Essentials of Neonatal Ventilation

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Essentials of

Neonatal Ventilation

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Since the late 1960s, there has been considerable debate about the best way to provide respiratory support for preterm infants with RDS. Early attempts to ventilate infants met with limited success and survivors often suffered from chronic lung disease. In the early 1970s, Gregory et al. reported success in using CPAP to care for preterm infants with RDS; however, despite its simplic ity, there was little interest in using that technology. As ventilators increased in sophistication (and complexity), noninvasive ventilation was viewed as a modality that could supplement invasive ventilation, but not as a pri mary mode. Furthermore, the randomized clinical trials of surfactant suggested that most premature infants with RDS should be intubated and administered surfactant. The pendulum began to swing back toward noninvasive ventilation in the last decade as randomized clinical trials demonstrated that early application of CPAP was better than routinely intubating infants and given surfactant. In 2018, the choices for respiratory support are even greater. Not only are there newer generation of ventilators, but the choices for noninvasive support commonly include nasal intermittent positive pressure ventilation and high-flow nasal cannula. This textbook, *Essentials of Neonatal Ven tilation*, edited by Rajiv, Satyan, and Vidysagar, offers cli nicians a complete source for the latest developments in respiratory care of critically ill newborn infants. This book is a unique addition because of its comprehensive nature and practical approach to respiratory care. The authors for each chapter are leaders in their fields. It is noteworthy that the book also addresses complications of mechani cal ventilation (e.g., bronchopulmonary dysplasia) and includes sections on common neonatal problems, ECMO and nursing care. The editors should be congratulated on assembling such a wonderful book.

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The evolution of assisted ventilation in newborn intensive care has made a unique paradigm shift. Noninvasive ven tilation, a significant milestone in the 1970s, has made a comeback in the current decade. Newer methods of syn chronization, gentle ventilation, and permissive hyper capnia using both invasive and noninvasive modes are the standard of care in neonatal intensive care today. This book is a Herculean attempt to standardize and optimize ventilatory care at the bedside. Each chapter is written by international experts in the field, hoping to ignite a path to the successful resolution of the pulmonary dysfunction, without lung and brain morbidity. Technologies of promise of the future are incorporated, and noninvasive monitoring and assessment are given significant emphasis. The neona tal intensivist is currently exposed to a huge arena of ever evolving technologies. The bedside practitioner will find this book helpful in knowing the benefits and limitations of these technologies and support neonatal gas exchange
without compromising neurodevelopmental outcome. More advanced technology is not always better. Sim ple techniques such as nasal CPAP with noninvasive monitoring have great outcomes in preterm and term infants with lung injury. This book gives great emphasis to this basic technology.

The chapters are designed to evolve from the basics to applied physiology and graduate through the assisted venti lation technologies. A section on cardiac issues in respiratory care, nutritional support, and ancillary care is deliberately magnified for the intensivist to manage accurately and objec tively a critical neonate with respiratory distress.

This book with E-Book facilities of videos on critical chapters supplemented by lecture presentations would prove to be a handy and reliable bedside companion for all NICUs all over the world. The presentations and illustra
tions are provided to assist in education of a new genera tion of neonatal providers. We gratefully acknowledge the authors for contributing to these chapters, and providing videos and illustrations to enhance the book.

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Rajiv gratefully acknowledges the didactic teaching of his fellow teacher Dr. Elizabeth John, whose extreme sensitivi ties to the adjustment of CPAP up or down still ring a bell in his ears. This singular caution to optimize continuous positive airway pressure or positive end-expiratory pressure laid the foundation of his strategy in any critical lung dis ease. This was the fulcrum of his success in neonatal venti lation in the last 30 years.

Rajiv acknowledges the heartfelt help of his teachers Dr. Vidyasagar, Dr. Georg Simbrunner, Dr. Ramanathan, Dr. Martin Keszler, and Dr. Dhanireddy for teaching him and for being authors of many chapters and reviewing many more of them. Dr. Vidyasagar was the first to agree to the concept of this book many years ago and has been the guiding light in the evolution of this book. Rajiv's close associates Dr. Prakash, Dr. Arun, and Dr. David Todd gave him exceptional chapters at a short notice. His junior asso ciates Dr. Nalinikant and Dr. Srinivas provided very unique, well-researched chapters. He is indebted to coeditor Satyan who joined the team in 2016 for his immortal illustrations and editorial stewardship. His illustrations offer an addi
tional tool for neonatal providers to educate students and parents.

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This book is a unique joint effort of a highly talented provider-publisher team. Last but not the least, Rajiv thanks his wife Bindoo for silently bearing with him all the time less lapses at home while he was playing Archimedes for the development of this book.

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Online supplementary materials

Please visit MedEnact (https://www.medenact.com/Home) to access the videos and lecture PPTs.

Introduction and History of Ventilation

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1

Introduction

This book was conceived several years ago, when there appeared to be a distinct lacuna of comprehensive bed side ventilatory management guides in neonatal care his tory. Currently, there are excellent textbooks to refer to and obtain broad concepts on the approach to providing respiratory assistance to a baby in distress, but a detailed evidence-based book on bedside management is miss ing. In this book we attempted to provide the readers an evidence-based practice bedside guidelines. In doing so, we sought the contributions from the most experi enced leaders in the field. This book is an honest attempt to get the world's best pioneers in each area to contrib ute their signature chapters of their research to give the neonatal intensivist, detailed bedside ventilation navi gation in critical situations. We earnestly hope readers will find these guidelines useful in managing critically ill neonates.

This book is divided into eight sections. Here are some of the highlights of these sections. **Section I** reviews the history of neonatal ventilation. **Section II** deals with basic chapters covering embryology and physiology of pulmo nary disease, with the time frame from extreme prematurity at the limits of viability to dysmorphology in the full-term infant. The delivery process and golden first hour are addressed in detail, due to its long-term impact on respira
tory and neurological morbidity.

Section III deals with the *basics of neonatal ventilation* and evolves through the genesis of lung injury to lung mechan ics. The chapters on ventilator give deep insight to the reader on the limitations and benefits of its application. The chapters progress to the provision of mechanical ven tilation and its attendant complications, which are again discussed in detail.

Section IV is an in-depth analysis in real time of the various *respiratory care devices* currently available for the neonate. These chapters give an operating framework and the bedside navigation in critically ill babies with trouble shooting algorithms by authentic authors.

Section V is the heart of this book with *comprehensive bedside management guidelines* of the common respiratory conditions faced in neonatal intensive care. They offer detailed flowcharts, algorithms, and case scenarios in com
plicated respiratory care management. There is a separate chapter on the management of the 23–25 weeks' gestation babies: "micropremies"—a challenge for any intensivist.

Section VI deals in-depth for all the *common cardiac conditions* complicating respiratory care. Management of shock and cyanotic heart disease, PDA, and arrhythmias are discussed. Functional echo is comprehensively discussed as it is evolving as the new standard of care.

No ventilator support will be successful without strong ancillary support. **Section VII** details all critical aspects of *ancillary care* of the ventilated neonate, including monitor ing, infection control, nutrition, and procedures.

It is heartening to note that there is emergence of an increasing number of neonatal intensive care units (NICUs) to improve survival among low- and middle-income coun tries (LMCs). Ventilatory support is an essential part of the neonatal intensive care. Proper ventilator care requires a combination of skilled personnel, appropriate equipment, and ancillary support which are the prerequisites for opti mal outcome but are difficult to fulfill in some LMCs. Sev eral chapters in the book offer guidelines to assist pioneers in LMCs in establishing ventilatory support in their pro spective units and teach physicians, trainees, and nurses.

Besides the rich evidence-based content of the book, it has several unique features to help the practitioner better manage infants requiring ventilatory care. This book is *digi tally enhanced* with illustrations and *videos* linked to their respective chapters and *lecture PowerPoint* to most chapters of this book to give the intensivist a 360-degree compre hension of neonatal ventilation.

This book is intended for neonatologists, intensivists, postgraduates (residents and fellows), respiratory thera pists, and neonatal nurses as a ready bedside reckoner for urgent consult.

We thank all the authors for their contributions to this book. Because of our goal to make this book reader friendly, the authors were burdened with additional tasks of preparing video clips and PowerPoint presentation of their chapters. We sincerely thank them for complying with our requests and making the *book very unique in its presenta tion*. We hope the readers will find these

educational tools valuable in their practice.
I want to thank my secretarial staff Mr. Iftekar, Mr. Jason, and Mrs. Serly for their sincere commitment to the devel opment of this book. We thank ELSEVIER publisher and its staff Ayan Dhar and Sheenam Aggarwal for their innovation, receptivity and patience during the publication of this book.

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2

Evolution of Neonatal Ventilation a Retrospective View

Dharmapuri Vidyasagar, PhD (Hon)

Introduction

The author of this article is fortunate to have personally seen the evolution of improved neonatal intensive care and neonatal ventilation in the United States over last half cen tury [1]. He along with Dr. George F. Smith, a geneticist and Head of the Department of Pediatrics at the Illinois Masonic Hospital and Professor at the University of Illinois, Chicago, were interested in medical history and organized a symposium on "Historical Perspective of Perinatal Medi cine in 1980." Many giants in the field of neonatology participated in this symposium. The proceedings were sup ported and published by the Mead Johnson, Nutritional Division in two volumes (Fig. 2.1A–B); however, they were not copyrighted [2]. Fortunately, later they were placed on the website "Neonatology on the Web" **created by Dr. Ray Duncan** of Mount Sinai Hospital, Los Angeles. The two volumes on the Internet are readily available for interested readers at the website [3] (permission to reproduce figures by personal communication).

These books contain valuable historical information that would have been lost but for the ingenious method of placing the proceedings on the web. I am grateful to Dr. Duncan for this innovative method of preserving the historical volumes. The material from these books in part form the basis of the current chapter.

The history of assisted ventilation of a newborn is closely intertwined with evolution of neonatology. Therefore, it would be appropriated first to review the evolution of the specialty of neonatology then delve into the evolution of neonatal ventilation.

The story of development of neonatology and respiratory care of a newborn, particularly of the premature babies, has been told by several authors in the past [1,4–10].

The chapter is written from the perspective of both a witness and participant of these developments over the past 50 years. Following narration is based on the above referenced material. The material related to the develop ment of neonatal ventilation is based on several reports [4–8] and three major symposia: Ross symposium in 1968, Paris symposium in 1969, and the Chicago sympo sium in 1980 [2].

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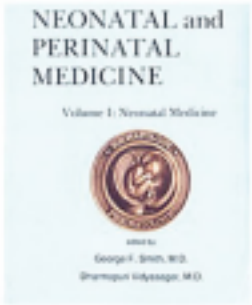

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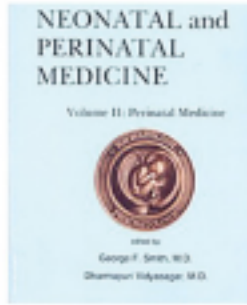

Introduction
1. Perinatal Medicine — Nicholas M. Nelson
2. Perspectives in Neonatology — Thomas E. Cone, Jr.
3. Thermoregulation in the Newborn Infant — Leo Stern

(B)

THE CONTENTS OF THE SYMPOSIUM

	Introduction	
1.	Perinatal Medicine	Nicholas M. Nelson
2.	Perspectives in Neonatology	Thomas E. Cone, Jr.
3.	Thermoregulation in the Newborn Infant	Leo Stern
4.	Neonatal Feeding	Martin H. Greenberg
5.	The Nutrition of Premature Infants	Lewis A. Barness
6.	Neonatal Jaundice: A Selected Retrospective	Lawrence M. Gartner
7.	The Rise and Fall of Rh Disease	A. Zipursky
8.	Nursing in Neonatology	Mitzi L. Duxbury
9.	Maternal Bonding: An Overview	Roberto Sosa
10.	The Obstetric View of Premature Labor	M. Yusoff Dawood
11.	Birth Asphyxia	Phillip J. Goldstein
12.	Infectious Diseases of the Newborn Infant -- Historical Perspectives	Jerome O. Klein
13.	Immunobiology of the Fetus and Newborn -- Historical Perspectives and Recent Advances	Aditya Kaul and George F. Smith
14.	Researches in Perinatal Circulation	John Lind
15.	Assisted Ventilation in Newborn Infants	Mildred T. Stahlman
16.	The Treatment of Hyaline Membrane Disease	Victor Chernick
17.	Retrolental Fibroplasia: A Medical and Legal Tragedy	Richard L. Day
18.	Historical Perspectives and Recent Advances of Neonatal Monitoring	Dharmapuri Vidyasagar
19.	Biochemical Monitoring	Parvin Justice, Shanta Nath, and Dharmapuri Vidyasagar
20.	Congenital Abnormalities and Genetic Concepts in Neonatology	George F. Smith
21.	Neonatal Surgery: Historical Perspectives and a Glimpse of the Future	Kevin C. Pringle
22.	The Impact of Regionalization on Neonatal Outcome	L. Joseph Butterfield
23.	The Developmental Outcome of Premature Infants	Lula O. Lubchenco
24.	Maternity and Infant Care Services in Chicago Retrospectus: Our Legacy, Our Challenge	Donald Dye and Karen Tarpey
25.	Julius Hess, M.D.	Alwin C. Rambar
26.	William Harvey in Perinatal Perspective	Billy F. Andrews
27.	Soranus of Ephesus: Who Was He and What Did He Do?	T. N. K. Raju
28.	Some Famous "High Risk" Newborn Babies	T. N. K. Raju

Fig. 2.1 (A) Images of the cover pages of two volumes of symposium; Historical Perspectives and Recent Advances in Neonatal and Perinatal Medicine held in Chicago 1980, published by Mead Johnson Nutritional Division. Columbus OHIO. (B) The list of contents and presenters of two volumes. Note the list of illustrious personalities who participated in the symposium. Neonatology on the web. Available from: http://www.neonatology.org/classics/mj1980/ [3].

The development of neonatology

Until the mid-20th century, the primary care of newly born infants was provided by the obstetricians. In the

mid-20th century, pediatricians began to take care of the newborn. The premature babies were viewed as a medical curiosity and exhibited for public view at various exhibi
tions [11]. However, the excellent scientific work of many investigators, both in the United States and Europe, led to better understanding of physiology and pathology of the mature term newborn and premature babies. These studies showed that a premature newborn required spe
cial thermal and nutritional care. These understandings lead to the development of premature care centers. Dr. Julius Hess in Chicago [12] was the leading authority on premature care in those days [13]. In 1914, he opened the first 24-bed premature care center at the Sarah Mor
ris Hospital of Michael Reese Hospital (now defunct). Dr. Hess (Fig. 2.2) was the head of Department of Pedi atrics at University of Illinois, Chicago and the head of pediatrics at Michael Reese hospital. He along with the help of his nurse Evelyn Lundeen provided the state of the art care of its time for premature babies. With their expert care, they showed increased survival of premature babies.

The Chicago Board of Health had established several cen ters in the city for the care of premature babies. Premature babies born in the community hospitals were mandated to be transported to one of these centers, if they survived the first 24 h after birth. Dr. Hess developed an incubator with the help of an engineer, "the Hess incubator" (Fig. 2.3) [14]. He also developed a transport incubator (Fig. 2.4), which could be plugged into taxis of Chicago for electric power for transportation of the babies to premature care centers within Chicago.

Both Dr. Hess and nurse Lundeen wrote several papers and books [13] on the care of premature babies, mainly on care of the newborn, particularly the premature babies and their feedings. With these advances, the care of the pre
mature infants in Chicago improved greatly. Indeed, the premature care center at the Sarah Morris Hospital gained national and international fame. It became the center of academic learning in premature baby care for doctors and nurses from around the world.

Fig. 2.2 Photograph of Dr. Julius Hess (1876–1953) Who was In-Charge of the Premature Care Center at Sarah Morris Hospital/Michael Reese Hospital in Chicago. Neonatology on the web. Available from: http://www. neonatology.org/classics/mj1980/ [3].

Fig. 2.3 The Hess Incubator Designed for Care of Premature Babies, Developed by Dr. Hess With the Help of an Engineer. Neonatology on the web. Available from: http://www.neonatology.org/classics/mj1980/ [3].

Dr. Geoffrey Dawes in Oxford, England [18–20] and investigators in the laboratories of Julius Comroe, United States studied neonatal physiology extensively. Dr. Clement Smith, Professor of Pediatrics at Harvard Medical School, published his book on the physiology of a newborn infant

Fig. 2.4 The Hess Transport Incubator. Dr. Hess also developed a portable incubator for transporting babies from community hospitals to designated Premature Care Centers in Chicago. Note: the incubator had an adopter to be connected to taxis of Chicago for power during transport. Neonatology on the web. Available from: http://www.neonatology.org/ classics/mj1980/ [3].

The birth of modern neonatal intensive care unit (NICU)

In October 1960, Dr. Loius Gluck established the first known neonatal intensive care unit (NICU) at Yale-New Haven Hospital, United States. Prior to this time, premature infants were often isolated in small cubicles and had little direct contact with doctors and parents because of fear of infections. With focus on hand washing, Dr. Gluck's design for NICU took shape with the help of US$ 3 million from a benefactor whose premature grandson he had saved [15]. It was set up as a one big open room, filled with newborns in their incubators. This development had a profound influ ence on the subsequent direction of care of the sick new born, including premature babies in the United States and rest of the world.

The birth of a new specialty: neonatology—the newborn medicine

The scientific basis of newborn care improved significantly with the work of several physiologists: the work of Joseph Barcroft brought new understanding of the fetus [16,17]; [21]. These seminal developments in understanding of the fetal and neonatal physiology laid the foundation for the clinicians to develop an evidence-based neonatal care in coming decades.

Dr. Alexander Schaffer [22] was the first one to coin the term *Neonatology* as the science of newborn medicine and *Neonatologist* as one practicing neonatal medicine in the preface to his book ***Diseases of the Newborn*** (published by Saunders in 1960). It is interesting to note that in a short span of 15 years of coining the term *Neonatology, it became* an established Board Certifiable Pediatric sub specialty. The first *Neonatal–Perinatal Medicine* specialty board examination was conducted in 1975. The author was one of the 355 candidates certified at the first board examination.

The growth of neonatology continued by leaps and bounds from 1970 onward (Fig. 2.5). The scientific explo ration of neonatal illnesses and developing evidence-based therapeutic interventions also grew exponentially leading to steady decrease in neonatal mortality rates (NMR) as shown in Fig. 2.5.

Fig. 2.5 highlights the advances made in different areas of neonatology during the 20th century and also shows the impact of these developments on steady decline of NMR in the United States and the United Kingdom. It shows development in six major areas of neonatol ogy: (1) improved thermal care, (2) improved nutrition, (3) improved nursing care and opening of premature care centers and NICUs, (4) prevention of infections, (5) improved care of infants in respiratory distress and finally, (6) improved perinatal care and resuscitation in the delivery room and ventilation. In the past century, these improvements have resulted in increased neonatal survival.

The evolution of ventilator care of the newborn

As prematurity was the major contributing factor to high NMR and the respiratory problems particularly hyaline membrane disease (HMD) was the major cause of NMR, they received greatest attention in basic and clinical research. These investigative efforts were further boosted with the tragic death of prematurely born son of the then President Kennedy.

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NICU, neonatal intensive care unit; TPN, total parenteral nutrition. steadys in the Un


The Boston Globe
MORNING EDITION
BABY SPED TO BOSTON
Has Trouble Breathing; Kennedy Stands by Here
Whole World Taken By Littlest Kennedy

in respiratory distress. The use of oxygen in the treatment of neonates with respiratory distress has been reported for more than a century. In 1907, Budin recommended oxygen "supplied through a funnel, the large opening of which is placed beside the infant's face," for the treatment of cyanotic episodes in newborns [23]. In the 1930s, Hess developed an incubator capable of delivering approximately 40% oxygen for extended periods of time [12,23]. By the 1940s, a commercially available incubator capable of providing a high concentration of oxygen facilitated the liberal use of oxygen for the treatment of cyanosis, apnea, and periodic breathing of newborns.

Throughout this time, oxygen administration was guided by the clinical observations of skin color, as well as the respiratory rate, regularity, and work of breathing. It wasn't until the 1960s and 1970s that the technology of microsampling of blood gases was available [24]. In 1980s, noninvasive methods of transcutaneous oxygen monitoring became available. Pulse oximetry [25] and CO_2 try [26] became available in 1980s for more precise monitoring of oxygen saturation in the blood. It remains the standard method of monitoring blood oxygenation in a newborn.

The overall goal of oxygen therapy was to achieve adequate oxygenation using the lowest concentration of inspired oxygen. However, achieving this goal is complicated due to a number of factors. Routine administration of oxygen to all premature infants led to the catastrophic results of the development of retinopathy of prematurity (ROP) and related blindness [24,27]. However, a study to curtail oxygen therapy was associated with increased cerebral palsy [28–32].

Despite over 75 years of routine oxygen administration to newborn infants, administering optimal level of oxygenation and monitoring—one that avoids the detrimental effects of hypoxia on the one hand, and those caused by hyperoxia on the other hand—has been very difficult [33]. Current recommendations for oxygen saturation targets are different between the United States and Europe. The European recommendations are to keep the target oxygen saturations between 90% and 94% for premature infants requiring supplemental oxygen [34]. The American Academy of Pediatrics states that the ideal target oxygen saturation is not known and in some preterm infants, 91%–95% target may be safer than 85%–89% [33].

In order to achieve the goals of neonatal oxygen therapy, we need to develop and evaluate appropriate devices of oxygen delivery systems. The clinicians today need to have an adequate knowledge of the use of oxygen delivery equipment, and have the training on the concepts of neonatal oxygenation and equipment used to monitor the effects of oxygen therapy.

Fig. 2.6 The News of Death of Prematurely Born Baby Kennedy Printed in Boston Globe.

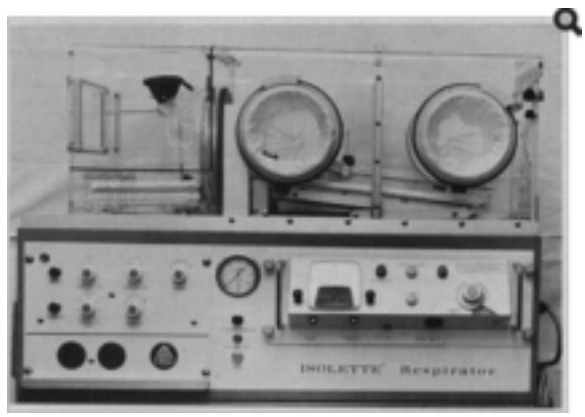
On August 7, 1963, Jacqueline Kennedy, wife of President Kennedy, gave birth to a premature baby (34-week GA, birth weight of 2.1 kg) [2] (Fig. 2.6, Boston Globe News item) in Boston who developed breathing difficulties, now what is known as the HMD. Usher's regime [3], infusion of 10% dextrose water with $NaHCO_3$ was the only known treatment for HMD. Neonatal ventilator care was not available even for the President's baby in the United States in 1963. Moreover, sending the President's baby to neighboring Canada where neonatal ventilation was available was not an option. The baby died after 2 days on August 9, 1963. The death of President Kennedy's baby was a day for national mourning. As the story of demise of baby Kennedy unfolded HMD, a disease of premature babies, became known to all in America. It was estimated that in 1960s about 25,000 babies died of HMD annually in the United States. With the death of baby Kennedy, the interest in research on disease HMD accelerated. The interest in newborn care increased.

Oxygen therapy

Prior to use of any form of assisted ventilation, administration of oxygen was the ***only*** available therapy for infants requiring delivery room resuscitation and infants

Usher regime

Prior to the introduction of neonatal ventilation in late 1950s and early 1960s, Dr. Robert Usher of Montreal, Canada after extensive studies in premature infants with HMD showed that they suffer from metabolic acidosis and hyperkalemia [35]. To counteract these changes he proposed a treatment regime of administering $NaHCO_3$ in 10% dextrose to infants in respiratory distress [35]. This



therapy became known as Usher regime resulted in signifi cant (50%) reduction of mortality in infants with HMD. The Usher regime was one of the major milestones in the treatment of HMD prior to initiation of assisted ventilation.

At this point, a retrospective view of experience with neonatal ventilation and neonatal ventilators is in order.

History of neonatal ventilation

Several reviewers have stated that it is difficult to time exactly when ventilation of the newborn was initiated and prob ably occurred in the late 1950s and 60s [10,36,37]. Downes in an editorial [38] refers to the work of Smythe and Bull from South Africa to have used successful long-term neo natal ventilation in infants afflicted with tetanus. These infants were treated with d-tubocurarine, tracheostomy, and ventilation; and the mortality was reduced from nearly 100% to 20%. However, these infants had normal lungs [38]. Initial reports of mechanical ventilation of newborns with pulmonary insufficiency were reported by Benson et al. and Donald et al. in 1958 [39,40]. The first highly suc cessful use of mechanical ventilation in premature infants with HMD was reported by Maria Delivoria-Papadopoulos in 1965 [41–43]. In this series, out of 20 infants with severe HMD, 7 survived (35%) and 6 of them were neurologically intact. Since then, several other investigators reported use of assisted ventilation in HMD with increasing success. Some used positive pressure ventilation, including Strang and Reynolds in London [44], Thomas et al. at Stanford [45], and de Heese et al. in Cape Town [46]. Historically, negative pressure ventilation was designed earlier in 1889 by Alexander Graham Bell [47,48]. He presented a paper to the American Association for the advancement of science in Montreal on the use of ventilator for newborn babies and was "met with little enthusiasm." The design and device are preserved at The Alexander Graham Bell museum in Nova Scotia, Canada [49]. Later in 1960s, Dr. Stahlman in Nash
ville, Tennessee [50], and Stern in Montreal, Canada [51] used negative pressure ventilation (Fig. 2.7) to treat babies with RDS. Chernick and Vidyasagar in Winnipeg, Canada [52,53] modified negative pressure ventilator to create constant negative distend pressure (similar to continuous positive airway pressure [CPAP]) without an endotracheal tube with success in the management of respiratory failure in newborn.

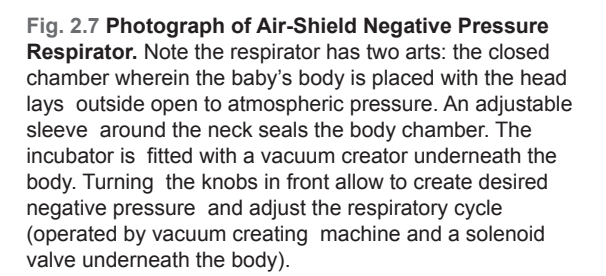


Fig. 2.7 Photograph of Air-Shield Negative Pressure Respirator. Note the respirator has two arts: the closed chamber wherein the baby's body is placed with the head lays outside open to atmospheric pressure. An adjustable sleeve around the neck seals the body chamber. The incubator is fitted with a vacuum creator underneath the body. Turning the knobs in front allow to create desired negative pressure and adjust the respiratory cycle (operated by vacuum creating machine and a solenoid valve underneath the body).

Readers should note that negative pressure ventilation is no more in use as we have developed several simpler non invasive methods of ventilation (see chapter on noninva sive ventilation in this book). However, the use of negative pressure respirator to support babies in respiratory distress remains an important phase in the history of neonatal ven tilation.

Ross symposium on neonatal intensive care

In 1968, a conference was organized on neonatal intensive care in Vermont by Ross laboratories. Several aspects of neonatal intensive care including design of these units and ventilation techniques were discussed at the conference [54]. Several leading neonatologists of the time from the United States and Canada participated in this conference. The conference was intended to share the experiences of different units and learn the problems of neonatal inten sive care units of the day. Presentations by various speakers showed the impact of intensive care on improved survival, complications, and long-term intact survival of babies cared in their respective units.

Survival with assisted ventilation was highest among infants with tetanus neonatorum who had no lung dis ease. It reversed the 80% mortality in tetanus prior to assisted ventilation to 80% survival with assisted venti lation. Survival rate in RDS although improved was still at 28%. The results of assisted ventilation in other respi ratory conditions were not so encouraging. At the end Dr. Lucey, the chairman of the conference, summarized the conference as follows: "Now that you have read the proceedings of this conference some will be frustrated and discouraged. Others will be encouraged to try to improve the care in their own nurseries. Hopefully this conference will have supplied with early but firm data to encourage you in these efforts and warn you of the problems involved" and cautioned "whereas intensive care is effective we still do not have a clear idea about the key elements of success. The construction of a new nursery or the purchase of a blood gas machine and res pirator do not an intensive care nursery make!". The key elements are intelligent personnel or as one participant put it "people who care intensely" (Dr. Nick Nelson of Harvard).

This is one of the earliest reports on the impact of mod ern neonatal intensive care including the results

of neonatal ventilation.

In 1969, another conference solely on assisted ventila tion was organized in Paris by Professor Alex Minkowski. In this symposium, clinician researchers from different countries shared their experiences with neonatal ventila tion. Representatives from France, Belgium, England, South Africa, Finland, Canada, and the United States participated in the symposium. A review of published proceedings in Biology of the Neonate (current name of this journal is "Neonatology") shows the struggles faced by the clinician researchers of the day in finding the right ventilator for the user in newborn, the optimal time for initiating ven tilation, monitoring babies on ventilation, and improving outcomes at this time [55–58].

In writing the summary of the symposium, Dr. Paul Swyer from Toronto, Canada who conducted the meeting ***raised the big question: whether neonatologists should con tinue to provide assisted ventilation! (Perhaps, more aggres sively) or whether the possible complications outweighed neonatal ventilation***.

However, the efforts to improve the clinical practice of providing assisted ventilation to the sick newborn contin ued.

The introduction of CPAP in managing infants with HMD by Gregory et al. in 1967 was a major breakthrough in neonatal respiratory management [59]. Using this approach he showed a significant improvement in sur vival of infants with HMD (16 of the 20 infants survived—including 10 less than 1500 g) [59].

Introduction of surfactant therapy in HMD/RDS

The invention of CPAP and the discovery [60–64] and pro duction of surfactant further reduced mechanical complica tions of ventilation in preterm newborns [65,66].

In 1959, Avery and Mead [63] reported that the low sur face tension in the lining of the lung permits stability of the alveoli at end expiration. Lacking such material, immature infants and infants dying with HMD, surface tension was higher than expected. They speculated that deficiency of surface-active material might be significant in the patho genesis of HMD. This article was cited 376 times in the period 1961–77.

In 1980, Fujiwara et al. from Japan reported successful use of an artificial surfactant in 10 preterm infants severely ill with HMD [67,68]. Following instillation of artificial sur factant, alveolar–arterial gradients decreased, the levels of inspired oxygen and peak inspiratory pressures decreased, and radiological abnormalities resolved. All survived. Raju et al. [69] reported that replacement therapy with surfactant in a randomized trial significantly improved oxygenation, reduced complications of neonatal ventilation such as air leak syndromes (pneumothorax and pulmonary interstitial emphysema), and improved survival without BPD. Soon after multiple randomized clinical trials of surfac tant replacement therapy substantiating improvement in survival of infants with RDS treated with surfactant [70]. These studies led to FDA approval of a surfactant "Sur vanta" for clinical use in 1993. Introduction of surfactant in the treatment of RDS remains a major milestone in the history of neonatology

The modern neonatal ventilators

Prior to 1970s, neonatologists had to use modified adult ventilators providing intermittent positive pressure ven tilation. However, these ventilators could not match the physiologic pattern of breathing at higher rates. Ventila tors designed specifically for the newborn appeared during mid-1970s–90s. Dr. Sola in this book discusses currently available ventilators incorporated with various functional modalities for use by the clinician. Goldsmith et al. [71] describe the milestones of technological developments in designing ventilators specifically for the newborns and premature infants—starting from the modified adult ven tilators to current highly sophisticated incorporation of space age technology into ventilators used currently in the NICUs.

The rhetoric question raised at the Paris symposium in 1969 regarding the value of assisted ventilation has been answered by the continued efforts to improve technologi cal, perinatal, and neonatal therapeutic advances to treat babies with HMD. Undoubtedly, assisted ventilation has improved overall survival of tiniest babies with HMD (24% mortality among extremely preterm infants <29 weeks of gestation and 2.9% mortality among moderately preterm infants, 29–33 weeks of gestation) [72], but the persistence of associated complications of ventilator-induced lung injury continue to vex the clinician and stimulate further research.

Summary

In summary technological innovations—*the likes of Hess incubator*—of early 20th century were the precursors of modern incubators. The premature care centers of early 20th century were the beginning of modern neonatal intensive care units. The evolution of incubator care of the premature infants, combined with the extensive basic and clinical research on fetal and neonatal physiology in the last century, gave birth to the subspecialty of neonatology.

Modern ventilatory care evolved from earlier efforts to save babies dying of neonatal tetanus. Similar earlier

efforts to ventilate premature babies with lung disease (HMD) were discouragingly poor. Persistent and continued efforts to develop ventilators to match neonatal physiology combined with modern space age microprocessors resulted in the modern neonatal ventilators. It was also realized that machines alone do not make an intensive care. It is the people (skilled nurses/doctors/respiratory therapists, support staff) who care "intensively" and make the intensive care unit.

With these principles of care the outcome results of modern ventilation in the premature newborn, supplemented with surfactant therapy, nutritional support and nursing care are exceedingly high even in the extreme premature babies (over 92% survival at 28 weeks) [73].

Today, it is estimated that in the United States alone 65,000 babies are ventilated annually [74]. Further, with global efforts of technology transfer to the developing countries, the practice of neonatal ventilator support particularly of the premature baby is widely used even in low- and middle-income countries [75]. While these developments are a very nice welcome, the novice should be cautioned in venturing into this territory without the expertise or the total organizational support needed for the operation of neonatal ventilation.

However, long-term ventilation is associated with pulmonary morbidity (CLD/BPD). Experts in the field have discussed various preventive aspects of ventilator-induced lung injury in this book. *Prevention of ventilation-induced lung injury (VILI) remains the major challenge for the future generation of neonatologists.* A summary of evolution of neonatal ventilation is shown in Fig. 2.8.

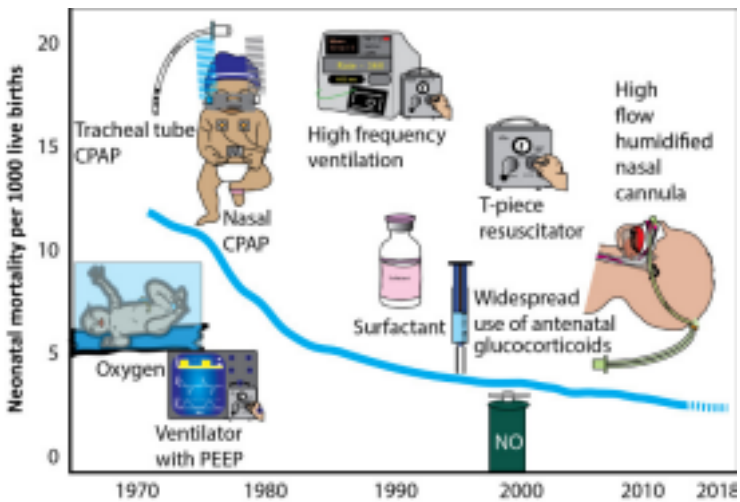


Fig. 2.8 Graph Showing Neonatal Mortality Rate and Various Innovations in Neonatal Respiratory Care. *CPAP*, Continuous positive airway pressure. Copyright: Satyan Lakshminrusimha.

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II

Lung Development and Interventions in the Prenatal and Perinatal Period

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3

Pathophysiology of Fetal Lung Development

Bobby Mathew, MBBS, MRCP, Lucky Jain, MD, MBA, Satyan Lakshminrusimha, MD

- Fetal lung development is a highly complex developmental process orchestrated by genetic, hormonal, and physical factors.
- Lung development proceeds from 4 weeks of gestation through childhood in five continuous but overlapping stages
- Specific disorders are associated with derangements, insults and exposures at various developmental stages and following preterm birth.
- Studies in animal models have significantly advanced our understanding of the molecular mechanisms of lung development.
- Recent studies with stem cells hold promise to further our knowledge towards development of potential therapeutic interventions in this vulnerable patient population.

Introduction

The primary function of the respiratory system is oxy genation and removal of carbon dioxide from the blood. This is accomplished through a highly complex system of airways and blood vessels that are closely related from an anatomical, functional, and developmental perspective. Gas exchange between the atmospheric air and the blood occurs across the double-layered alveolar–capillary mem brane. The lungs consists of extensive airway conducting sys tem, with many different specialized epithelial lining cells, neuroendocrine cells, and an expansive gas exchange zone composed of intricately arranged pulmonary epithelial cells and capillaries. Fetal lung development is a highly complex developmental process orchestrated by genetic, hormonal, and physical factors. This chapter briefly describes the devel opment of the lungs, the disorders associated with derange ments at various developmental stages, and the effects of exposure to adverse intrauterine environment from various insults during gestation and following preterm birth [1].

Embryology

The lungs develop from the primitive foregut endoderm and the surrounding mesoderm. All of the three germ layers give origin to the different tissues of the lung. The pulmo nary epithelium is derived from the endoderm. The pul monary vasculature, the cartilage, the airway, and vascular smooth muscle and connective tissues are of mesodermal origin. The neural innervation of the lung is of ectodermal origin. Reciprocal mesenchymal–epithelial inductive inter actions are mediated through direct cell-to-cell contact, soluble factors, and spatiotemporal- and concentration dependent activation of different growth factors and genes lead to coordinated development of the lungs. Mesen chyme influences epithelial growth and morphology, pat terning of ductal branching, and activates specific patterns of epithelial cytodifferentiation and functional activities [2]. Fetal lung development proceeds from 4 weeks of ges tation through childhood in five continuous but overlap ping stages (Fig. 3.1 and Table 3.1).

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Table 3.1 Stages of lung development and timing based on postmenstrual age (PMA)

Stages	Weeks (PMA)	Main events	Examples of anomalies resulting from disruption at this stage
Embryonic	5–9	Tracheobronchial branching	Tracheoesophageal fistula, esophageal atresia, pulmonary agenesis/aplasia.
Pseudoglandular	6–17	Elongation and repetitive branching of airways and pulmonary vascular development	of alveolar and capillary membranes Bronchogenic cysts, pulmonary hypoplasia, tracheobronchomalacia, intralobar pulmonary sequestration, alveolar capillary dysplasia, congenital diaphragmatic hernia and pulmonary vascular lymphangiectasis
Canalicular	16–26	Differentiation of type I and II cells, surfactant and lung liquid production; alveolar–capillary interface begins to form	Pulmonary hypoplasia, alveolar capillary dysplasia Bronchopulmonary dysplasia following preterm birth
Saccular	24–38	Formation of air sacs and better apposition	
Alveolar	36 weeks to postnatal age (2–8 years)	Secondary septa formation and fusion and thinning of double-capillary network	

Disruption of each stage can lead to specific congenital or developmental anomalies of the lung.

Embryonic stage

This stage extends from 5 to 9 weeks of postmenstrual age (PMA). The major events during the embryonic stage are the formation of the lung bud and the development of the major airways to the level of segmental bronchi. At 28 days of gestation a group of cells in the ventral foregut endoderm are committed to become respiratory epithelial progenitors by localized expression of the homeobox gene Nkx2-1 [3]. At 5 weeks of PMA, these cells give rise to lung buds that appears as a ventral outpouchings from the prim itive gut endoderm and grows into the surrounding meso
derm anterior to and parallel to the developing esophagus. The trachea is formed by the fusion of lung buds by 6 weeks of PMA. Epithelial cells (endodermal origin) invade the surrounding mesoderm and undergo a series of branching giving rise to the tracheobronchial tree. By the 7th week of PMA, bifurcation of the lung buds occurs, two on the left and three on the right. In the subsequent week, a further round of branching occurs which gives rise to segmental branches, 8–9 on the left and 10 on the right and estab lishes the bronchopulmonary segments of the lung. The separation of trachea and esophagus is complete by the end of this stage. The pulmonary artery branches from the sixth aortic arch and the pulmonary veins emerging from the left atrium are established. Perturbations in development dur
ing this stage can lead to tracheoesophageal fistula, esopha geal atresia, and pulmonary agenesis/aplasia.

Pseudoglandular stage

This stage extends from 6 to 18 weeks of PMA. During this stage the developing lungs assumes a glandular appearance with multiple branching epithelial tubes surrounded by abundant mesenchyme. The main event that occurs dur
ing this stage is the elongation and repetitive branching of the airways, differentiation of the epithelial linings of the respiratory tree, and the development of airway smooth muscle and cartilage. Branching morphogenesis is tightly controlled temporally and spatially with proximal–distal (P–D) patterning, resulting in generation of proximal epi
thelial progenitors giving rise to neuroendocrine, muco ciliary, and basal cells of the conducting airways and distal epithelial progenitors yielding pnuemocytes in the periph ery of the lungs [4–6]. The P–D patterning is brought about by differential expression of transcription factors, Sox2 in the proximal airway lining cells and Sox 9 in the distal epithelium of the lungs [7,8]. The cartilage extends into the segmental bronchi and smooth muscle to the respira tory bronchioles. Vascular development during this stage includes the development of pulmonary arterial system in parallel to the airway branching and the pulmonary veins and lymphatics extending into the interlobular septa. Clo sure of the pleuroperitoneal cavity occurs during this stage. Breathing movements are first noted around 10 weeks of PMA. Congenital abnormalities during this stage of development include bronchogenic cysts, pulmonary hypoplasia, tracheobronchomalacia, intralobar pulmonary sequestration, alveolar capillary dysplasia, congenital dia phragmatic hernia, and pulmonary vascular lymphangiec tasis.

Canalicular stage

This stage extends between 16 and 26 weeks of gesta tion. Canalization of the lung parenchyma with increas ing pulmonary capillary network, formation of the air blood barrier, differentiation of the epithelial cells in the lung are the main events in this stage. The alveolar lining cells—the type 1 and 2 alveolar cells appear in the sec ond half of this stage. The lumen of the airways enlarge, with thinning of the alveolar septa and an exponential increase in development of the capillary bed with greater apposition of the airway and the vasculature resulting in the formation of the immature yet functional air–blood barrier. The conducting airways are lined by fully differen tiated ciliated cells, submucosal glands, smooth muscle, and cartilage as far distally as in the mature lung. Respira tory bronchioles and alveolar ducts develop during this stage. The epithelial cells secrete fetal lung fluid and the alveolar type 2 cells begin to produce surfactant. Infants born toward the end of this stage have severe respiratory insufficiency but can survive with surfactant replacement therapy and intensive care. Abnormalities associated with this stage of lung development are pulmonary hypoplasia due to impairment of the thoracic cavity or loss of fetal lung fluid as in oligohydramnios and alveolar capillary dysplasia.

Saccular stage

This stage extends between 24 and 38 weeks of gesta tion. Formation of alveolar ducts and saccules occurs by the expansion and dilation of the terminal clusters of the acinar tubules. Intersaccular and interductal septa develop which contain a double capillary network. Greater appo sition of the capillaries and the type 1 alveolar epithelial cells with fusion of the basal lamina of the type 1 alveolar epithelial cells and the endothelium of the capillary results in the formation of alveolar–capillary membrane. Further maturation of the type 2 alveolar epithelial cells occurs as evidenced by increase in number and size of the lamellar bodies and increase in amounts of tubular myelin in the airspaces.

Alveolar stage

The alveolar stage of lung development extends from 36 weeks of PMA to 2 years postnatal and is characterized by the maturation of the alveolar–capillary membrane and the formation of secondary septa, which divide the terminal saccules into alveolar ducts and alveoli. The alveolar septum is thick and contains a double capillary network at the beginning of this stage. Development of secondary septa/crests with further lengthening, thinning, and fusion of the double capillary network leads to closer apposition of the alveolar capillary interface and increase in surface area for gas exchange and the formation of the mature alveolus. Alveolarization occurs in two phases. The initial phase in the first 2 years of life of rapid increase in alveolar numbers with decreased volumetric expansion is termed bulk alveolarization. This is followed in childhood through young adolescence by a period of slower increase in number and increased growth of the alveoli resulting in increased lung volumes [9,10]. At term gestation, the mature lung has approximately 150 million alveoli and this increases to about 480 million by adulthood.

Pulmonary vascular development

The pulmonary vascular system consists of the pulmonary arterial and venous systems and pulmonary lymphatics. Converse to what was believed earlier, vascular morphogenesis starts early in the embryonic phase with the development of a primitive vascular plexus around the lung bud [11]. The pulmonary vasculature develops form mesoderm progenitor cells, which are committed to endothelial lineage with specific markers, such as VGFR2, CD31, and Sox17. The two major processes through which pulmonary blood vessels develop are vasculogenesis and angiogenesis. Vasculogenesis involves the de novo formation of blood vessels through primitive endothelial cells forming tubes or sinusoids. Angiogenesis is the process by which new vessels are formed by sprouting or branching from preexisting vessels. The main pulmonary artery is formed by vasculogenesis and so are the blood vessels at periphery of the lung. Angiogenesis accounts for the formation of the proximal pulmonary arteries and veins [12]. The development of the pulmonary arterial system closely mirrors the airway system. All the preacinar arteries and veins are formed by the end of the pseudoglandular stage. In the canalicular stage, there is a rapid increase in blood vessel formation and closer apposition of the blood vessels to the pulmonary epithelium. During the saccular and alveolar stages, fusion of the basement membrane of the alveolar epithelial cells to the pulmonary endothelial cell further decreases the diffusion distance and increases the efficiency of gas exchange of the alveolar–capillary membrane. Alveolar and pulmonary vascular development is exceedingly interdependent processes and perturbation of pulmonary vascular development leads to impairment of alveolarization [13–15].

Transcription factors and growth factors in lung development

Lung development is dependent on interactions between the epithelium and the mesenchyme and modulated by multiple signaling pathways. Several transcription factors, growth factors, and their receptors with specific temporal and spatial profiles play vital role in different stages of lung development. The role of different factors in lung development has been elucidated by gain or loss of function studies in null, mutant, and transgenic mouse models. The progenitors for the future respiratory tract are first identified around 28-day gestation by localized expression of homeo box gene Nkx2-1 in a subset of cells in the ventral foregut endoderm. NKX2-1/Thyroid transcription factor (TTF1) is a key regulator involved in all stages of lung development from the embryonic stage through to alveolarization in the postnatal period. In experimental animals, disruption of NKX2-1 results in nonseparation of the trachea from the esophagus, severe lung hypoplasia, impairment of branching morphogenesis and epithelial differentiation, and abnormalities in surfactant homeostasis [16,17]. In the earliest stage of development, Forkhead box A1 and 2 (FOXA) is expressed in the ventral foregut endoderm at the initiation of lung bud formation along with the NKX2-1. Mutation of the Foxf1 is the underlying genetic abnormality in alveolar–capillary dysplasia [18,19]. Fibroblast growth factors (FGF) regulate an array of functions, including migration, cellular proliferation, and differentiation. FGF10, a mitogen, and chemoattractant for the epithelium and its receptor FGFR2IIIb play an important role in the branching morphogenesis. FGF10 deficient mice have arrested development at the stage of the trachea with no pulmonary branching [20,21]. Sonic hedgehog (Shh) plays an important role in epithelial mesenchymal signaling with deficiency leading to decreased cell proliferation and increased apoptosis and overexpression resulting in mesenchymal hypercellularity and smaller lungs with dysfunctional alveoli [22,23]. Other genes and transcription factors, such as HOX, Myc, GATA, Wnts, BMPs, play crucial roles in the branching morphogenesis [24–28]. Elastogenesis is critical for secondary septation in the stage of alveolarization. Elastin deposition occurs at the sites of interalveolar septa formation. Platelet-derived growth factor, a key chemoattractant for myofibroblasts, FGF18, retinoic acid have an important role in elastogenesis, secondary septation, and alveolarization. Retinoic acid upregulates tropoelastin gene expression and mRNA expression of FGF18, PGDF, and its receptors. Vitamin A deficiency has been shown to delay alveolar development, and supplementation results in increasing number of alveoli in rat pups [29]. Vitamin A

supplementation has been shown to decrease mortality and the risk of bronchopulmonary dysplasia in preterm infants [30]. Remodeling of the extracellular matrix is brought about by the matrix metalloproteinases (MMP2 and MMP14) and the tissue inhibitors of metalloprotein ases (TIMP). Low levels of MMP2 in tracheal secretions were found to be associated with an increased risk of bron chopulmonary dysplasia in preterm infants [31].

Vascular endothelial growth factor (VEGF) plays a major role both in blood vessel formation and alveolarization (Fig. 3.2). In experimental animals, ablation of the VEGF gene caused abnormal spatial organization of blood ves
sels, severe cardiovascular abnormalities, and in utero death. VEGF-mediated angiogenesis is brought about in part through nitric oxide. In newborn mice, treatment with VEGF inhibitor SU5416 decreased lung endothelial nitric oxide synthase (eNOS) activity resulting in right ven
tricular hypertrophy (RVH) and decreased radial alveolar count (RAC). Inhaled nitric oxide treatment prevented the development of RVH and improved the RAC [32]. VEGF expression is tightly controlled during lung development, as seen in experimental studies in mice; overexpression of VEGF resulted in pulmonary vascular leak and hemorrhage alveolar inflammation and death [33]. Other important mediators of pulmonary vascular development include epidermal growth factor (EGF), transforming growth fac tor, angiopoietins, BMPs platelet-derived growth factors, and transcription factors such as HIF, Hox, Fox, and Sox that play a critical role in lung development.

Maturation of pulmonary surfactant system

Pulmonary surfactant is synthesized and secreted by the type 2 alveolar cells. Type 2 cells are first recognized in the late canalicular stage. In utero, type 2 cells secrete only small amounts of surfactant even at term gestation. Surfac
tant synthesis and secretion are tightly regulated by hor monal, physical, and chemical stimuli. Regulation of type 2 alveolar epithelial cells, maturation, and surfactant release are influenced by late-term elevations of intracellular cyclic 3′-5′ adenosine monophosphate (cAMP), cortisol, thyroid hormone, catecholamines, and through stimulation of beta adrenoceptors and natriuretic peptide receptors [34,35] (Fig. 3.3). Lamellar bodies, the storage form of surfactant, first appear in the fetal lungs between 20 and 24 weeks of gestation. The surfactant pool size of preterm infants with RDS is about 10 mg/kg as compared to 100 mg/kg in term infants [36]. The rate of synthesis and clearance of surfactant is about 10-fold less than in the adult [37]. However, birth even at extreme preterm gestation, the sur factant system is turned on and these infants are able to

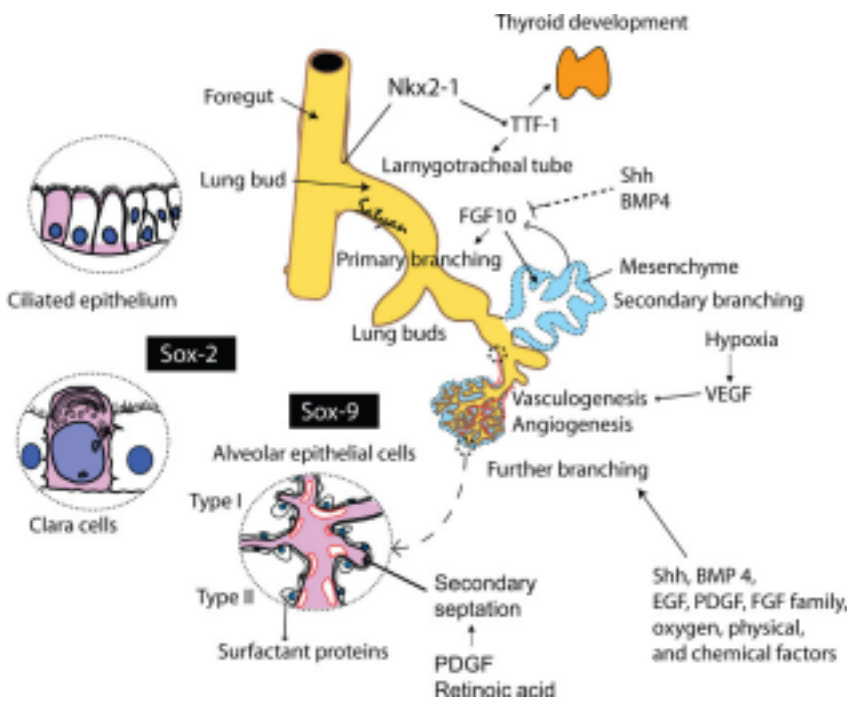

Fig. 3.2 Development of the Respiratory System —Role of Genes, Growth Factors and Transcription Factors. Localized expression of NKX2-1 on the endodermal cells on the ventral surface of the primitive foregut commits them to respiratory cell

lineage. At 5-week PMA, lung buds appear as two ventral outpouchings and grow into the surrounding mesoderm. Positive signaling by fibroblast growth factor 10 (FGF 10) and negative signaling by Sonic Hedgehog (Shh), bone morphogenetic protein 4 (BMP4), Sprouty 2 (spry2) facilitate primary and secondary branching. Further branching is facilitated by Shh, BMP4, spry2, transforming growth factor β (TGFβ), epidermal growth factor (EGF), platelet-derived growth factor (PGDF), and fibroblast growth factors (FGFs). PGDF and retinoic acid (RA) have important role in secondary septation and alveolarization. Thyroid transcription factor-1 (TTF-1) and GATA-6 are important in cell differentiation and the development of the surfactant system. Forkhead homolog 4 (HFH-4) plays an important role in differentiation of ciliated epithelial cell lineage. Differential expression of the Sox2 and Sox9 leads to the proximal distal patterning of airway development. *VEGF*, Vascular endothelial growth factor. Copyright: Satyan Lakshminrusimha.

produce though lower but adequate amounts of surfactant by 4–7 days of life without the need for further exogenous surfactant replacement therapy [38]. Changes in composi tion of surfactant also occur with advancing gestation, and are the basis of tests for lung maturity in fetus, such as leci thin to sphingomyelin (*L*:*S*) ratio [39]. The phospholipid composition of the surfactant also changes with gestation with an increase in content of phosphatidylcholine and the ratio of phosphatidylglycerol to phosphatidylinositol [40]. The presence of phosphatidylglycerol in the amniotic fluid is considered as positive test for lung maturity. The preterm lung is also deficient in surfactant proteins (SPs) [41,42]. The decreased level of SPs in the preterm decreases its effi ciency at improving the lung compliance and increases the susceptibility to inactivation. SP-A and SP-D are water-solu ble collectins, decreased levels of which lead to impairment of host defense from decreased phagocytic and opso nization functions [43]. SP-B and SP-C are hydrophobic peptides associated with surfactant phospholipids and are stored in the lamellar bodies. SP-B is absolutely critical to surfactant function, as it is an essential for synthesis, assem bly and functioning of surfactant, and deficiency leads to death in the newborn period. They have antiinflammatory and antioxidant properties, and a lower level in preterm infants translates to increased susceptibility to infection, inflammation, and hyperoxia-mediated lung injury [44].

Intrauterine exposures and its effect on lung development

Smoking

The fetus is indirectly exposed to many environmental pol lutants through the transplacental route. Maternal smoking

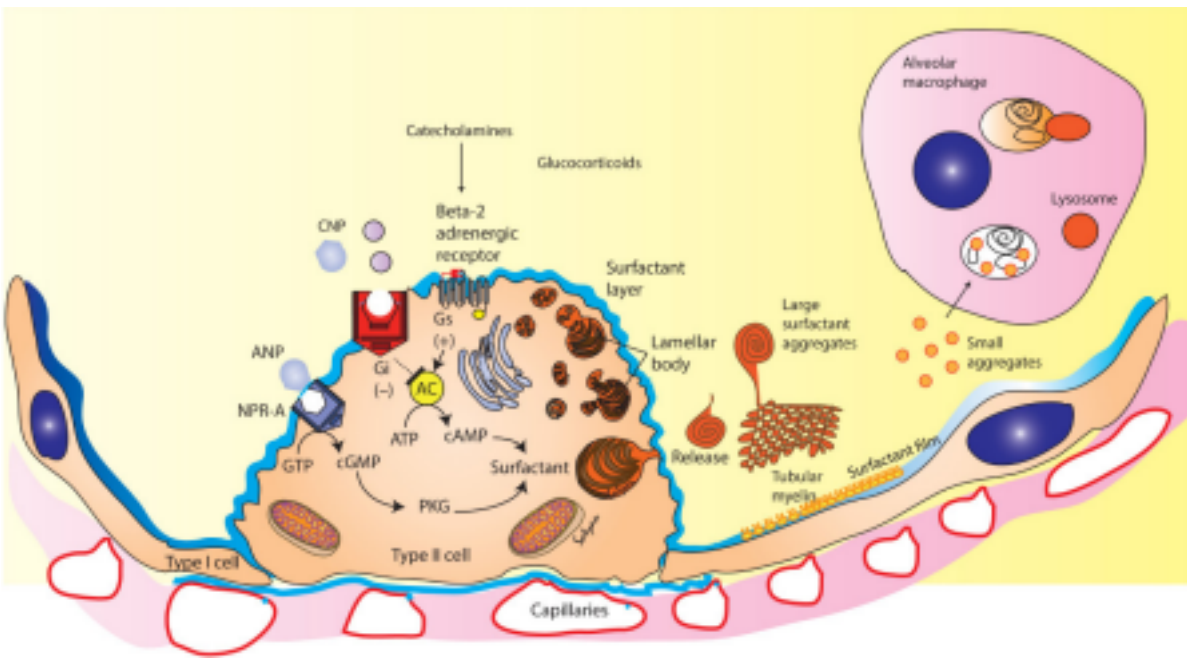

Fig. 3.3 Control of Surfactant Secretion. Catecholamines act through the adenylyl cyclase stimulate surfactant secretion. ANP at lower doses binds to the NPR-A receptor and stimulates surfactant release. At higher doses, ANP also binds to the NPR-C receptor and inhibits beta-2 agonist stimulation of surfactant release. *CNP*, C-type natriuretic peptid. Copyright: Satyan Lakshminrusimha.

during pregnancy has been the most extensively studied among toxic exposures to the fetus. Cigarette smoking in pregnancy leads to premature birth, poor intrauter ine growth, and increases perinatal mortality. Nicotine in cigarette smoke crosses the placenta and through binding to the nicotinic acetylcholine receptors in the developing lung leads to long-term structural and functional abnor malities. In animal models, antenatal nicotine exposure is associated with decreased alveolar septation, elastin con tent, and lung volume and increased lamellar bodies and collagen [45,46]. Abnormalities in lung function include decrease in functional residual capacity, forced expiratory volume and compliance [47,48]. Abnormalities in airways with increased number airways of smaller diameter result in increased resistance to airflow [49]. This translates to an increased incidence of lower respiratory illness, such as reactive airways disease and asthma in childhood [50].

Intrauterine growth restriction (IUGR)/maternal undernutrition

Intrauterine growth restriction (IUGR) results from multi ple etiologic factors, disorders of abnormal placental func tion, decreased fetal perfusion resulting in deficient oxygen and nutrient delivery, maternal undernutrition, systemic illness, exposures to drugs and toxins or from factors intrinsic to the fetus. In animal models, fetal growth restric tion has been shown to decrease the overall lung volume, the alveolar surface area and increase the thickness of the alveolar–capillary membrane resulting in decreased diffus ing capacity [51–53]. In a maternal hyperthermia model of IUGR in fetal sheep, decreased pulmonary alveolar and vas cular growth and endothelial dysfunction were shown to be the underlying mechanisms for pulmonary hypertension. In a retrospective study of infants' ≤28 weeks gestation at birth with moderate to severe BPD, birth weight below 25th percentile was found to be an independent predictor for pulmonary hypertension [54]. Studies in animal mod els have also shown an increased risk of development of pulmonary hypertension and cardiac dysfunction with age in IUGR [55].

Chorioamnionitis

Ascending infection from the lower genital tract spreads to the amniotic cavity through the choriodecidual plane. Common etiologic agents causing chorioamnionitis and precipitating preterm labor are *Ureaplasma*, *Mycoplasma*, and *Fusobacterium*. Studies of intraamniotic injections with bacterial products, such as lipopolysaccharide (LPS)

or proinflammatory cytokines (IL-1 Beta IL-1 alpha), lead to increase in pulmonary surfactant, lung maturation, and improved compliance [56,57]. This functional maturation is brought about at the expense of structural lung develop ment with decrease in the number and increase in size of the alveoli leading to decreased surface area for gas exchange [58]. Intraamniotic injection of LPS in fetal sheep leads to hypertrophy of the smooth muscle and fibroblast prolif
eration in the adventitia resulting in pulmonary vascular remodeling and increased pulmonary vascular resistance contributing to the development of pulmonary hyperten sion [59,60]. The effect of chorioamnionitis on long-term pulmonary outcomes is not well established. However, the available evidence in preterm infants with chorioamnion itis suggests an increased risk of bronchopulmonary dys plasia in newborn period and reactive airways disease in childhood [61,62].

Physical factors: lung liquid and fetal breathing movements

Lung fluid is secreted by the epithelial cells by active transport of chloride ions into the lumen of the lung. The near term fetal lung in sheep secretes about 4–5 mL/kg/h of fetal lung fluid and the lungs contain about 25–40 mL/kg body weight, which is approximately equal to or slightly higher than the functional residual capacity of the term lung. The intralu minal pressure in the lungs is higher than the intraamniotic pressure by about 2 mmHg and fetal lung fluid drains inter mittently with breathing movements into the amniotic cav ity (Fig. 3.4). This distending pressure is vital and promotes the development of the lungs in the fetus. Moessinger et al. have demonstrated that the loss of fetal lung fluid results in lung hypoplasia in fetal lambs [63]. Oligohydramnios as it occurs in fetuses with renal agenesis (Potter's syndrome), preterm prelabor rupture of membranes leads to an increased risk of pulmonary hypoplasia and the risk increases with the time and duration of oligohydramnios. The increased volume of fetal lung liquid causes lung hyperplasia, and this is the basis of the fetal endoluminal tracheal occlusion (FETO) procedure in fetuses with antenatal diagnosis of con genital diaphragmatic hernia. (NCT02710968 and others at clinicaltrials.gov).

Fetal breathing movements are required for optimal lung development. In human fetuses, breathing movements start around 10-week gestation and the frequency increases with advancing gestation. At term gestation, breathing movements occur about 30% of the time. In utero transec
tion of the phrenic nerve during in utero development on day 24.5 in rabbit fetus resulted in hypoplastic lungs [64].

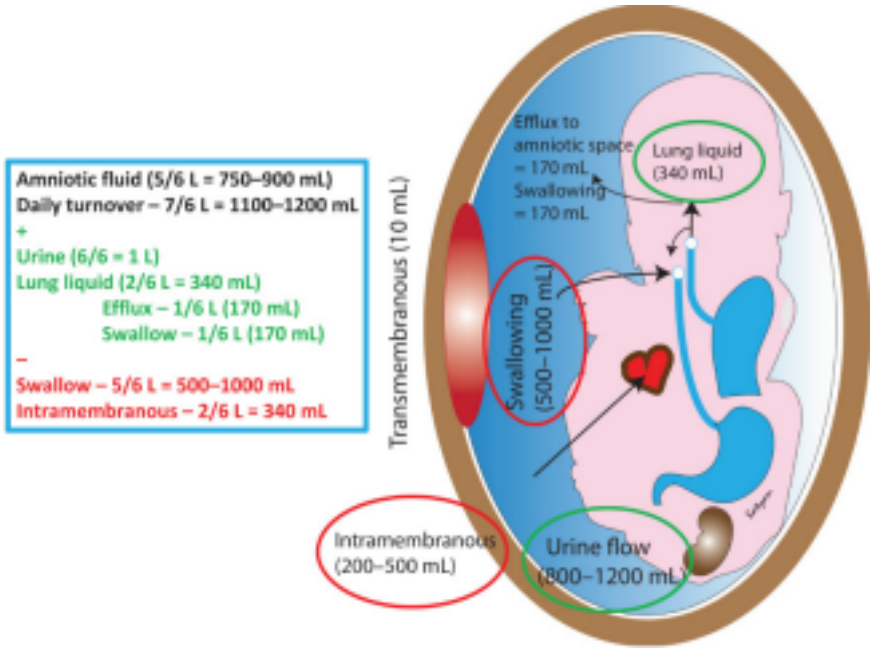

Fig. 3.4 Amniotic Fluid and Lung liquid dynamics. *Green*—indicates factors contributing to increase in amniotic fluid. *Red* indicates factors depleting amniotic fluid. Fetal lung liquid is the second most important contributor to amniotic fluid volume (the primary contributor being fetal urine). The volumes are shown as fractions with a denominator of 6 for ease. Copyright: Satyan Lakshminrusimha.

Peristaltic contractile activity of the airway propagates dis tal movement of the lung fluid, expansion of the lung buds, and promotes lung growth and development. Restriction of chest cavity impairs lung growth. This could result from extrinsic restriction, as it occurs with abnormalities of chest shape, for example, thoracic dystrophies, severe kyphosco liosis or congenital diaphragmatic hernia, lung masses/ cysts, or effusions.

In preparation for postnatal gas exchange, the alveo lar epithelium shifts from a fluid secreting to a reabsorb ing membrane (Fig. 3.5). This is brought about through changes in transmembrane transport channels, humoral factors, and changes in oxygen tension. The effects of these are also modified by the gestational age at birth, labor, and mode of delivery. During late gestation, an increase in circulating catecholamines and elevation in intracel lular cAMP levels result in maturation of the pulmonary epithelium preparing the lungs for surfactant secretion and fluid clearance. At the onset of labor, active transcellular movement of sodium from the lumen to the interstitial space and further into the pulmonary lymphatics and to the venous system is facilitated by the epithelial sodium channel (ENaC) on the luminal side and the sodium potas sium ATPase (Na,K-ATPase) and sodium potassium chlo ride cotransporter (NaKCC1) on the basolateral membrane [65]. This effect is blocked by the sodium channel blocker amiloride [66]. ENaC knockout mice have delayed alveolar fluid clearance in the newborn period with improvement on rescue with αENaC transgene [67]. Epinephrine causes lung fluid resorption through beta adrenergic pathway and this effect is blocked by propranolol [68]. Thyroid hor

mone and glucocorticoids play a key role in advancing the absorptive response of the pulmonary epithelium to cat echolamines [69]. Exposure to prenatal steroids has been shown to increase the levels of αENaC mRNA in the fetal rat lungs [70]. The increase in PaO_2 as seen following birth inhibits fluid secretion in lung explants from late gestation but not in early gestations [71]. However, this effect can be induced at earlier gestation on treatment with thyroid or steroid hormones. Preterm premature rupture of mem

branes leads to fetal lung maturation as evidenced by rapid acceleration of the rate of increased L/S ratio to levels seen with lung maturity.

Glucocorticoids

Glucocorticoids induce accelerated maturation of the lung with thinning of the alveolar wall and fusion of the double capillary network and maturation of the surfactant system resulting in decreased severity of respiratory distress syn drome in infants born preterm. However, this also causes inhibition of vascular development and earlier termina tion of the septation leading to fewer and larger alveoli with decrease in lung surface area for gas exchange [72,73].

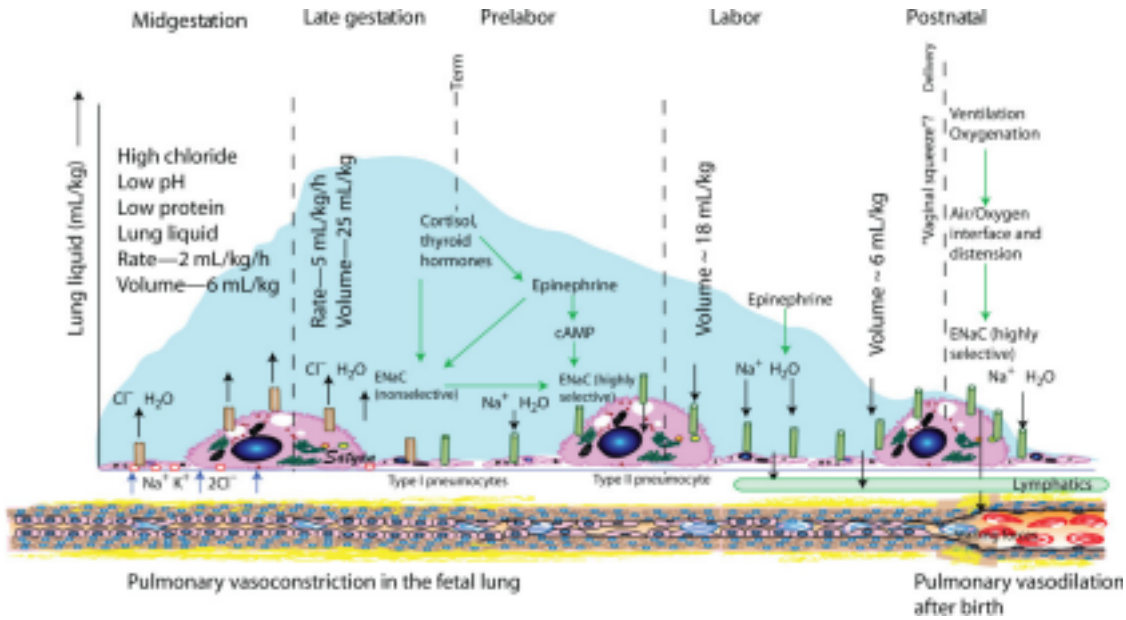

Fig. 3.5 Changes in lung liquid volume during various phases of gestation, term birth, and postnatal period. Factors contributing to secretion and resorption of lung liquid are shown. The vertical axis represents lung liquid volume in mL/kg. *cAMP*, Cyclic 3′-5′ adenosine monophosphate; *ENaC*, epithelial sodium channel. Copyright: Satyan Lakshminrusimha.

development of

Expectant mothers with threatened preterm labor before 34 weeks of gestation are routinely given a single course of antenatal steroids. Infants born 24 h to 7 days following complete course of antenatal steroids have decreased severity of respiratory distress syndrome intraventricular hemorrhage and mortality. However, infants whose mothers received multiple courses of antenatal steroids had decreased birth weight, length, and head circumference with no improvement in neonatal morbidities [74].

Premature birth and oxygen exposure

The fetal lung develops in a hypoxemic environment. Low oxygen tension promotes optimal fetal lung development through hypoxia inducible factor (HIF) and its effect on VEGF. Extremely preterm infants born toward the end of the canalicular stage of lung development are capable of surviving with intensive care, surfactant replacement therapy, and assisted ventilation. The gas exchange units at this stage consist of terminal clusters of acinar tubules, alveolar ducts, and saccules and a primitive alveolar–capillary membrane. Exposure to hyperoxia and ventilator-induced lung injury are inevitable consequences of extreme preterm birth. Inhibition of VEGF (due to hyperoxia) leads to impairment of both vascularization and alveolarization. Exposure to hyperoxia also causes oxidative stress-mediated lung damage, which overwhelms the immature antioxidant capabilities of the preterm lungs that lead to the bronchopulmonary dysplasia and long-term pulmonary morbidity in survivors of preterm birth.

Conclusions

Arrest of lung development, intrauterine/perinatal and postnatal infections, and iatrogenic lung injury remains the cause of major morbidity and mortality in infants born extremely preterm. Current treatment modalities are targeted at decreasing ventilator-induced lung injury, optimizing nutrition, prevention and treatment of infections, gastroesophageal reflux, which cause impaired lung development and deterioration of lung function. Timely and effective antenatal care, minimizing noxious exposures, and ensuring adequate fetal and postnatal growth can to a degree mitigate the developmental consequences to the lung of preterm birth. Studies in animal models have significantly advanced our understanding of the molecular mechanisms of lung development. However, significant gaps in our knowledge remain. Inaccessibility to the lung during fetal development has limited our ability to study their role in human lung development. The emerging field of study using induced pluripotent stem cells (iPSCs) offers the potential to recapitulate the molecular mechanisms in vitro. Further advances in these techniques is likely to provide an in vitro model to study lung development and derangements associated with disease states, design

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new drugs, and develop lung tissue that can used for transplant in patients with end-stage lung disease.

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4

Transition in the Delivery Room: Current NRP Recommendations

Máximo Vento, MD, PhD

- Both anticipation and debriefing are vital for a good resuscitation.
- Keep the delivery room at 26ºC.
  - The team should have a leader, taking care of the respiratory airways, and caregivers taking care of monitoring and providing drugs if necessary.
  - Allow for delayed cord clamping at least 1 min except in an extreme emergency when stripping of the cord could be performed by the obstetrician in 20 seconds.
- Initiate pulse oximetry monitoring immediately after birth.
- Initiate respiratory support with noninvasive ventilation (bag & mask; nasal route) with a rhythm of 30 breaths per minute.
- Use of oxygen:
  - In term infants and preterm infants with a gestational age of >32 weeks, use an inspired fraction of oxygen (FiO_2) of .21
  - In preterm infants with 28-32 weeks' gestation use an initial FiO_2 of 0.21-0.3
  - In preterm infants <28 weeks' gestation use an initial FiO_2 of 03
  - titrate FiO_2 according to SpO_2 and heart rate response
- If drug (epinephrine) administratie

Introduction

The achievement of a significant reduction in maternal and child mortality in the last 25 years has been widely acknowl edged. However, it is striking that the reduction in mortal ity in the neonatal period (<28 days after birth) has lagged significantly as compared with the postneonatal mortality (>28 days and 5 years of age) [1]. Worldwide 130 million babies are born every year and approximately 2.8 million of newborn infants die during the neonatal period, and 73% of these deaths occur during the first week of postnatal life and represent early neonatal deaths (ENND). Out of these ENND, almost

40% die in the first hours as a consequence of birth-related complications. Birth asphyxia still represents 11% of ENND in high-income countries but reaches 30%– 40% in low-income countries, especially in rural areas [2,3].

Overall, 10% of all newborn infant require some form of intervention in the first minutes after birth (Fig. 4.1). New born infants undergo complex respiratory and cardiocircula tory changes during fetal-to-neonatal transition, and failure to achieve these changes represents the most frequent cause of postnatal maladaptation. Therefore, the essential goal of neonatal resuscitation is ventilation of the lungs as opposed to the adult resuscitation focusing on cardiac activity [4]. Breathing initiates a sequence of events that lead to increased oxygenation, decreased pulmonary vascular resistance (PVR), increased pulmonary blood flow, and closure of intra- and extracardiac shunts in the first minutes after birth [5].

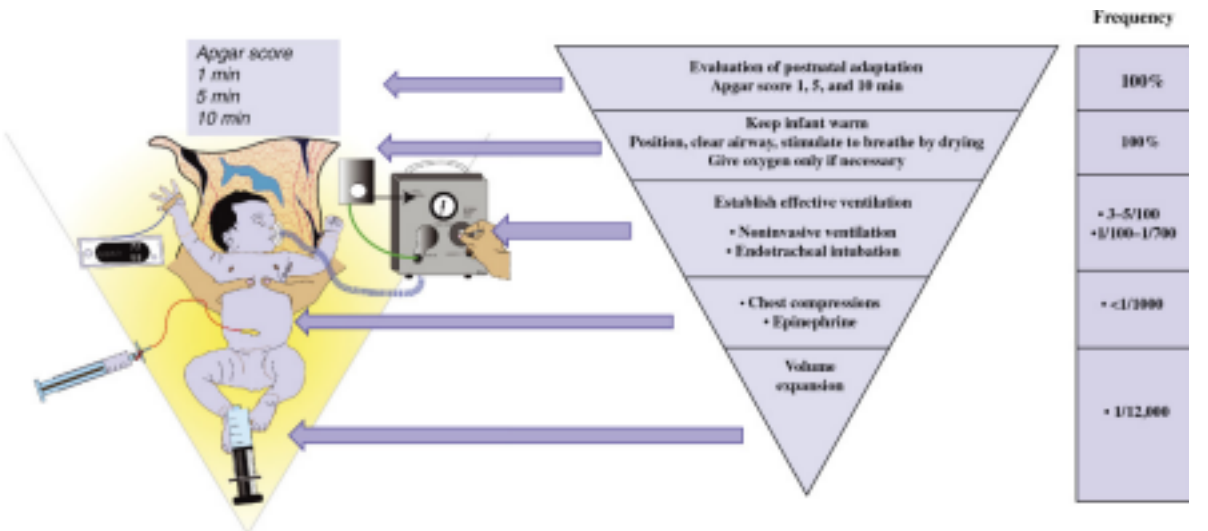

Fig. 4.1 Frequency of the Different Interventions Performed in the Delivery Room in the Newborn infant. Modified from Vento M, Saugstad OD. Resuscitation of the term and preterm infant. Semin Fetal Neonatal Med 2010;15:216–222 [6]. Copyright: Satyan Lakshminrusimha.

Physiologic changes in the fetal-to-neonatal transition

Fetal circulation

In the fetus, gas exchange does not occur in the lungs but in the placenta. Deoxygenated blood from the systemic circulation reaches the placental circulation via the umbil ical arteries where gas exchange takes place and returns oxygenated via the umbilical vein to the fetal arterial cir culation. The fetal circulation is designed in such a way that the preferential streaming of oxygenated blood is directed to brain and myocardium due to the presence of intracardiac (*foramen ovale*) and extracardiac (*ductus arte riosus*) shunts. Hence, the oxygenated blood bypasses the hepatic circulation via the *ductus venosus*, and reaches the right atrium via the inferior vena cava and the left atrium across the *foramen ovale*. Oxygenated blood reaches the left ventricle and is ejected into the aorta, thus reaching myocardium and brain. In addition, deoxygenated blood coming from the lower part of the body reaches the right auricle via inferior vena cava and is ejected by the right ventricle through the pulmonary artery. The high PVR drives the right ventricular output to the descending aorta via the *ductus arteriosus*. Thus, the deoxygenated blood is directed to the placenta. Of note, during fetal life the lung only receives 16% of the combined ventricular output [7,8] (Fig. 4.2).

Fetal gas exchange

During gestation, gas exchange is driven by the differential partial pressures of oxygen and carbon dioxide between the mother and fetus blood across the placental intervillous space. The fetal arterial partial pressure of oxygen (P_aO_2) *in utero* at the end of gestation is approximately 25–30 mmHg (3.0–3.5 kPa). Immediately after birth, P_aO_2 rises to 80–90 mmHg (10.5–12.0 kPa) and stays within this range until the adult life. Despite the great difference in P_aO_2, oxygen delivery to tissue does not substantially differ between the fetus and the newborn. First, the fetus is endowed

with fetal-type hemoglobin that has a greater affinity for oxygen and provides with increased oxygen saturation (SpO_2) for a given P_aO_2. In addition, the cardiac output in the fetus is significantly greater than during infancy or childhood (250–300 mL/kg/min). Moreover, venous return coming from the placenta is redirected to organs with high oxygen needs *ex utero*. At the end of gestation the intervillous partial pressure of oxygen reaches 45–48 mmHg, and these values correspond to an SpO_2 of 50%–60% in the fetus [9,10].

Antioxidant defenses and surfactant production during fetal life

The genes that express the enzymatic machinery respon sible for the synthesis of surfactant, antioxidant enzymes, and sulfur disulfide couples only get activated late in gesta tion preparing the fetus for aerobic respiration. Experimen tal studies in rabbits have shown that antioxidant enzymes

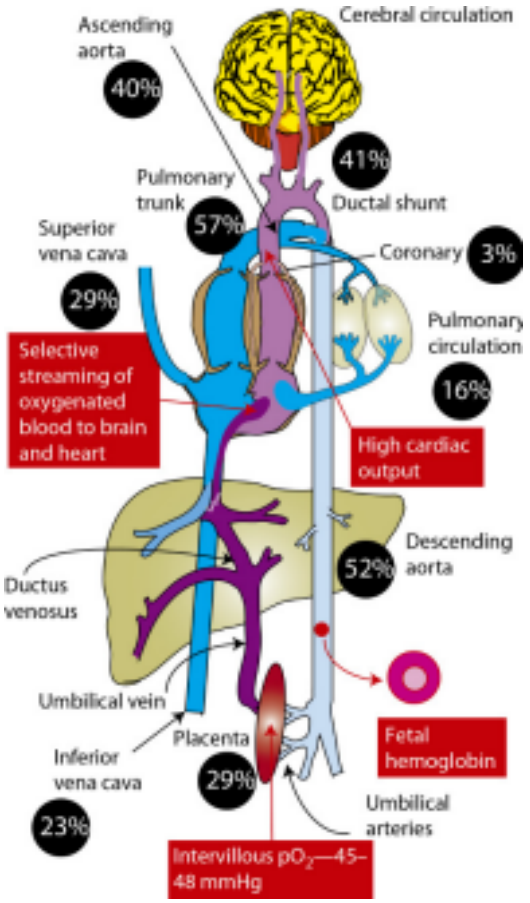

Fig. 4.2 Diagram Representing Fetal Circulation.
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such as superoxide dismutases (SOD), catalase (CAT), and glutathione peroxidases (GPx) develop in the last weeks of gestation [11] paralleling the maturation pattern of surfac tant. Moreover, pulmonary surfactant contains substantial amounts of these antioxidant enzymes to help prevent oxi dative damage to lung structures by reactive oxygen species (ROS) [12]. In addition, the limiting enzyme for the syn thesis of glutathione (GSH) is *γ-cystathionase* which converts cystathionine in L-cysteine and is not expressed until late in gestation. GSH is a ubiquitous tripeptide (γ-glutamyl

rendering L-cysteine a conditionally essential amino acid for extremely preterm infants [13,14].

Surfactant is a complex macroaggregate of phospho lipids and specific proteins that has tensioactive and anti infective properties. Surfactant drastically reduces alveolar surface tension opposing to alveolar collapse during the expiratory phase of respiration, promoting the acquisition of a lung function residual capacity, and also contribut ing to the lung's defense system. Surfactant synthesis and secretion are first detected in the human fetus type II pneu mocytes in the canalicular stage of lung development at 20–22 weeks of gestation. However, secretion of surfactant into the amniotic fluid is detectable only after 30–32 weeks of gestation. Consequently, babies born before 32 weeks of gestation are at a greater risk of developing respiratory dis tress syndrome secondary to surfactant deficiency [15,16].

Transition in the delivery room

Cardiorespiratory changes in the first minutes after birth in the term infant

Immediately after birth, term babies cry and initiate respira tory efforts. Ventilation causes immediate dilatation of the pulmonary vessels, the right ventricular output is redirected toward the pulmonary circulation, and oxygenated venous blood returns to the left atrium via pulmonary veins pro viding left ventricular preload. Circulatory changes lead to closure of the intra- and extracardiac shunts. Few minutes

cysteinil-glycine) present in the cytoplasm of the cells and the most relevant cytoplasmic nonenzymatic antioxidant. Under normal conditions, two molecules of reduced GSH can combine to form a disulfide bond (GS═SG) and reduce ROS with two electrons. GSH is also the main deter minant of the redox status of cell cytoplasm. Remarkably, studies performed in preterm infants have shown that the expression of γ-cystathionase also occurs late in gestation

after birth, the newborn baby establishes an adult-type cir culation with two circuits in parallel, pulmonary and sys temic, without admixture of oxygenated and deoxygenated blood [17]. During the first breaths, term infants generate very high inspiratory and expiratory pressures with a mean of (−) 50 cmH_2O during

inspiration and +60 to 70 cmH_2O during expiration [18]. In addition, at the end of expiration braking maneuvers such as closure of the glottis avoid alve olar collapse by keeping a positive end-expiratory pressure (PEEP). The negative hydrostatic pressure created during inspiration constitutes the physical force that thrusts the fluid filling the lung to the surrounding tissue and contrib utes to lung aeration [19,20]. The surfactant layer expands on the alveolar surface acting as a tensioactive factor that counteracts the elastic recoil forces that tend to collapse the alveoli during expiration. The gas remaining at the end of expiration in the lung constitutes the functional residual capacity (FRC). FRC notably enhances gas exchange and reduces the amount of pressure needed to open the lung in the following inspiratory movements. Hence, after ini tial lung expansion and establishment of FRC, subsequent respirations in the newborn infant will only need to reach

negative thoracic pressures of −20 to −25 cmH_2O to allow sufficient air to reach the alveolar space and achieve sta ble gas exchange. Such negative intrathoracic pressures can be accomplished with gentle contractions of the dia phragm [20].

Consequences of preterm birth on postnatal adaptation

Circumstances surrounding the preterm delivery are somewhat different. Both the immaturity of the thoracic cage and the weakness of the thoracic muscles hinder the achievement of high negative intrathoracic pressures during inspiration and the enhanced elastic recoil and lack of surfactant that prompt lung collapse during expiration. The consequences are the limitation of lung aeration and fluid reabsorption during inspiration and the tendency toward atelectasis during expiration and avoidance of the establishment of FRC. Altogether, these circumstances hamper effective gas exchange and lead to respiratory insufficiency with tendency to hypoxemia and hypercarbia. Therefore, one of the principal efforts of the caregivers in the delivery room (DR) is to establish an effective ventila tion and oxygenation, especially in the very preterm infants (<32 weeks of gestation) [16].

Oxidative stress during the fetal-to-neonatal transition

Even with a mature antioxidant defense system and breath ing room air, the burden of oxygen free radicals generated during the fetal-to-neonatal transition will inevitably cause an oxidative stress in the immediate postnatal period. In experiments performed with term rat pups, it was shown that normal deliveries cause oxidative stress as evidenced by a significant reduction of the reduced to oxidized (GSH/ GSSG) GSH ratio in isolated hepatocytes [21]. GSH, the most relevant nonenzymatic antioxidant, is further reduced in the fetal-to-neonatal transition when rat pups are reox ygenated with higher oxygen concentrations and pro apoptotic and proinflammatory pathways are secondarily activated in brain and lung [22,23]. However, offspring of pregnant mice delivered and kept in a low oxygen atmo sphere mimicking *in utero* milieu (FiO_2 = 0.14) exhibited an increased GSH/GSSG ratio in lung on day 1 and in the brain on day 7 after birth as compared with pups born in room air (FiO_2 = 0.21). The activation of the NRF-2-related antioxidant genes was significantly increased in lung and brain. Apparently, a smooth transition from the lower oxy gen milieu *in utero* to the relatively hyperoxic milieu *ex utero* seemed to be protective [24].

Studies in a hypoxic piglet model of hypoxia-reoxygen ation showed that the use of pure oxygen caused not only an increased concentration of extracellular glycerol in the brain striatum but also increased matrix metalloprotein ases in lung, liver, heart, and brain compared with the use of room air. Interestingly, there is clear dose-dependent oxygen toxicity, and elimination of biomarkers of oxida tive damage caused to protein and DNA significantly cor related to the FiO_2 provided during resuscitation [25]. Translating these findings in experimental animals into the clinical setting would imply avoiding targeting high satura tions too rapidly in preterm infants after birth. Stabiliza tion with high oxygen concentrations is not only toxic to the lungs but also to different organs such as heart, liver, and brain.

Current NRP recommendations

International guidelines have set up algorithms to guide caregivers in the DR and to take decisions when difficul ties in postnatal adaptation arise. The most relevant clinical parameters that need to be assessed immediately after birth by caregivers are breathing, heart rate (HR), and peripheral oxygen saturation measured by pulse oximetry (SpO_2) [26]. Fig. 4.3 summarizes the resuscitation flow diagram.

Anticipation

Information provided by the obstetric team before birth is important to anticipate the necessary personnel and material needed and design the best strategy for an effec tive resuscitation. Ideally, at every delivery there should be at least one caregiver responsible for the newly born with the adequate skills to assess the infant's status, initiate resuscitation, apply positive pressure ventilation, perform endotracheal intubation (ET) and chest compressions, and administer medication. Of note, most of the babies (but not all) requiring active resuscitation are to be identified before birth allowing for the recruitment of a team of skilled pro
fessionals under the leadership of an expert neonatologist and briefing of the expected difficulties

according to the type and circumstances of the delivery [28]. The Delivery Room Intensive Care Unit (DRICU) concept recommends that referral centers, where high-risk pregnancies are cen
tralized, trained caregivers as well as monitoring and venti latory devices should be available round the clock all year through to provide optimal resuscitation [29]. Interven tions that have proven to improve outcomes of extremely preterm low birth weight (ELBW) infants should be consid ered before birth. Such interventions include the following:

1. The use of tocolytics to prevent preterm birth to allow fetal maturation.
2. Transfer to a regional referral center with expertise in the treatment of ELBW infants.

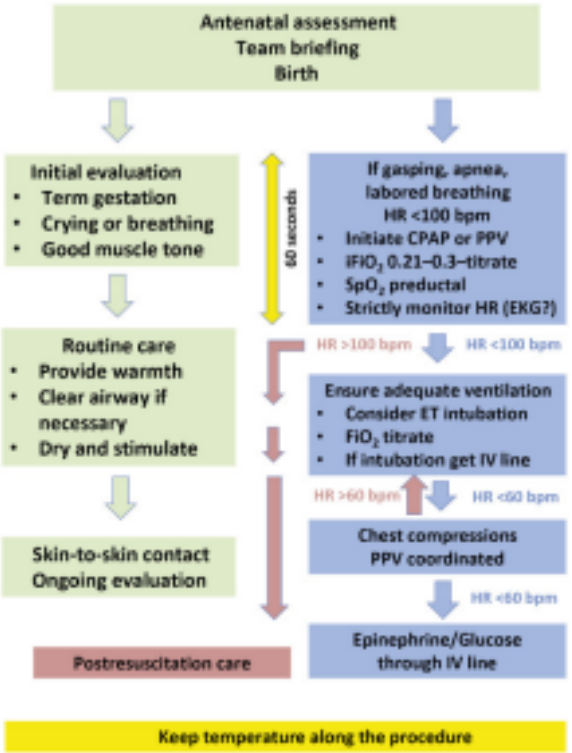

Fig. 4.3 Flow Diagram of the Interventions Performed in the Delivery Room According to the Infant's Clinical Status and Response Following the ILCOR 2015 Guidelines [27].

3. Antibiotics in case of preterm rupture of membranes to avoid fetal infections.
4. Antenatal steroids to mature fetal lung.
5. Magnesium sulfate administered to the mother shortly before birth as an efficacious neuroprotective drug to the fetus [26].

Initial steps in stabilization: assessment and intervention

Newborn infants should be evaluated in the DR in the first 60 s after birth during the so-called "golden minute." Gesta tional age, the presence of spontaneous breathing or crying and good tone and active movements should be immedi ately assessed. Cord clamping should be delayed between 30 and 60 s in all babies unless and have a good tone (flexed extremities) should be briefly dried with a warm towel, gently stimulated and immedi ately put in skin-to-skin contact with the mother and cov ered with a warm blanket. Importantly, baby's head should be slightly hyperextended to facilitate breathing and if oral secretions are adverted, they could be wiped with gauze. Breastfeeding should be promoted immediately after birth. Approximately after one 1 h vitamin K and erythromycin eye drops should be administered [31].

Delayed cord clamping or umbilical cord milking

Delayed cord clamping (DCC) for at least 60 s after birth is now recommended for term infants. It provides an additional blood volume that increases hemoglobin con centrations at 24–48 h and iron stores at 3–6 months. However, DCC is associated with an increased rate and intensity of neonatal hyperbilirubinemia and the need for phototherapy [32]. The driving forces for blood flow from the placenta to the baby are respiratory movements, cry ing, and uterine contractions, and these factors play a more important role than time to cord clamping. Physiology based cord clamping has recently emerged whereby the timing of cord clamping should be based on the infant's physiology rather than time [26]. DCC in preterm infants increases blood volumes by up to 25%, especially after immediate resuscitation is needed. The benefits of placental transfusion in babies that require active resuscitation are being actively investigated in translational animal models and clinical trials. The time of birth should be recorded when the body of the baby is expelled from the *introitus* or uterine incision [30]. Babies at term who breathe or cry spontaneously and vigorously vaginal birth. Moreover, if the blood flow is allowed for 180 s, there is a substantial reduction in intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), and/or need for transfusion while no negative side effects for mother of infant have been described [33]. Umbilical cord milking (UCM) from the placental end of the cord toward the baby can be a valid alternative to delayed cord clamping and especially useful for preterm infants who need resusci tation. UCM is achieved by stripping the cord toward the infant 2–4 times before it is clamped. UCM is performed within 20 s and allows for an earlier access for resuscitation. In preterm infants, UCM increases superior vena cava flow, right ventricular output, blood pressure, and urine output and hemoglobin concentration. However, no differences with DCC have

been found in relation to death, cardio vascular stability, IVH, and long-term neurodevelopmental outcomes. Despite these potential benefits, ILCOR 2015 recommended against the routine use of DCC or UCM for infants born at ≤28 weeks of gestation considering that the available evidence was still too weak to openly recom mend these techniques. However, they supported both

techniques on an individual basis or in a research setting. In the latter years after the publication of the guidelines, new and supportive information has been reported. In a recent meta-analyses, seven randomized controlled tri als (RCTs) comparing immediate UCM in preterm infants <33 weeks with immediate cord clamping were analyzed

and showed that UCM reduced the risk of IVH of all grades and chronic lung disease. Moreover, UCM offered advan tages over delayed cord clamping in newborn infant that were deemed too unstable and were at highest risk of severe IVH and death. However, although some studies have shown similar long-term follow-up outcomes in babies undergoing DCC, UCM, or immediate cord clamping, they were not adequately powered for neurodevelopmental fol low-up. Further ongoing trials will soon provide us with relevant information in this regard [34].

Heart rate monitoring

Bradycardia (HR <100 bpm) is probably the most reliable clinical sign that informs the caregiver on the severity of neonatal depression. Persistence of low HR indicates the need for chest compression and administration of epi nephrine, while a rapid increase in HR reveals successful ventilation and a better prognosis [6,35]. Traditionally, HR has been assessed by auscultation. More recently, HR is routinely assessed using a pulse oximeter and a reference range put together in healthy term and preterm babies not needing resuscitation at birth [36]. However, HR estimate by auscultation and/or pulse oximetry may be inaccurate, and detection of HR by pulse oximeter can be delayed by several minutes. New ECG devices easy to adhere to the newborn's skin, giving accurate readings in few seconds, are being developed and will be routinely used in the future. Meanwhile, according to ILCOR 2015 HR monitoring by auscultation and/or pulse oximetry still remains crucial to inform of the infant's response to resuscitation [27].

Temperature control

Maintaining newly born babies within a normothermic range (36.5–37.5°C) is a strong recommendation because hyper- and/or hypothermia has been associated with nega tive outcomes, especially in preterm infants [37]. Term new born infants should be resuscitated under a radiant heater. ELBW infants are especially prone to heat loss and therefore during resuscitation the room temperature should be kept at 23–25°C, and babies should be wrapped in a polyethyl ene bag without being dried and with a thermal mattress underneath. However, there is an inherent risk for hyper thermia with the use of exothermic mattresses in addition to plastic covers. Hyperthermia increases the risk of subse quent adverse neurological outcome. If babies need ventila tion, the gas source should also be heated and humidified because cold gases may be injurious to the lungs. Once the babies are adequately protected from heat loss, skin-to skin contact and kangaroo care can be safely performed in babies >30 weeks of gestation [27]. In asphyxiated term or near-term infants, therapeutic hypothermia should be initiated within 6 h after birth. Although evidence for

turning off the radiant heater is lacking, this procedure is widely spread among neonatologists. There is an inherent risk in this practice to provoke severe hypothermia with severe negative consequences, and frequent or continuous monitoring of core body temperature is important. There

fore, hypothermia should only be initiated in the DR when infants' meet clinical, neurological, and electrophysiologi cal criteria recommended in RCTs [38].

Clearing the airway

Routine suction of the upper airways should be avoided for it may stimulate a vagal reflex and induce bradycardia. In addition, repeated suctioning of the trachea in the absence of secretions can deteriorate pulmonary compliance and oxygenation and reduction in cerebral blood flow velocity. Contrarily, in the presence of secretions there is an increase in respiratory resistance and subsequent increase in work of breathing [28]. Distressed fetuses, however, can pass meco nium into the amniotic fluid that can pass into the lower respiratory airway if fetus gasps as a response to hypoxia. Meconium aspiration syndrome occurs when meconium aspirated into the lower respiratory airways causes obstruc

tion and severe respiratory failure and frequently persistent pulmonary hypertension with severe hypoxemia. In RCTs, the incidence of mortality in the meconium aspiration syn drome was not improved by early tracheal intubation and suctioning neither in vigorous nor in nonvigorous new born infants with meconium-stained amniotic fluid. There fore, intubation and aspiration of the trachea immediately after birth is not further recommended despite the presence of meconium-stained amniotic fluid [39,40].

Normal oxygen saturation ranges in the delivery room

Whenever resuscitation is anticipated, the use of a pulse oximeter with a preductal location (right hand or wrist) to inform about cerebral oxygen saturation (SpO_2) has become a standard of care. Reliable SpO_2 and HR are achieved after 90–120 s after birth [31]. Of note, assess

ment of the infant's color has been withdrawn from the initial evaluation because of the lack of reliability, although tongue inspection has been proposed as an alternative for deliveries in rural areas of developing countries [41,42].

Oxygen toxicity limits the use of color for the stabiliza tion of term or preterm infants. The relative hypoxia *in utero* followed by a sudden increase in the oxygen availability to tissues after birth causes a physiologic oxidative stress. However, during severe ischemia reperfusion in perinatal asphyxia or as a consequence of the immaturity of the lungs and antioxidant defenses in preterm infants, a burst of oxy gen free radicals is generated. Free radicals cause significant direct damage to tissue/organs and trigger a generalized

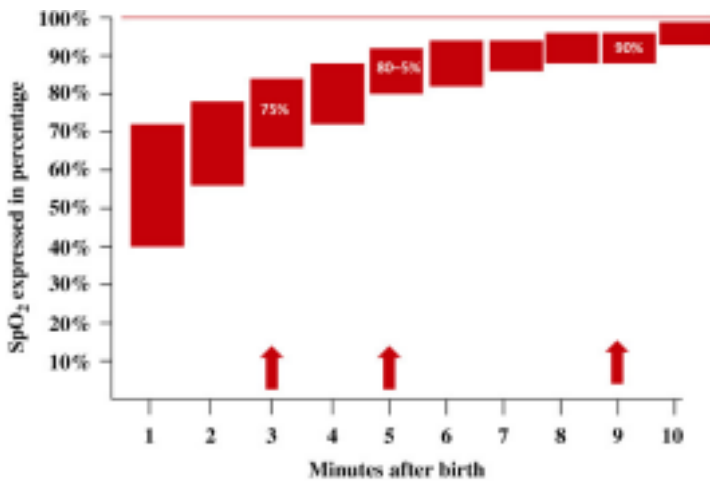

Fig. 4.4 Centiles of Preductal Oxygen Saturation Measured by Pulse Oximetry (SpO_2) in the First Minutes After Birth According to Dawson et al. [43].

inflammatory response with deleterious consequences [23].

To avoid the negative consequences of hypo- or hyperoxia, recommended ranges for SpO_2 and HR for the first 10 min after birth have been defined (Figs. 4.4 and 4.5) [43,44].

These centile charts were developed retrieving oxygen satu ration and pulse from healthy term and preterm babies not needing resuscitation after birth. Keeping the newly born term or preterm infants within the 10th–90th centile of these charts provides with the best available reference to optimize oxygen supplementation [36,43]. DR caregivers should adjust FiO_2 every 15–30 s according to the pulse oximeter readings, increasing or decreasing FiO_2 by 0.1 every 15–30 s to keep SpO_2 within the chosen centiles for a given time after birth. It is extremely important to keep

HR always above 100 bpm avoiding bradycardia. Persistent bradycardia requires the assessment of an adequate mask positioning and adjustment, evaluation of chest excursions, and rapid increase of FiO_2. The lack of response after performing these maneuvers requires immediate

Oxygen supplementation in term and preterm infants

Traditionally, 100% oxygen was systematically used for resuscitation irrespective of gestational age or severity of depression [6]. In a meta-analysis performed including more than 2000 asphyxiated patients, it was shown that the use of 100% oxygen upon resuscitation significantly increased mortality as compared to the use of room air [47]. Since 2010 ILCOR guidelines recommend the initial use of room air in the resuscitation of term and near term in the first minutes and oxygen titration according to the infant's response [28].

Fig. 4.5 Flow Chart Describing the Interventions in Preterm Infants With Severe Depression at Birth Based on ILCOR 2015 guidelines and experts' recommendations [27,45,46].

In very preterm infants below 32 weeks of gestation, however, there is an ongoing uncertainty regarding the optimal initial FiO_2. Preterm infants have immature lungs lacking surfactant that frequently require positive pressure ventilation and supplemental oxygen. However, preterm infants are especially sensitive to both hyperoxia and hypoxia [48]. The use of higher initial FiO_2 (>0.9) during resuscitation has been associated with increased biomarkers of oxidative stress and chronic lung disease [49–52]. The first study that compared the use of 0.21 versus 1.0 as initial FiO_2 in preterm infants with gestational age ≤28 weeks showed that after 2 min, 30% of the patients were switched to 1.0 FiO_2 because of persistent bradycardia, and at 3 min, the remaining 60% needed also a FiO_2 of 1.0 because they did not achieve targeted SpO_2 of 70% at 3 min [53]. In two recent studies, the use of room air in extremely preterm infants has been associated with an increased mortality. The Canadian Neonatal Network published a retrospective cohort study comparing infant's ≤27 weeks' gestation before and after the recommendations regarding the initial FiO_2 for preterm switched from 1.0 to <1.0 titrated oxygen supplementation. Remarkably, the lower oxygen group showed a significantly higher incidence of severe neurologic injury or death. However, data about oxygen exposure for each individual infant, and therefore, the cumulative oxygen exposure received during resuscitation, were not available and it could be misleading to attribute specific outcomes to the initial FiO_2 used at delivery. The investigators cautioned that a policy of initial stabilization with lower oxygen could be linked to a higher risk of severe neurologic injury or death in very preterm infants compared to starting with 100% oxygen [54]. More recently, Oei et al. [55] reported results of a randomized controlled unmasked trial performed in preterm infants comparing initial FiO_2 of 0.21 versus 1.0 in preterm infants <32 weeks of gestation. The primary outcome of this study was death and/or major disability at 2 years with a targeted SpO_2 of 65%–95% at 5 min and 85%–95% until NICU admission. This study showed unexpectedly that babies <28 weeks of gestation who received an initial FiO_2 of 0.21 had a higher mortality during hospitalization (risk ratio = 3.9; CI: 1.1–13.4; P = 0.01). However, although the study was underpowered for the post hoc analysis because many participants rejected to initiate resuscitation with a FiO_2 =1.0, the final results have drawn attention toward the apparent increased risk of using air to initiate resuscitation especially in very preterm infants [55]. Aiming to narrow the limits of initial FiO_2 to balance the risk of oxidative stress and lung complications when supplementing with 100% oxygen versus prolonged bradycardia, hemodynamic instability and risk of mortality when using room air have launched studies comparing lower (<0.3) or higher (>0.6) initial FiO_2. Oei et al. [56] have summarized results in a recent updated review and meta-analysis. The study has reviewed the outcomes of RCTs that included preterm infants ≤28 weeks of gestation assigned to receive an initial FiO_2 of ≤0.3 (low) or ≥0.6 (high) fraction of inspired oxygen at delivery. A total of 251 infants in the low oxygen and 253 in the high oxygen group with a mean gestational age of 26 weeks were assessed from 8 studies. The main outcome measures were death in hospital, BPD, ROP, IVH, PDA, and NEC. No differences for the main outcomes were found. Of note, mortality was lower in the low oxygen arms of masked studies and higher in low oxygen arms of unmasked studies, but taking all studies together there were no differences in the overall risk of death or other major morbidities when resuscitation is initiated with higher (>0.6) or lower (<0.3) FiO_2 [56]. At present, the initial FiO_2 recommended for term and near-term infants is 0.21 and for preterm infants is 0.3.

However, it is extremely important to adequately titrate oxygen to achieve SpO_2 values shown in Dawson's nomo gram. Hence, achievement of SpO_2 of 80%–85% at 5 min and 90%–95% at 10 min while keeping HR >100 bpm is essential to avoid prolonged hypoxemia and/or bradycar dia that could be deleterious for the newborn infant [57].

Ventilation: continuous positive airway pressure and intermittent positive pressure ventilation

Ventilation is required in about 3%–5% of all newborn infants. Remarkably, the lesser the gestational age the greater the proportion of infants needing respiratory sup port at birth. Immaturity of the lung, muscle weakness, lack of surfactant, increased elastic recoil, and compliant chest wall all contribute to make it difficult for the preterm infant to establish an effective ventilation and gas exchange [6]. The respiratory management of the newborn infant will greatly depend on whether the infant breathes spontane ously and therefore just needs additional support or does not breathe at all, in which case the entire respiratory pro cess will have to be supported by the resuscitating team.

Noninvasive ventilation (nasal or mask continuous positive airway pressure [CPAP]) has rendered efficacious avoiding many of the complications traditionally associ ated with endotracheal ventilation that included BPD, neurodevelopmental impairment, or death as has been shown in a recent meta-analysis [58]. The ILCOR 2015 guidelines recommend for spontaneously breathing pre term infants requiring respiratory support in the DR to start with CPAP instead of intubation and intermittent positive pressure ventilation (IPPV). However, there is a great vari ability between babies even with similar gestational ages. Therefore, caregivers in the DR should take into consider ation gestational age, gender, antenatal steroid administra tion, FiO_2 needed to keep SpO_2 within accepted ranges, and intensity of work of breathing [27]. European guide-

lines recommend to stabilize preterm infants with face mask CPAP of at least 6 cmH_2O and maximum around 8–10 cmH_2O via mask or nasal prongs. During the proce dure, careful attention should be given to chest excursions and rapid increase in HR and SpO_2. Inspired oxygen should be adjusted as described before. In persistently apneic and/ or bradycardic patients, peak positive inspiratory pressure (PIP) of 20–25 cmH_2O should be provided. If the patient does not respond, intubation is indicated [16]. HR is the most reliable clinical parameter revealing a successful resuscitation. It increases immediately after the initiation of effective ventilation [35]. In fact, it is more reliable than observing chest movements. Chest rise may be a reflection of an excessive tidal volume that may injure the lung [6]. In preterm infant needing positive pressure ventilation it is recommended that PEEP of 5 cmH_2O is provided; no recommendations in this regard have been made in rela tion to term infants. However, it is a routine practice in many hospitals to provide PEEP always when IPPV is given independent of the gestational age of the newborn infant.

Ventilation of the newborn infant can be performed with a self-inflating bag, flow-inflating bag, or a T-piece resuscitator (for a review, see Ref. [59]). Of note, the use of T-piece resuscitator is progressively replacing self-inflating and flow-inflating bags as shown in recent surveys [60–62]. T-piece device consists of an inlet arm to the patient through which the gas flows into an interface (facemask, nasal prongs, or endotracheal tube) (Fig. 4.6). PIP is achieved by occluding the escape of gas through the outlet hole using a thumb or a finger. The pressure is displayed in a manometer and can be adjusted with the release valve.

Moreover, the inflation time can be regulated adjusting the duration of the occlusion of the outlet hole. CPAP or PEEP is delivered automatically and the pressure varied by adjusting the outlet valve. This controls the rate of escape of gas when the outlet is not occluded and generates a preset level of CPAP or PEEP [6]. Studies performed in manikins have shown that T-piece resuscitator ensures the inspira tory pressure, PEEP, tidal volume, and inspiratory time are administered more consistently compared with the self inflating bag [63]. However, previous clinical trials were not sufficiently compelling to consider T-piece superior to self-inflating bag [27]. In a recent prospective observa tional study performed in 1962 preterm infants from 23 to 33 weeks of gestation, the use of T-piece (74.2%) or self inflating bag (25.8%) was compared. Neonatologists chose freely to use either one or the other device. The major out comes were survival to hospital discharge, BPD, IPVH, and PVL. The logistic regression analysis adjusted for maternal characteristics, obstetric, and neonatal morbidities showed that T-piece resuscitation increased the chance of survival to hospital discharge without major morbidities [64]. As an interface, masks (round or anatomically shaped), mono nasal tubes, or binasal prongs can be used. Some studies suggest that a nasal interface may be superior to the oral route in newborn infant anticipating less airway obstruc tion; however, no comparative data are available for DR care. PPV via a mask may be difficult and is often ham pered by leak and airway obstruction, resulting in low tidal volumes and thereby inadequate ventilation. Therefore, one of the most important skills of caregivers in this field is an optimal mask holding technique. Correct placement of

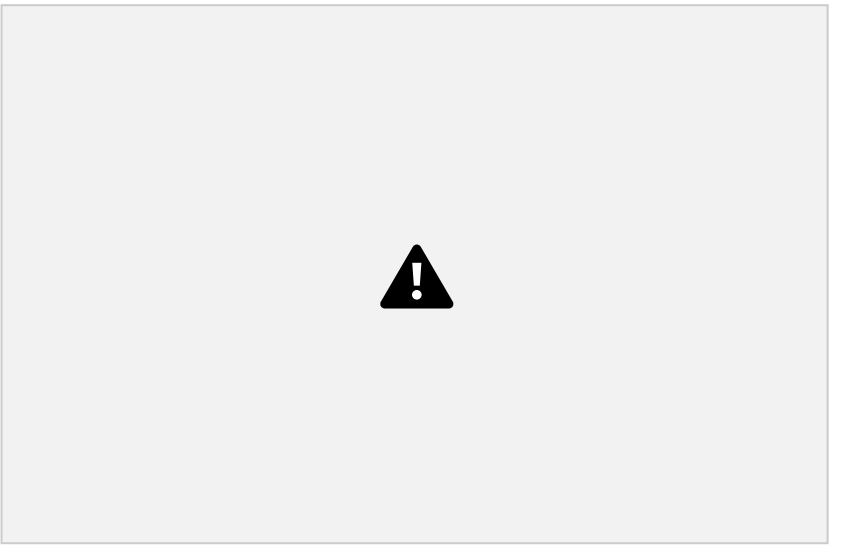

Fig. 4.6 **Scheme of the T-Piece Resuscitator Setup.**

the mask and an adequate chin lift are necessary. The rim of the mask should be placed on the tip of the chin and the mask should cover both mouth and nose, but not the eyes. Apparently, the best hold is achieved by the OK-rim hold (thumb and index finger form a C-shape) technique (Figs. 4.7 and 4.8) [65].

Endotracheal intubation and/or laryngeal mask

ET is indicated when noninvasive ventilation is rendered ineffective, when chest compressions are performed or in special situations such as diaphragmatic hernia [28]. The

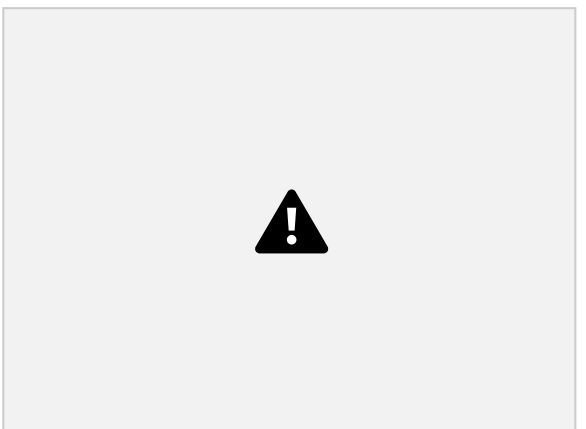

Fig. 4.7 **Photograph Showing the Positioning of the Face Mask** [64].

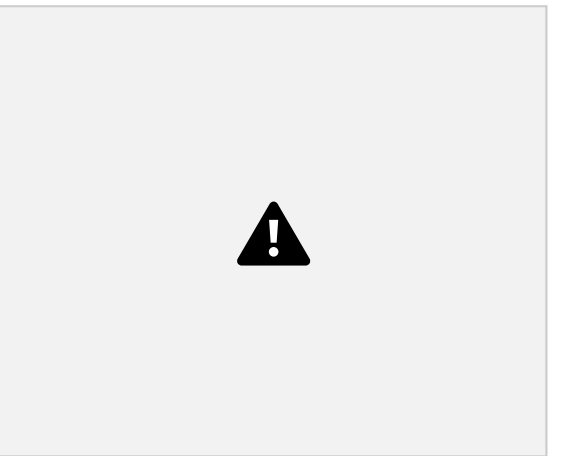

Fig. 4.8 **Outcomes After Extremely Severe Depression at Birth With Apgar Score 0 at 1, 5, and 10 min and Ulterior Moderate Body Hypothermia** [66].

ILCOR 2015 guidelines do not recommend routine tracheal intubation for meconium suctioning even in depressed infants born through meconium-stained amniotic fluid [27]. Successful tracheal intubation immediately increases HR and air entry can be assessed by auscultation over both lung fields. In addition, CO_2 detectors can be used to confirm that the tracheal tube is in the right position. A positive detection of CO_2 exhalation accompanied by a good cardiac output confirms placement of the tube, and a negative test result strongly suggests esophageal intubation. Occasionally, low lung perfusion can give a negative result despite the tube being in the trachea. A Cochrane review in 2014 did not find any studies specifically addressing this issue and therefore the pretended

advantages of using CO_2 detectors rely on the individual experience of caregivers or teams [67].

The increasing use of noninvasive ventilation has sub stantially reduced the need for ET both in the DR and in the NICU and subsequently the opportunity to learn and the skills of providers. ET is considered the most difficult technique to teach and learn in neonatal resuscitation. In this scenario the use of laryngeal mask (LM) has been sug gested as a valid alternative to access the lower respiratory airways, especially in late preterm and term infants. Several RCTs in late preterm and term infants have evidenced the feasibility, efficacy, and safety of using the LM to resusci tate late preterm (>34 weeks of gestation) and term infants when mask ventilation rendered ineffective and ET was not feasible or unsuccessful. Studies comparing resuscitation with LM versus bag and mask ventilation showed a greater resuscitation rate with LM. Moreover, the total ventilation time was shorter with LM than with bag and mask, and the success with the first attempt was 98.5% with a short insertion time of <10 s. In addition, the use of LM has also been compared with ET and no differences in successfully performing the technique and in the clinical recovery of depressed neonatal patients in the DR have been found. Therefore, it has been concluded that LM is a valid alter native when ET is not feasible or the providers have not acquired or maintained the necessary skills to successfully and rapidly perform ET [68–70].

Circulatory support

Chest compressions (CC) are indicated when HR remains <60 bpm despite adequate ventilation and oxygen supple mentation for 30 s. As ventilation is the mainstay of neona tal resuscitation, before initiating CC the resuscitating team should ensure that effective ventilation is being performed without increase in HR [28]. The aim of CC is to improve cerebral and myocardial perfusion. The former improves neurological outcome and the latter increases the likeli hood of a faster return of spontaneous circulation (ROSC). The quality of CC depends upon the rate, the ratio CC to ventilation, and applied force by the provider. Although increased rate would be apparently more efficient as shown in mathematical modeling or in experimental studies with manikins or piglet models, increasing and unavoid able fatigue in the provider render higher rates ineffective. Therefore, during the process of CC, although respirations, HR, and SpO_2 should be closely monitored, reassessed, and coordinated, compressions should be continuously performed as interruptions will compromise maintenance of systemic and coronary perfusion and worsen prognosis [71]. ILCOR 2015 guidelines recommend to deliver CC on the lower third of the sternum and to a depth of approxi mately one-third of the anterior–posterior diameter of the chest using both thumbs to compress the sternum and the rest of the fingers encircling the thorax and support ing the back. The rate compression to ventilation should be 3:1 allowing the chest to re-expand during relaxation for a total of 90 compressions and 30 ventilations/min. Oxygen supplementation during CC has not been studied in the human. Experiments in animal models have shown differ ent results regarding the levels of oxidative stress biomark ers or histological damage to organs such as CNS, heart, or lung. Of note, none of the studies showed an advantage in the use of 100% oxygen during CC. However, from a clinical point of view, when during resuscitation the pro vider has reached the stage of needing CC to overcome bradycardia, it seems prudent to use effective ventilation and increase oxygen concentration to try to achieve ROSC. However, when the HR recovers, high FiO_2 should be rap idly weaned based on preductal SpO_2 to avoid additional oxidative damage [27].

Drugs: epinephrine

Only seldom are drugs used during resuscitation. Drugs are indicated when the newborn infant remains bradycardic and profoundly hypoxemic despite being adequately venti lated through an endotracheal tube with 100% oxygen and receiving chest compressions. Under these circumstances, administration of epinephrine and/or volume expansion may be indicated [6]. The use of bicarbonate, naloxone, or vasopressors is not currently considered part of the acute resuscitation but can, under special circumstances, be used in the postresuscitation [72,73].

Epinephrine causes an intense peripheral vasoconstric tion, thus increasing aortic flow pressure gradient. During chest compression, oxygenated blood pumped by the left ventricle is redirected toward the dilated coronary arteries with less pressure gradient contributing to mitochondrial ATP synthesis, activation of myocardial contractions, and ROSC [45]. Intravenous administration, and especially through the umbilical vein which is easily accessible, is the preferred and the most efficacious route for epi nephrine administration during neonatal resuscitation.

Following the principles of DRICU of providing maximal care in the DR, a group of neonatal providers should be available for complex resuscitations involving drugs. One neonatal provider secures the airway, one provides chest compressions, and another gains access to the umbilical vein [29,74]. Another accessible route is via endotracheal tube. Of note, the plasma concentration achieved is lower and the time to reach the peak concentration is slower as compared to the intravenous route. Notwithstanding, it is a valid alternative when the patient is severely bradycardic and there is no intravenous line accessible. Finally, the last possible alternatives are the intraosseous or the intramus cular access. However, there is very

limited information and most of the caregivers are not comfortable with these techniques and prefer the tracheal route. Remarkably, the intramuscular route causes significant tissue damage at the site of injection [45]. The current recommendations indi cate that epinephrine should be repeated every 3–5 min if the HR remains bradycardic (<60 bpm) [74]. Occasion
ally, repeated and high doses of epinephrine are needed to overcome a severe neonatal depression. The consequence is a generalized vasoconstriction causing hypertension and tachycardia. Moreover, vasoconstriction reduces blood flow in renal and mesenteric territories, elevation of pul
monary arterial pressure, and increase myocardial oxygen consumption. All these complications may lead to long term morbidities such as intestinal perforation, renal insuf ficiency, or persistent pulmonary hypertension. Finally, an imbalance of various neurotransmitters has been described reducing the threshold for seizures [28].

Volume expansion

Volume expansion should be provided when evidence or suspicion of blood loss is present and the infant does not overcome bradycardia despite the application of other resuscitative measures. As mentioned it is mandatory that the resuscitation team early anticipates the need for a peripheral or central (cord vein) route for volume admin istration. An isotonic crystalloid solution or blood may be considered for volume expansion. The recommended dose is 10 mL/kg, which may need to be repeated. Remarkably, when resuscitating premature infants, it is reasonable to avoid giving volume expanders too rapidly because rapid infusions of large volumes could cause IVH [74].

Ethical considerations

When should resuscitation not be initiated?

Resuscitation efforts after delivery are not indicated under certain circumstance in which there is no possibility of survival. Although infrequent, caregiver in the DR may have to confront this situation. In such cases, initiation of neonatal resuscitation is not ethical and should not be offered. The most frequent circumstance is extreme pre maturity. To date, newborn infants <22 weeks of gestation do not have a chance of survival as opposed to previous guidelines that put the limit at 23 weeks and birth weight of 400 g. However, limiting the resuscitation efforts based on the gestational age frequently depends on the tradi tions or beliefs in different countries or cultures and guide lines may vary from one country to another. Moreover, assessment of gestational age may also incur errors that may preclude resuscitation in a baby who is really within an acceptable gestational age for initiating resuscitation maneuvers. Therefore, caregivers in the DR confronted with a baby around 22 weeks of gestational should also consider other factors such as physical maturity, heartbeat, or reac tivity before deciding not to initiate resuscitation. Other cases include chromosomal abnormalities and severe congenital malformations. In cases where there is uncer tainty about survival or a high risk of severe morbidity, the parents should be included in decisions regarding resusci tation plans. It is very relevant that each hospital has its own statistical information regarding these different clini cal conditions. This facilitates neonatologist to provide par ents with accurate and homogenous information. In these cases, after appropriate prenatal counseling, the parent's desires should be taken into account to guide resuscitation efforts [74].

When should resuscitation be withdrawn?

The current international neonatal resuscitation guide lines uniformly suggest ceasing resuscitation efforts after 10 min of effective resuscitation that includes ventilation, chest compressions, and the use of intravenous epineph rine without achieving ROSC. The ILCOR 2015 guidelines indicate that the outcome of infants with Apgar of zero at 10 min was "almost universally poor" and supported the cessation of resuscitation at 10 min of no detectable heartbeat [27]. Similar recommendations are indicated by the European Resuscitation Council and the American Heart Association [45,46,74]. This guidance is based on previously published retrospective data that revealed that babies with 0 Apgar score at 10 min resuscitated for more than 10 min either died or had severe neurodevelopmental impairment [75,76]. However, the improvement in resus citation and postresuscitation care and the introduction of therapeutic hypothermia have drastically changed the prog nosis of extremely depressed newly born babies. Fig. 4.6 summarizes the outcomes of babies who had Apgar score of 0 at 10 min and were transferred to the NICU and treated with therapeutic hypothermia. Out of a total of 79, 21% of these infants survived without neurological impairment while 23% had poor outcomes, and 51% of them died [66]. These numbers, however, should be analyzed with caution as they refer only to babies who made it to the NICU and not to those who died in the DR.

Outcomes of severely depressed extremely preterm infants showed a completely different scenario. In a recent review study, outcome of preterm infants <28 weeks of gestation with severe depression were analyzed. Only 0.6% of infants with an Apgar score of 0 at 1 min survived to the NICU and 0.09% were discharged from the hospital. Remarkably, none of the infants with an Apgar score of 0 at 5 min survived [77]. Ethical considerations are extremely important when taking the decision to continue or with draw resuscitation

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procedures in the DR. The “best interest” of the infant should always be a priority. If survival would imply severe limitations in life’s quality or assuring only a very short survival, it is generally considered ethical to withhold or withdraw resuscitation efforts. In the case of an uncertain prognosis as it frequently happens, either with holding or withdrawing is ethically equivalent. However, withholding treatment has the advantage of retrieving addi tional information in the NICU that will allow better judg ment of the infants’ prognosis. Parents should be always informed about ongoing resuscitation and should give their consent regarding withdrawal of therapeutic efforts. However, when the resuscitation team has already decided that withholding resuscitation is medically unacceptable it would be arguable if the parents should give their consent for ceasing therapeutic efforts [78]. It is important to com municate with the parents and involve them in the deci sion-making process to provide family-centered care in the DRNICU.

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5

Sustained Lung Inflation

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- Transpulmonary pressure following the first breaths plays an important role in fluid removal from the lung at birth.
- Sustained inflation (SI), in which an initial inflating pressure is held for a prolonged duration may assist in lung fluid clearance and establishment of functional residual capacity (FRC).
- Data from experimental animal studies suggest that SI results in uniform lung aeration, better lung function, and stable cerebral oxygen delivery when compared to conventional ventilation.
- In randomized clinical trials (Italian SLI trial and international SAIL trial), some safety concerns arose. SLI trial demonstrated a higher but nonsignificant incidence of pneumothorax in very preterm infants (25–29 weeks gestation). Preliminary data from the SAIL trial showed an excess of early deaths (<48 h of age) in the SI arm (7.5% vs. 1.4%) but no difference in pneumothorax and intraventricular hemorrhage in extremely preterm infants (23–26 weeks gestation) who required resuscitation at birth.
- Further studies of this promising technique evaluating differences in mortality and long-term outcomes are needed.

Physiology of the respiratory transition after birth

In the physiological transition from intra- to extrauterine life, aeration of the lung and clearance of fetal lung liquid from the alveoli are crucial steps during initial adaptation of the newborn, especially in the preterm infant, whose lungs are immature and extremely fragile. Therefore, facili tating the neonatal adaptation while minimizing lung injury is an enormous challenge for the neonatologist. The respiratory transition is usually recognized as a three-phase process [1], which reflects the three physiologi cal status of the lung during transition to extrauterine life. In the first phase of the respiratory transition, the lungs are fluid-filled, and for this reason no gas exchange can occur. Immediately after birth, the term infant usually takes a few deep breaths, which generate a large tidal volume and trigger a cascade of physiological events promoting the clearance of the fluid from the lungs and the establishment of pulmonary gas exchanges. All these changes are critical for initiating postnatal circulation and for the achieve ment of an early and adequate functional residual capacity (FRC).

The mechanism of lung fluid reabsorption and lung aeration at birth has been recently clarified, as the activa tion of epithelial sodium channels could not completely explain the rate of fluid clearance observed at birth in healthy newborns. Experimental studies, in fact, showed

that the transpulmonary pressure following the first breaths can overcome the airflow resistance, and is indeed the main determinant of the fluid removal from the lung.

During the second phase, lung fluid should be prevented from reentering the lung. In order to maintain the lung volume without a continuous opening and closing of the alveoli, endogenous surfactant and positive end-expiratory pressure (PEEP) play an important role in reducing surface tension and preventing alveoli collapse, respectively. The third phase, then, is characterized by the initiation of gas exchange and the subsequent establishment of car diorespiratory homeostasis.

While all these transitions are made by the full-term healthy newborn by himself within a few minutes after birth, preterm infants must deal with several physiologi cal impairments to properly aerate the lung. These include a high compliance of the chest wall and a weak respira tory musculature, ineffective function of epithelial chan nels, structural immaturity of the lungs, and insufficient surfactant composition, production, and storage. Accord ingly, almost all extremely preterm babies require respira tory support during neonatal transition [2].

When infants fail to create the transepithelial pressure gradient necessary for the lung liquid clearance, applying positive pressure to the airways helps in achieving this goal. After a preterm infant has cleared the liquid from the lungs, gas exchange becomes possible in the recruited alveoli. This liquid, however, initially remains in the sur
rounding interstitial tissues with a great risk of reenter ing the alveoli and interfering with gas exchange. For this reason, maintaining a constant distending pressure in the airway using continuous positive airway pressure (CPAP) is important in this early phase to avoid losing the acquired FRC.

Definition and rationale for sustained inflations

As we have previously mentioned, preterm infants, espe cially those of extremely low gestational age, are not capa ble of generating a subatmospheric pressure around the distal airways.

These infants, however, need a more uniform lung aeration to avoid wide and dangerous ventilation–perfu sion mismatches, which are responsible for the ineffective increase in pulmonary blood flow and heart rate after birth.

The standard practice to promote lung aeration is inter mittent positive pressure ventilation (IPPV) with PEEP and/or CPAP in apneic or spontaneously breathing infants, respectively.

However, to date the best method to favor lung aeration while avoiding harmful trauma to the fragile preterm lung still remains under investigation.

Using large transpulmonary peak pressure with short inflation times certainly contributes to heterogeneity of lung aeration, but could result in overdistention and injury to already aerated regions [3]. This is the reason why an alternative approach has been proposed. It is the so-called "sustained inflation" (SI), in which an initial inflating
pressure is held for a prolonged duration (15–20 s) using the physiological time constant of the lungs.

Several decades ago, Boon et al. [4], studying the for mation of FRC and tidal volume in asphyxiated intubated neonates, demonstrated that 13–32 cmH_2O was the nec essary pressure to move air from trachea to distal airways. In the same period, Vyas et al. [5] described the effects of prolonged inflations (5 s) in the same population, and showed that time, rather than pressure, was responsible for the establishment of an adequate FRC.

Although these initial findings were of great interest, SI remained understudied for many years.

Recently, there is a renewed interest in this technique and its potential effects on premature babies.

What literature says

Experimental animal studies

Several studies were conducted on animals about the effects of SI, both in asphyxiated and premature models. In these experiments, SI seems to provide satisfactory results in improving respiratory transition, contributing in estab
lishing FRC and in enhancing gas exchange immediately after birth.

Using preterm rabbit model, te Pas et al. [3] demon strated that a combination of SI and PEEP was the most effective to uniformly aerate the lung and fully recruit an adequate FRC. Moreover, they also showed that using lon ger inspiration times contributes significantly in the uni formity of lung aeration. Sobotka et al. [6] demonstrated better lung function in lamb model treated with SI and more stable cerebral oxygen delivery without adverse cir culatory effects.

Klingenberg et al. [7] found that in asphyxiated lambs an initial SI lasting 30 s shortens the time necessary to recover adequate heart rate, blood pressure, and oxygenation when compared with standard duration inflations.

Human studies

van Vonderen et al. [8] observed that SI was not effective unless the preterm infants were spontaneously breathing.

As most of the FRC gain occurs when the baby breathes, the role of spontaneous breathing and active glottis adduction appears to be crucial to make SI effective. Similar results are described by Lista et al. [9] using respiratory function monitoring.

The use of near-infrared spectroscopy (NIRS) during SI has led to interesting results, which highlight the need for further studies including physiological and clinical out comes in premature babies.

Fuchs et al. [10] used NIRS to measure preductal arte rial oxygen saturation and cerebral tissue oxygenation in a group of preterm infants treated with SI and compared results with a group of preterm infants requiring CPAP only. Increase in cerebral oxygen saturation in the SI group was almost as rapid, suggesting that the intrathoracic pres sure increase imposed by SI does not affect gas exchange and brain perfusion.

Schwaberger et al. [11] randomized 40 preterm infants comparing the effects of SI with “standard” respiratory care on cerebral blood volume. It remained essentially unchanged in the SI-treated infants, while decreased in the first 15 min after birth in the control group with no adverse neurological effects.

A few observational studies have been conducted com paring outcomes of preterm infants treated with SI with a control group. Even if these studies are not homogeneous in terms of population, definition of SI, respiratory man agement in the control group, and main outcomes, they showed the feasibility and safety of treating preterm infants with SI. Moreover, although they are all limited by the use of historical controls, they suggest essential preliminary data for the design of randomized controlled trials (RCTs).

Randomized clinical trials

Given the lack of a standardized definition of SI in terms of duration, peak pressure to apply, and number of inflations to perform, there is no homogeneity in the use of SI itself in all of the RCTs currently available. To date, there are five published RCTs of SI in preterm neonates, the results of which can be used to assume a provisional conclusion on its efficacy and safety. The recently concluded multicenter international trial, the SAIL trial [12], compared IPPV and SI in extremely preterm infants with BPD and death as pri mary outcomes (details below).

One of the main concerns that has arisen in regard to SI is the safety of this maneuver, and specifically the risk for air leaks.

In the Italian SLI trial (Lista et al.) [13], there was a higher but nonsignificant incidence of pneumothorax in very preterm infants (25–29 weeks of gestational age) who underwent SI, in respect to the control group. Similar findings in a population of late preterm infants characterized the study of Mercadante et al. [14]. In both these trials, SI was performed regardless of respiratory status, and infants belonging to the SI arm received this procedure prophylactically. Nevertheless, of note, in the SLI trial the incidence of pneumothorax occurred at a median age of 70 h. It is possible, then, that other fac tors influenced the incidence of air leaks (i.e., surfactant administration timing). It must be underlined that if SI is the respiratory parameters. Theoretically, it is possible that the caregivers may not have paid enough attention to this issue and this could explain the tendency toward increased incidence of air leaks and pneumothorax in the following days. In addition, the last Cochrane Review [15] did not mention in the main results any concerns about air leaks or pneumothorax related to SI.

Harling et al. [16] enrolled 52 preterm infants to receive either a 5-s SI or a 2-s conventional lung inflation (IPPV). They collected bronchoalveolar lavage fluid immediately after intubation and after 12 h, and then they measured cytokine concentration. They did not find any significant differences between the two groups, neither in cytokine lev

els nor in other clinical outcomes (mortality, BPD). te Pas and Walther randomized 207 preterm infants comparing two DR protocols. SIs (10-s inflation with 20 cmH_2O, which could be increased to 25 cmH_2O for another 10 s depending on individual response) were delivered with a T-piece via nasopharyngeal tube, and nasal CPAP was started after 1–2 SIs. In the control group, infants were treated with IPPV via self-inflating bag and facemask, and CPAP was not used in the DR. The primary outcome was the need for mechanical ventilation in the first 72 h of life, which was significantly lower in the SI group. Sur factant was administered less in the SI arm, and moder ate–severe BPD rate seemed to favor the SI-treated infants. However, as these protocols were a package of interven tions, it is difficult to isolate the individual effect of SI on clinical outcomes [17].

Two systematic reviews about the use of SI in preterm infants have been recently published [15,18]. Schmolzer et al. found a significant reduction in the intubation and need of mechanical ventilation rate in the first 72 h of life in SI groups, with no differences in mortal ity, BPD rate, IVH, or air leaks.

The last Cochrane Review did not find any significant difference in terms of mortality or BPD, but only in the duration of MV, which was shortened in the SI group. The authors concluded suggesting caution in the interpretation of this result, as it could be influenced by study characteris

tics other than the intervention.

Preliminary data from the SAIL trial showed an excess of early deaths (<48 h of age) in the SI arm (7.5% vs. 1.4%) but no difference in pneumothorax and intraventricular hemorrhage in extremely preterm infants (23–26 weeks gestation) who required resuscitation at birth. DSMB upon review halted the trial for harm after recruiting 460 infants (out of a total desired sample of

592). The detailed analy
sis of the early mortality causes still needs to be clarified in order to understand which could be the possible link between SI and early death. Anyway long-term outcome (death and BPD occurrence) were similar between SI and control group. According to the results of the SAIL trial and the SLI trial, it seems that further researches are warranted

visit MedEnact to access the video on SLI.

to better understand the effect of SI and its use in delivery room management of preterm infants with signs of RDS or at risk of respiratory failure.

Current recommendations

Given the current evidence available, SI seems to be a prom ising technique to optimize neonatal transition after birth. However, it must be considered still an experimental therapy, as there is insufficient data to advocate its use in clinical set tings. The latest ERC guidelines on neonatal resuscitation argue against the routine use of initial SI for preterm infants without spontaneous respiration immediately after birth, but allow SI to be considered in individual clinical circumstances or research settings [19]. However, they recommend main taining the initial pressure for 2–3 s for the first five positive pressure inflations during resuscitation.

Despite the lack of strong evidence, we suggest some key practical points for performing SIs in the delivery room. The parameters are chosen according to those set in clinical studies.

- **Peak pressure**: It would be desirable to start with 20–30 cmH_2O according to gestational age.
- **Duration of SI**: It ranges from 5 to 20 s. Animal studies have shown that inflations lasting less than 5 s are not effective to clear the fluid from the lungs.
- **Number of SIs**: There is no consensus about it. Most clinical studies have performed 1–3 SIs, with different approaches in terms of delivered pressure (same peak pressure for the all SIs or progressively increased peak pressures from 20 to 25 cmH_2O if no response was obtained after the first maneuver).
- **Time between SIs**: Even if there is lack of evidence regarding this aspect, it is reasonable to suggest to leave enough time between one SI and the next one to observe the infant's response. However, observation time should be limited to avoid reducing the efficacy of the second SLI due to airway obstruction.
- **Monitoring of SI's efficacy**: Verifying the effects of SI in real time remains quite challenging in the delivery room. As chest expansion could be difficult to evaluate, the efficacy of the SI maneuver should be judged based on heart rate and SpO_2 response. The routine use of devices targeted at the measurement of respiratory patterns and tidal volume and/or end-tidal CO_2 may be helpful to verify the efficacy of this intervention as well.

It is indeed clear that further evidence from well designed RCTs is needed to determine in more detail how, and in which clinical circumstances, SI should be used.

Unresolved issues about SI

At present, there are still several aspects of SI that need to be better clarified in order to recommend the use of this maneuver as a routine care procedure.

- What is the ideal and safest SI peak to deliver?
- What is the ideal duration of SI?
- What is the optimal number of SIs to perform?
- Might we use different parameters for different GA?
- Should SI be used as a prophylactic or rescue maneuver?
- What is the role of spontaneous breathing on the efficacy of SI?
- How can the SI maneuver be monitored and how can it be tailored to individual response?
- What is the best interface to deliver SI?
- Should surfactant replacement therapy be administered prior to, or after, SI?
- Is SI use feasible in asphyxiated infants?
- How can we minimize the risk of air leak related to SI?
- What are the effects of SI on tissue oxygenation (cerebral, pulmonary, cardiac, etc.)?
- Does SI have a significant impact on relevant clinical outcomes (death, BPD, etc.)?

Online Supplementary Material **Please**

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III

Applied Physiology, and Ventilator Support: General Considerations

6

Introduction to Lung Mechanics

Jegen Kandasamy, MD, Namasivayam Ambalavanan, MD

- Overview of respiratory mechanics
- Mechanics of the respiratory pump
- Elastic and resistive properties of the respiratory system
- Respiratory mechanics in disease

Introduction

The primary function of the respiratory system is translation of neural output into mechanical events that allow air to flow in and out of the lungs and facilitate gas exchange at the alveolar–vascular interface [1]. The conversion of force generated by respiratory muscles into pressure changes across the respiratory system is dependent on the mechanical characteristics of the respiratory system. Tidal changes in lung volume are created by stretching elastic components in the respiratory system, and resistive elements in the airway and lung tissue are overcome to create flow of air through the respiratory tree. This chapter will detail the mechanical characteristics of the respiratory system, their interactions with one another, and their role in the function of the neonatal respiratory system during various disease states.

Overview of respiratory mechanics

The mechanical elements of the respiratory system can be described as consisting of a pump and a load. The pump is made up of structures in the thoracoabdominal wall including the ribs, sternum, and the muscles of inspiration and expiration. The load that the respiratory pump acts on consists of the elastic and resistive properties of the chest wall, lungs, and airways. Elastic recoil of the chest wall and the lungs are opposing forces that determine the resting (end-expiratory) volume of the respiratory system (Fig. 6.1). At this point of the respiratory cycle, the inwardly directed elastic recoil of the lung is balanced by the elastic recoil of the chest wall which is directed outward to create a small negative intrapleural pressure (P_{pl}) of −3 to −6 cm H_2O with respect to the atmospheric pressure (P_{atm}) which is assumed to be zero in this setting. The volume of air left in the alveoli at the end of normal expiration largely depends on the magnitude of this negative P_{pl} (see Section: Elastic properties of the respiratory system).

In this resting state, the pressure at the airway opening (P_{ao}) as well as the alveolar pressure (P_{al}) are both at equilibrium with P_{atm} and therefore zero as well. During inspiration, the respiratory muscles contract to expand intrathoracic volume. This outward chest wall movement

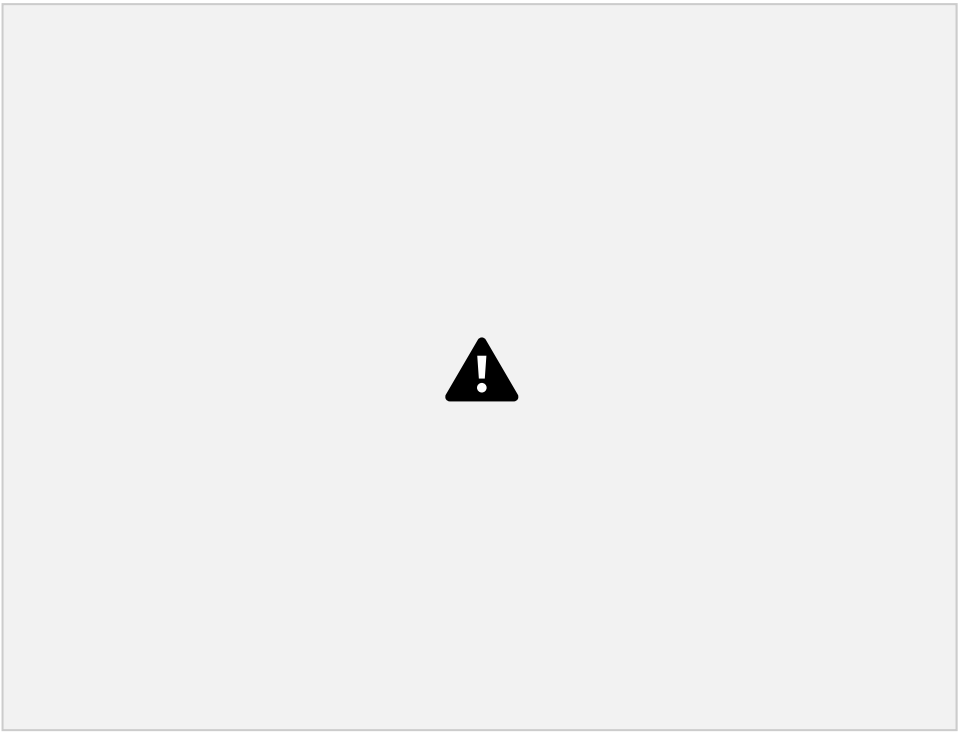


Fig. 6.1 The Resting State of the Respiratory System. Atmospheric pressure is assumed to be 0 mmHg in lung mechanics. Functional residual capacity is generated by the negative intrapleural pressure created by the opposing recoils of the chest wall and the lung.

decreases P_{pl} further and expands the alveoli and terminal airways. This creates a pressure differential between P_{ao} (which remains zero) and P_{al} (which is now negative) that drives air into the lungs. At the end of inspiration, the respiratory muscles relax and the chest wall collapses inward. This increases P_{pl} back to its baseline and releases the expansionary force placed on the alveoli that recoil back toward their resting volume. The positive P_{al} created in this process overcomes the resistance to flow created by the terminal airways and forces air out of the lungs, thereby completing the cycle and returning the respiratory system to its resting state [2–4].

The pressure differential that opens the alveoli ($P_{al} - P_{pl}$) and the driving pressure for airflow ($P_{ao} - P_{al}$) are both required to create the volume and airflow changes neces sary to permit normal respiration. The total pressure that is required to drive respiration—referred to as the transpul monary pressure (P_{tp})—is traditionally $P_{alv} - P_{pl}$ (difference between alveolar pressure and pleural pressure), but as we can more readily measure alveolar opening pressure (P_{ao}) but not P_{alv}, which approximates P_{alv} at end inspiration, P_{tp} is usually estimated $P_{ao} - P_{pl}$ (difference between airway opening pressure and intrapleural pressure).

Physical principles of respiratory mechanics

The mechanical properties that determine lung volume and airflow changes through the respiratory system during inspiration and expiration in the manner described earlier are elastance, conductance, and inertance [5]. Elastance is the tendency of a hollow organ to recoil to its initial size after removal of the distending pressure. Elastance of the entire respiratory system includes the elastance of the chest wall and that of the lungs. Compliance is the reciprocal of elastance and measures distensibility. It is defined as the change in volume (V) of a hollow organ per unit change in the distending pressure (P).

$$\text{Compliance } (C\ V\ ) / = \Delta\ \Delta P$$

Respiratory conductance represents the instantaneous amount of airflow in the lungs (Q), defined as the volume of air moved per unit time (t) per unit amount of pres sure difference between the airway opening and the alve oli. Resistance, which measures the impedance to airflow offered by the tissues of the respiratory system, is the recip rocal of conductance.

$$\text{Re sistance } (\ )\ R\ P = \Delta\ /(dV/\ )\ dt = \Delta P\ Q/$$

The total pressure difference that is required to overcome inertia during motion in the respiratory system and acceler ate airflow is called total respiratory

inertance.

Inertance (I P) / = Δ dQ / dt

Very minimal pressure is required to accelerate airflow through the respiratory tract. Respiratory system inertance becomes a significant factor only when respiratory fre

each breath can be obtained by rearranging and adding the first two equations mentioned previously.

quency is as high as those used in high-frequency ventila

= – = + =

tion; during tidal breathing and conventional ventilation,

P P P P P E V

+ R Q t

this factor can be safely ignored [6].

Lung mechanics can be highly heterogeneous and vary in different regions, especially during disease states. How

ever, a single-compartment model can be used to simplify

the various concepts of lung mechanics [7]. In one such model (Fig. 6.2), the alveolar compartment (with a volume of V) is represented by a pair of canisters that slide against each other and are connected to each other by a spring with elastic recoil of E and a resistive element R_t. The spring rep

resents the elastic recoil (elastance) stored in the respiratory system when it is stretched beyond its resting volume. This recoil is used by the respiratory system for lung deflation during expiration which is usually passive during normal tidal breathing and does not require additional work by the respiratory pump. R_t represents the resistance to airflow offered by the tissues that make up the lungs and the chest wall (viscous resistance). Inflow to this system is through a tube that represents the airways and offers its own resis tance (R_{aw}) to airflow.

The pressures required to overcome elastance (P_{el}) and resistance (P_{res}) and allow ventilation to proceed during

P P total e = + l r P V es = + / * C R Q

P_{tp} which was described in the previous section and P_{total} represent the same entity, namely the pressure that needs to be generated by the respiratory pump to overcome respira tory system elasticity and resistance (offered by the airways as well as lung tissue) and allow ventilation to proceed unimpeded. These mechanical concepts can be summed up into one equation, which is referred to as the equation of motion for the respiratory system.

* (pressure required to

tp ao pl el res

overcome elastance) * (pressure required to overcome

viscous or tissue resistance) * (pressure required to

more simply,

R Q aw

+

overcome airway resistance) or

represents elastance of the lung, and R_t and R_{aw} represent resistance of the lung tissue and airway, respectively.

P E tp = + * * V R t a Q R+ w *Q

Airflow in the respiratory system is terminated when P_{ao} equilibrates with P_{al}. The time taken for this pressure equili

bration to be achieved determines the rate of emptying and filling of alveoli and therefore determines the duration of a single breath. If all respiration was passive and the lung an ideal single-compartment model, the rate of filling or emptying of the lung can be determined using its compli

ance and resistance to calculate the time constant of the respiratory system (τ) [8].

τ = · C R = ΔV P / * Δ ΔP Q/ / = ΔV Q

In other words, τ is the rate of change of volume for a given airflow rate within the idealized respiratory system. Based on this model, lung inflation and deflation is an exponential process that is 63% complete after one τ, 87% complete after two τ, and almost fully complete after three time constants (95%) have elapsed (Fig. 6.3). Smaller τ

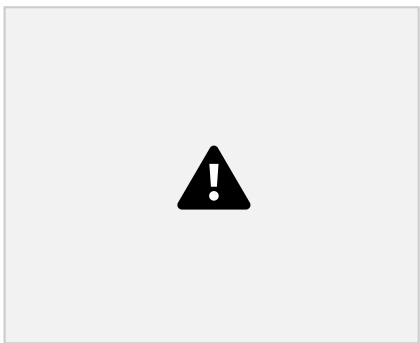


Fig. 6.2 An Idealized Single-Compartment Model of the Respiratory System. V represents lung volume, E

Fig. 6.3 Changes in Lung Pressure for Every Time Constant That Elapses in a Single Breath.

values allow for quicker $P_{ao} - P_{al}$ equilibration and com pletion of the respiratory cycle and correspondingly faster respiratory rates. Studies have shown that the respiratory rates of various animal species correlate closely with their τ values. Larger mammals have longer τ and slower respira tory rates and smaller bird species have shorter τ and faster rates [9]. The τ varies in infants with various respiratory diseases. Knowledge of these variations can help clinicians determine the appropriate inspiratory time (I-time) and respiratory rate that will permit lung inflation and deflation to be fully complete with every breath. Since inspiration is an active process, it is not strictly a linear time-invari
ant model and time constants often overestimate the time lungs take to inflate.

Energy is expended for the work of the respiratory pump that moves air through the respiratory system. The total work (force × displacement) done by the respi ratory system over a single breath can be derived from the pressure required (the force component) to effect changes in the volume of the respiratory system (the dis placement component). Assuming that work of breath ing is constant for every breath, work of breathing per minute can be calculated if the respiratory rate (RR) is known [5].

Clinical scenario 1

A 7-day-old 26-week gestational age (GA) newborn infant who is being mechanically ventilated is noted to have metabolic acidosis on the latest blood gas. The nurse also tells you that the infant has been hypoten
sive and responded minimally to vasopressors. When you review the previous blood gases you notice that in the last 4 h the infant had respiratory acidosis and that his ventilator rates were increased to correct this, without much success. You notice the flow waveform on the ventilator that is shown in Fig. 6.4A. What is the cause of this infant's worsening blood gases, how can this be confirmed, and what corrective and preventive measures can be taken?

Answer

The ventilator waveform depicts incomplete emptying of the lungs during expiration (Fig. 6.4B). As discussed ear lier, any increase in the time constant can increase the time required to complete exhalation. Mucus plugs can obstruct endotracheal tubes (ETTs), increase airway resistance, and increase τ values. If respiratory rates are increased without ensuring that the inspiratory time:expiratory time (I:E) ratio is appropriate to allow expiration to be complete, breaths can "stack" and cause air trapping in the lungs. This can create increased positive pressure on the mediastinal structures, such as the right heart, and reduce venous fill ing and cardiac output leading to metabolic acidosis. Pay ing attention to the ventilator flow waveforms to ensure that adequate time is being provided for exhalation to be complete will allow for quicker detection of this phenom enon. Other clues could be a measured positive end-expi ratory pressure (PEEP) on the ventilator that is higher than the "set" PEEP (so-called "auto"-PEEP), and chest X-ray findings of flattened diaphragms and horizontally aligned ribs that indicate overdistended lungs. Decreasing the I-time can increase lung emptying and tidal volume changes and decrease the hypercarbia and respiratory acidosis. When lungs are overdistended, increasing lung emptying will also relieve right heart pressure and improve cardiac output and oxygenation.

Work of breathing/minute work of breathing/breath =

*RR * *RR = Δ Δ P V

As illustrated in Fig. 6.5, energy is required for work done to overcome elastic forces (portion ABCA) and resis tive forces during inspiration (ADCA) as well as for resis tive work during expiration (ACEA). Most of the work required to overcome the frictional airway and tissue resis tive forces is dissipated as heat. Under conditions of nor mal tidal breathing, the expiratory phase is non-energy requiring and passive. However, during pathologic states, such as airway obstruction that lead to flow limitation, expiration can require active contraction of the abdomi nal wall and internal intercostal muscles, a process that consumes energy and increases work of breathing, as is often noted in infants with bronchopulmonary dysplasia (BPD) [10].

Newborn infants have high respiratory rates and work of breathing due to their smaller body sizes [11]. They have high body surface area to volume ratios due to which they lose heat excessively through the convective and evapora
tive routes, a phenomenon that is more severe in prema turely born infants. Increased metabolic rates are therefore necessary to generate more heat to maintain their body temperature. To sustain such high metabolic rates, their oxygen consumption needs be increased, which requires increased minute ventilation (tidal volume × RR). Since their small lung volumes prevent them from being able to greatly increase their tidal volume, newborn infants achieve higher minute ventilation by breathing at faster rates which increases their work of breathing significantly. However, when corrected for such high metabolic rates, newborn infants have similar work of breathing when compared to adults [12].

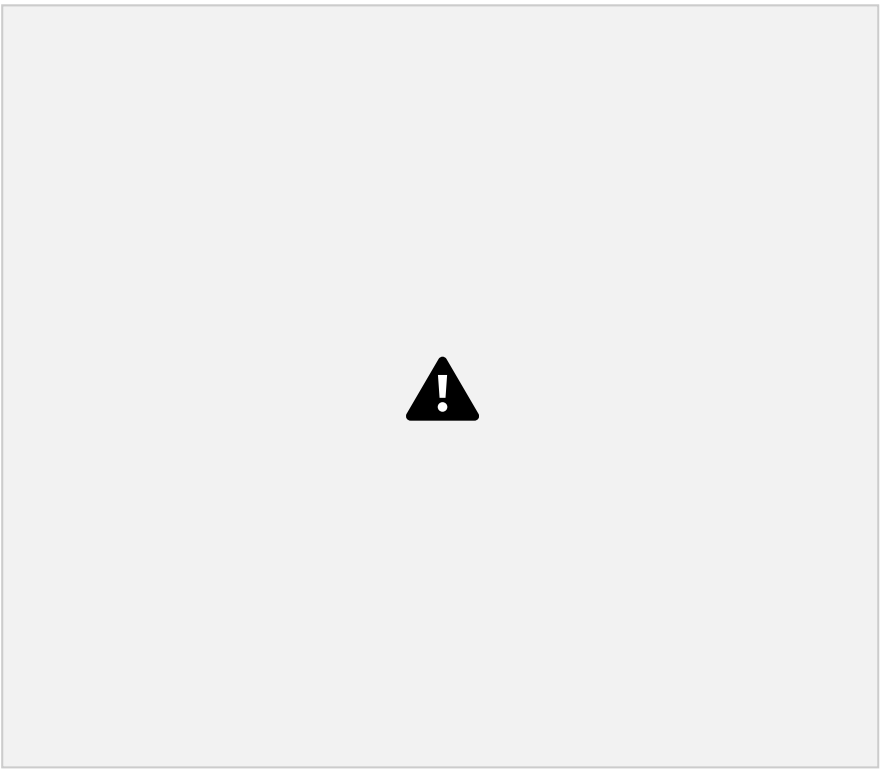


Fig. 6.4 (A) and (B) show a waveform with incomplete expiration that when unrecognized can lead to auto-PEEP.

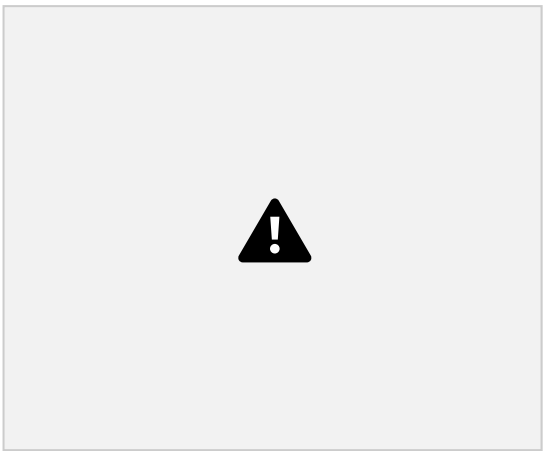


Fig. 6.5 A Typical Dynamic Pressure–Volume (PV) Plot That Illustrates Work of Breathing. The area shaded in *gray* (ADCA) represents the work done to overcome resistance during inspiration, while the *yellow-shaded areas* represent work done to overcome elastic forces during inspiration (ABCA) and to overcome resistive forces during expiration (ACEA). Also, note that lung volumes at any given pressure are higher during expiration than inspiration (hysteresis).

Mechanics of the respiratory pump

All the mechanical work that is required for breathing is performed by the structures that make up the respiratory pump which is comprised of the inspiratory and expiratory muscles that act like levers and the skeletal and connective tissue structures of the thoracoabdominal cage that function like a fulcrum around which respiratory motion occurs (Fig. 6.6).

Muscles of inspiration

These include the diaphragm and the external intercostal muscles. The diaphragm is the primary generator of the pressure changes required for inspiration. Its muscle fibers originate from the lumbar spine, the xiphoid process of the sternum, and lower six rib pairs and insert into a central tendon that is pulled downward and forward during contraction of the diaphragm. This downward

motion of the diaphragm increases the anteroposterior and vertical dimensions of the thorax, generates negative P_{pl}, and causes air to flow into the lungs [13]. The area of the lowermost rib cage that is in direct contact with the diaphragm is called the appositional area.

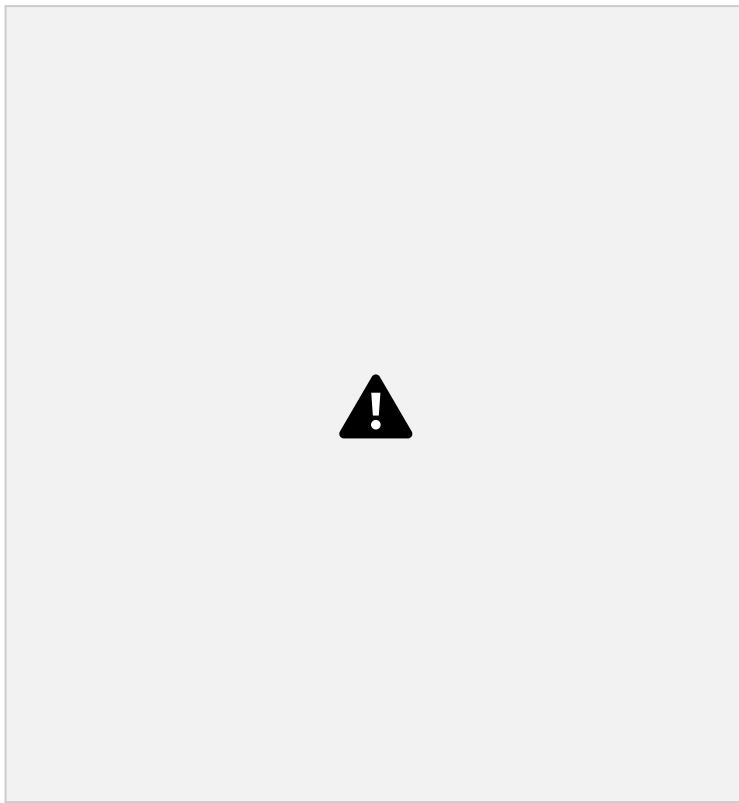


Fig. 6.6 Mechanics of Neonatal Breathing Compared to Breathing in Older Children and Adults. Copyright: Satyan Lakshminrusimha.

The larger this area, the greater is the ability of the diaphragm to expand intrathoracic volume. A larger zone of apposition also allows the increased intra-abdominal pressure generated by the downward diaphragmatic movement to be transmit
ted more efficiently to the chest wall. This effect "splints" the chest wall and increases its outward motion during inspira tion [14]. The tension generated by a muscle fiber is directly proportional to its initial length. Diaphragmatic flattening, often caused by overdistended lungs, shortens the diaphrag
matic muscle fibers and decreases its contractile strength. At birth, the diaphragm has a low muscle mass and is composed of fewer fatigue-resistant fast-oxidative fibers (10% at 24 weeks, 20% at term gestation) compared to the adult (60%), though its dimensions increase rapidly with postnatal growth and body weight gain [1,15,16]. There fore, the newborn's diaphragm has low contractile strength. Despite these disadvantages the newborn's diaphragm can generate pressures that are adequate for tidal breathing. Dur ing the first several breaths after birth, negative intrapleural pressures as high as 100 cm H_2O are achieved when the newborn cries. In addition, tidal P_{pl} swings during normal respiration are similar in magnitude (5–7 cm H_2O) to that generated by older infants and adults [17]. This is made pos sible by the mechanical laws that govern the motion of con tractile spherical structures. For a given radius of curvature (r), the pressure generated (P) by a spherical structure with wall tension (T) is given by the law of Laplace as follows:

$$P\,T = 2\,/r$$

According to this principle, the pressure generated by the newborn's diaphragm with its small radius of curva ture is higher for any given wall tension than the adult's diaphragm whose radius of curvature is larger. In addition, any such pressure generated by the neonatal diaphragm is also applied to a proportionally smaller thoracic area when compared to older children and adults. Recent studies have also shown that muscle fiber composition does not always correlate well with diaphragmatic fatigability and that the neonatal diaphragm can indeed generate high pressures when

required [9]. In the absence of other pathology, these factors allow the diaphragm of even the most premature infant to function without being fatigued for long periods of time. Therefore, diaphragmatic function is usually not a limiting factor in the neonatal respiratory system.

The external intercostal muscles run between ribs and slope downward and anteriorly. Due to their course in the intercostal spaces and the angular inclination of the ribs in the thoracic cage, external intercostal muscle activity is great
est in the dorsal portions of the anterior intercostal spaces. During contraction, they elevate the ribs and pull them to a more anterior position to increase the lateral and antero posterior diameters of the thorax. This stabilizing action of the intercostal muscles minimizes the inward collapse of the highly compliant neonatal chest wall with diaphragmatic contraction. They also reduce diaphragmatic shortening and improve its mechanical efficiency [18]. However, in the new born, the intercostal muscles run a shorter distance from their origin on the upper rib to their insertion to the lower rib reducing their length and therefore their contractility when compared to adults. In addition, newborns, especially premature infants, spend 80% of their sleep in the rapid eye movement (REM) phase; they also sleep longer (>18–20 h/ day). During this sleep phase, intercostal muscle tone is subjected to both phasic and tonic inhibition which causes these muscles to become inactive and significantly decreases chest wall stability and movement in the newborn [19].

Muscles of expiration

Expiration is mostly passive. However, during conditions that cause airflow obstruction, the muscles of the abdominal wall—the internal and external oblique as well as the rectus and transversus abdominis—contract to raise intra-abdom
inal pressure and push up the diaphragm to cause forced expiratory flow [20]. The internal intercostal muscles which run between ribs in the opposite direction to the external intercostals also contract to cause the ribs to move down
ward and inward to decrease thoracic volume. Their con
traction also stabilizes the chest wall and prevents it from moving forward when expiration is actively forced [18].

Chest wall

At birth, the ribs articulate at almost right angles to their corresponding vertebral bodies. This creates a circular tho racic configuration in which the diaphragm is flatter and operates over a less efficient portion of its force–length curve. The rounded shape of the infant thorax also leads to a decreased surface area of the zone of apposition. Due to this, there is inefficient transmission of intra-abdominal pressure that is generated during inspiration to the thorax. In addition, the newborn's chest wall is made of pliable ribs, thin muscles, and is primarily cartilaginous rather than skeletal in composition. These features are even more pronounced at lower GAs, which causes the preterm new born's chest wall to be highly compliant and paradoxi cally move inward when P_{pl} becomes more negative during inspiration. Therefore, the premature infant's inspiratory

muscles need to work harder to generate additional nega tive pressure in the intrapleural space to achieve adequate tidal volumes. The newborn attempts to improve chest wall stability during such conditions by recruiting the acces sory muscles of inspiration, such as the scalene muscles, sternomastoids, and alae nasae. The active contraction of these muscles is responsible for the characteristic signs of respiratory distress that are often noted in young infants, such as sternal and intercostal retractions and head bob bing [21]. This abnormally high chest wall compliance (C_{cw}) is one of the most important factors that prevent pre
mature infants from being able to establish normal lung function. C_{cw} slowly decreases in infancy and lung compli
ance (C_l) which is low at birth increases with age. C_{cw} and C_l become nearly equal by 2 years of age [22].

Clinical scenario 2

The nurse taking care of a mechanically ventilated infant informs you during morning rounds that turning him to the prone position improves the infant's oxygenation. The student physician on rounds with you wants to know the physiologic mechanism behind this phenomenon. While you both are at the infant's bedside you notice that the infant's oxygen saturation is decreasing again and he requires increased ventilator settings to improve his oxygen
ation. Why would prone positioning cause only a transient improvement of this infant's oxygenation?

Answer

Newborn infants have a thin anterior abdominal wall muscu lature that can accommodate a large volume without gener ating much intra-abdominal pressure. In addition, the lower appositional area of the diaphragm reduces intra-abdominal pressure transmission to the diaphragm. These two factors lead to insufficient expansion of the lower ribs and decrease the mechanical efficiency of inspiration. In the prone posi tion, the protuberant infant's abdomen is effectively splinted, leading to increased intra-abdominal pressure generation that causes increased diaphragmatic efficiency and improved ven tilation overall. Additionally, the superior (anterior) diaphragm moves better in the supine position when compared to the inferior (posterior) diaphragm, but perfusion is preferentially directed to the dependent portions of the lungs (the inferior regions). This creates increased ventilation–perfusion (mis match) and decreased oxygenation. When the infant is turned to the

prone position, the posterior diaphragmatic portion is now able to move better leading to better ventilation and per fusion, though any such effect is likely to be transient since prolonged prone position will tend to lead to better perfu sion in the anterior (and now inferior) regions of the lung. A recent study of prone positioning (which is commonly done for infants in neonatal intensive care units) showed that there are no consistent short- or long-term benefits from this prac tice for infants with respiratory distress syndrome (RDS) [23].

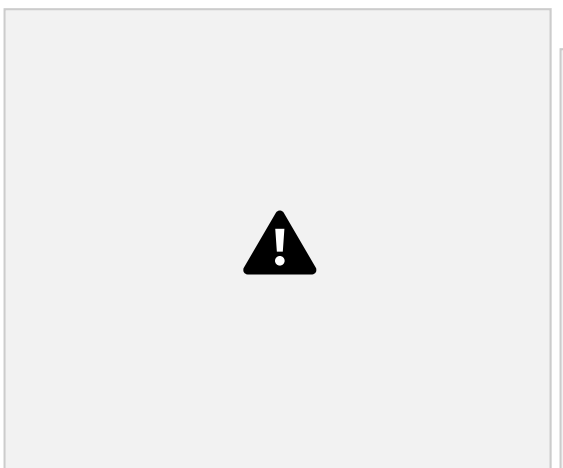
Elastic properties of the respiratory system

Elastic properties of the alveoli, chest wall, and airways determine changes in lung volume for a given amount of pressure in the respiratory system [24]. The slope of a pres sure–volume (PV) curve between P_{tp} measurements made in a lung that is distended to various known volumes of air represents the *static* compliance of the lung (C_l). Slopes of PV plots of lung volumes against transthoracic pressure (the difference between P_{pl} and P_{atm}) represent the com pliance of the chest wall (Fig. 6.7). Similarly, the slope of a plot of the difference between P_{ao} and P_{atm} against lung volumes represents the compliance of the entire respira tory system (C_{rs}) [25]. $C_{l\text{-}dyn}$ measurements can closely approximate static compliance measurements. PV plots are available on most modern ventilators and can be useful to calculate *dynamic* compliance of the lung ($C_{l\text{-}dyn}$) in the ven tilated infant [26,27].

For any given pressure on a dynamic PV plot, lung vol ume is always greater during deflation than during inflation (Fig. 6.2). This implies that lung compliance is greater dur ing expiration than inspiration. This phenomenon is called hysteresis and is commonly observed in nonlinear systems, such as the lungs, which have different mechanical proper ties during different states of operation. Hysteresis can be exaggerated in the preterm newborn due to abnormally high expiratory air trapping within the lungs [28]. This is because negative P_{pl} is required during end-expiration to maintain the patency of smaller airways that lack the car tilaginous support available in the walls of the larger air ways. Since premature infants cannot generate adequate negative P_{pl} due to their high C_{cw}, they are often unable to maintain smaller airway patency in the dependent regions of the lung during end-expiration. This leads to incomplete expiration and increases lung closing volumes (maximal lung volume at which airway closure can be detected in the dependent parts of the lungs). This process can worsen fur ther at higher breathing frequencies since expiratory time is reduced at such high frequencies leading to increased air trapping.

Functional residual capacity (FRC) of the lung is defined as the volume of air that is in communication with the upper airway at end-expiration. FRC is low in preterm infants, since they are unable to create negative P_{pl} which is also required to establish an adequate FRC [29,30]. The low FRC of preterm infant lungs causes them to operate at a significant mechanical disadvantage. As shown in Fig. 6.8, dynamic PV plots of the normal lung assume a sigmoidal shape. Therefore, the slope of these plots is high est (and compliance is optimal) when lungs are inflated and deflated within the range of their FRC. Underinflation and atelectasis (low FRC) or air trapping and overexpan sion (high FRC) both cause $C_{l\text{-}dyn}$ to shift to the ends of the sigmoidal curve where it is low.

Preterm infants use several corrective measures that attempt to limit FRC loss. These include post-inspiratory activation of the diaphragm which can terminate expira tion before it is complete, high respiratory rates with a short expiratory time that increases alveolar air trapping even in



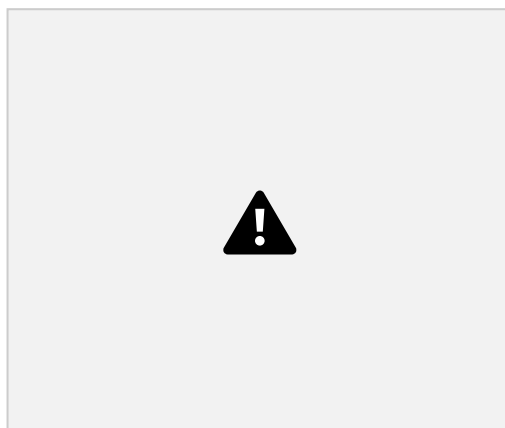


Fig.

6.7 Static Pressure–Volume Curves of the Newborn Respiratory System. Lung compliance is very low and chest wall compliance is much higher than in adults. Respiratory system compliance which is the sum of these two compliances is low.

Fig. 6.8 Pressure–Volume Curves at Different Levels of FRC. Underinflated lungs and overdistended lungs both lead to poor lung compliance.

nondependent areas as well as expiratory braking of the glottis that generates additional PEEP and is responsible for the characteristic grunting that is associated with premature infant breathing [31].

The pattern of low FRC and higher closing volumes seen in premature infants is the inverse of that seen in older children and adults and is associated with clinical consequences that include atelectasis, increased ventila tion–perfusion mismatch, and hypoxia. Lung compliance corrected for FRC is referred to as *specific* compliance. Specific compliance increases rapidly in the days after the newborn is born and approaches adult values, as intra alveolar pulmonary fluid is resorbed and replaced by air [32]. Specific compliance values are much lower in pre term infants than in older infants and adults despite their low FRCs since their lung compliance is disproportion ately lower.

While low FRC is usually the cause for their abnormally low $C_{l\text{-}dyn}$, premature infants ventilated at high respiratory rates can also have increased, rather than decreased FRC, as the cause for decreased dynamic lung compliance. This is because their developing lungs are still immature and have high heterogeneity of time constant values in different regions and air trapping can occur in regions of the lung with longer time constants, a phenomenon referred to as frequency dependence of dynamic compliance.

In addition to these dynamic factors, physical com ponents of the lung architecture also play a major role in determining lung compliance. These include surface tension forces in the alveoli, interstitial and intra-alve olar fluid content (which is usually not a major influ ence on lung compliance beyond the first several hours to days of life), and the amount of elastic connective tis sue in the lung. At birth, the airways and the alveoli of the lung contain a larger amount of elastic tissue with correspondingly higher amounts of collagen and elastin. With postnatal growth and maturation, connective tissue volume in the lung decreases and alveolar membranes become thinner which allows the lung to become more compliant [33].

The most important determinant of lung compliance is the physical force of surface tension (ST). The alveolus can be considered a spherical structure with an air–fluid interface covering its interior surface. At this interface, the polar molecules of water that line the alveolar epithelium are attracted more strongly to each other than to the mole cules of the gases in the air that they interface with. This can lead to alveolar contraction and volume reduction that can become severe enough to cause lung atelectasis. Based on the law of Laplace discussed earlier, an alveolus with radius r would require a distending pressure that is equal to ST/r to counteract these inward-directed surface tension forces. As can be deduced from this relationship, the smaller the alveolar size, the higher the pressure that is required to keep it open. This surface tension effect causes the alveoli to have a strong tendency to collapse when their radius is small, a state that exists during expiration. Therefore, unopposed surface tension forces would cause alveoli to become atel ectatic at end-expiration. At the beginning of inspiration, these collapsed alveoli would require high pressures to be generated through increased work by the respiratory pump to air to reopen and allow gas exchange to be carried out (Fig. 6.9).

The increased work of breathing that is required to overcome surface tension–induced atelectasis can over whelm the respiratory system and lead to respiratory failure [24]. Type II alveolar epithelial cells produce a surface-active phospholipid called surfactant that coun teracts and reduces the effects of surface tension in the alveoli and terminal airways. Its structure has hydrophilic ends that coat the surface of water molecules and prevent cohesive forces from bringing them closer to each other and lower surface tension. As the alveoli reduce in size during expiration, surfactant molecular density increases and its effectiveness increases when surface tension effects are at their highest in the air–fluid interface that lines the alveolar inner surface. In addition, when the alveoli expand during inspiration, surfactant function is reduced, leaving residual surface tension that is required to prevent alveolar overdistension.

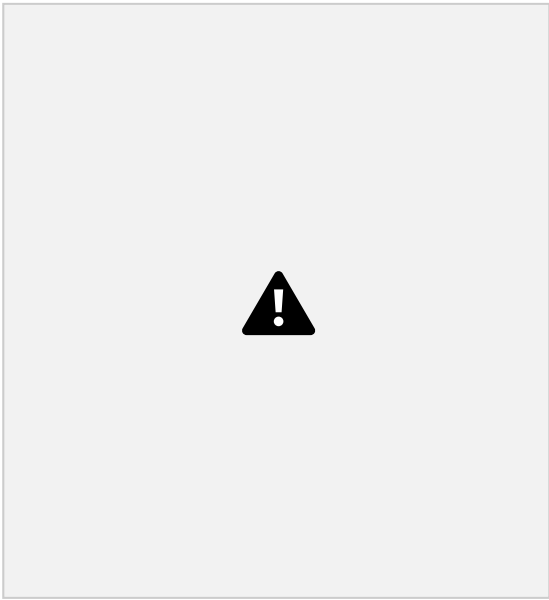


Fig. 6.9 Illustration of Laplace's Law. An alveolus of radius *r* requires a distending pressure equal to surface tension (*T*)/*r* to counteract inward-directed surface tension forces. Smaller the alveolar size, the higher the pressure that is required to keep it open. Copyright: Satyan Lakshminrusimha.