has been allowed, under certain circumstances, in the Netherlands for some years.

In the United States, the state of Oregon has a Death with Dignity Act. It is interesting, however, that physician-assisted suicide in both of these locations is not overwhelmingly frequent. In the rest of the United States, physician-assisted suicide is not allowed. Now, I believe there are alternatives to physician-assisted suicide. Support of a patient with a terminal illness can be very important and is being emphasised, particularly in the United States, and we can now take care of patients who are reaching terminal illness to keep them comfortable and free of pain. It is my belief that doctors should be healers, not killers. There are major problems with physician-assisted suicide. For example, is the patient truly terminally ill or just depressed? There is often existential despair in many patients who request physician-assisted suicide. End of life care is better now and supportive care of the dying is much better and is being emphasised and taught to students and residents. The Hospice movement to care for terminally ill individuals in the United States is a superb activity. Asch has written about the role of critical care nurses in euthanasia and assisted suicide [10].

There is a difference, I think, between euthanasia or assisted suicide and letting a patient go or die in the intensive care unit when they have a terminal illness and are deteriorating. In a patient with a severe stroke who is brain dead, I have no problem working with the family and at an appointed time with the family present, stopping ventilatory assistance. In that circumstance the patient, with sedation, will calmly die within a few minutes. This is not assisted suicide or euthanasia. It is simply allowing a patient to die who would not be supported without extensive life support systems. Some now contrast the poor or imminent prognosis of death in terribly sick patients versus the high cost of healthcare. Some raise the question as to whether terribly sick, terminally ill patients should be cared for, because everyone knows that the cost of healthcare is much higher in the last few days or months of life. The problem is, who determines when a patient is in the last few days or months of life? The Società Italiana di Anestesia Analgesia Rianimazione e Terapia Intensiva (SIAARTI) has provided excellent recommendations on the treatment of chronic cancer pain. This is a superb programme based on ISTAT (Italian National Institute of Statistics) data [11].

Vincent has described similarities of care in the United States and Europe and also some differences [12]. Similarities in the United States and Europe are that withholding therapy is done, do not resuscitate orders are used, there is consideration of the potential quality of life and futile care is not required. However, some differences are that 1) there is a separation of legal and ethical issues in Europe whereas these are combined in the United States; 2) families are much more involved in intensive care and other decisions in the United States; 3) there is less obligation to be completely open in Europe; and 4) advanced directives are more commonly used in the United States.

Giannini et al. wrote about end of life decisions in Milan in 2003. They found there was minimal intervention in dying patients. Few doctors sought ethical advice. Decisions were made by the medical team alone, for the most part. Family involvement was limited and the wishes of the patient were often ignored [13]. The Council of Europe, consisting of 40 European nations, had a convention for the protection of human rights and dignity of the human in 1997, and this is becoming an important force for ethical care of patients in Europe.

Finally, the technological imperative must be considered. This is a term I have used to describe the physician who can do something to a patient, and therefore believes that he/she must do it. Whether it be an operation or a therapy or whatever, it may not be in the patient's best interest. This has been written about by Barger-Lux and Heaney [14].

In conclusion, compassionate ethical treatment has two elements. The first element is that the physician must do the right thing. The second element is that the physician must do the right thing well – arete, or excellence. Fabris summarises the situation very well, 'When a patient is treated as "a suffering person" (why?) rather than "a defective machine" (how?), potential healing is accelerated' [15]. Lev Tolstoy said, 'The simplest and shortest ethical precept is to be served by others as little as possible and to serve others as much as possible.'

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