Goldsmith
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Assisted Ventilation of the NEONATE

Fifth Edition

SAUNDERS

Assisted Ventilation of the Neonate

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To our wives, Terri and Betsy, who have supported us for many years in every endeavor, including the five editions of this book

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Foreword

Over the past four to five decades, we have achieved a dramatic reduction in neonatal mortality, with a progressive decline in the gestational age for limits of viability of the smallest newborns. Acquisition of new therapeutic strategies from basic science and clinical research as well as the development of new technology are responsible for these achievements. An important technological advancement was the development of equipment and devices that allowed us to provide optimal ventilatory assistance for infants with respiratory failure. I am senior enough to remember the use of crude ventilators (often modifying ventilators used for adults) to deliver assisted ventilation to small infants in the late 1960s when I was developing a "neonatal unit" at Harbor General Hospital in Torrance, California. At that time, we struggled to help the premature infant in respiratory distress and, for all of our efforts, were often not successful despite using the most advanced technology available at the time. Today, more than 900 Neonatal Intensive Care Units (NICUs) in the United States have extremely sophisticated equipment to deliver these therapies. However, a well-built ship can sail well only with a team of well-trained and knowledgeable sailors. The first edition of the textbook, *Assisted Ventilation of the Neonate,* edited by J.P. Goldsmith and E.H. Karotkin, was published in 1981 and quickly became the standard reference in this field and an excellent resource for health care providers to acquire new knowledge and technique in treating neonates in respiratory failure. Publication of the second, third, and fourth editions attests to the excellent quality and usefulness of this text for neonatologists and their teams and the rapidly changing technology that was updated with each edition. The book contains excellent guidelines for assisted ventilation, with up-to-date descriptions of bedside methodologies and the rationale for providing all types of ventilatory care in sick and tiny infants. The book has also always included chapters that deal with the associated medical and nursing management of babies receiving ventilatory assistance such as nutrition, pharmacologic adjuncts, and cardiovascular care. The fifth edition continues the outstanding efforts by Drs. Goldsmith and Karotkin in maintaining the contributions by well-respected authors and expands the book to include a number of new and pertinent chapters related to the use of assisted ventilation of the neonate. New chapters include "Quality Improvement in Respiratory Care," "Ventilator-Associated Pneumonia," and "Human Factors and Safety in Ventilator Management." As the quality of neonatal care continues to improve in developing countries, the editors have also added a new chapter, "Neonatal Ventilation in Under-Resourced Settings." This chapter will prove very useful in further advancing efforts to lower the neonatal mortality and morbidity worldwide.

The editors should be congratulated for their outstanding contribution in the field of respiratory care of neonates. It is hoped their efforts will result in improved mortality rates and quality of survivors who require this highly intensive therapy.

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Preface

Over the past decade, we have continued to see technologic improvements in the design of neonatal mechanical ventilators in an effort to reduce damage produced by this therapy: ventilator-induced lung injury (VILI). Whereas half a century ago the goal of neonatologists was to improve survival, especially of the immature baby with surfactant deficiency, today the goal is improved survival without significant handicap. Over the years, smaller and more immature-gestation infants have been rescued; often, however, the price of survival was a life of handicap and hardship. In the early 1990s, we hit the wall—the gestational age below which conventional gas exchange could not adequately occur because of the anatomic and physiologic immaturity of the premature infant's lung. Controversy exists as to where that line should be drawn: 22 to 24 weeks' gestation, 400 to 600 g? Biologic variability allows that the line need not be drawn too sharply, so that each baby can be evaluated individually for viability and suitability for aggressive intervention. Moreover, newer guidelines give a larger role for the parents to participate in that decision and for the clinical team to try to make the parents as informed as possible. In the new millenium the decades-long trend of improving weight-specific survival for babies of 500 to 1500 g birth weight also leveled off. However, although the incidence of life-long handicap from chronic lung disease and intraventricular hemorrhage remains unacceptably high, there is encouraging news that the rates of these morbidities are slowly falling with the more uniform application of evidence-based therapies for the premature infant.

In recent years, emphasis has shifted from pushing back the envelope of gestational age and birth weight viability to improving functional outcomes of those babies who have the potential to be treated effectively. Despite evidence of survival of a number of the smallest and most immature babies without significant handicaps, most health care providers are acutely aware of the high incidence of handicap in infants who have been "saved" by our therapies. A large interinstitutional variance in the incidence of the two most recognizable sequelae of our treatment regimes—chronic lung disease and central nervous system injury—has led to an evidence-based search for the best therapies and protocols and, more recently, the uniform application of these therapies through quality improvement programs.

With particular reference to the topic of this text—assisted ventilation—we continue to search for new ways to ventilate infants without causing harm. Over the past decade, we have seen the acceptance of new modes of ventilation, specifically patient-assisted ventilation and volume-guaranteed ventilation, as potential methods to achieve this goal. We know that the vast majority of lung injury is man-made, the result of the therapy to treat respiratory failure, mostly in the premature infant. However, until there are social, molecular, and technologic solutions to prematurity and its associated diseases, we must continue to use the tools we have, despite their potentially damaging side effects. In this regard, the words of Dr. George Cassidy, writing more than 20 years ago in the foreword to the second edition of this text, are worth repeating: "The managements and techniques described in this text are nearly all empiric. . . . Since the methods proposed are those used by the experts, one might assume that these are the methods that work best. Not so. . . . Until we've had the opportunity to compare the 'best therapies' with each other, we'll continue to have uncertain truths to guide us. Awareness of this uncertainty makes us better doctors." Over the past two decades some of the "best therapies" have been evaluated and compared with other forms of treatment. Evidence evaluation, Cochrane meta-analysis reviews, and other studies in the field of neonatal pulmonary medicine have helped guide us to the treatment modalities that we use today. However, most therapies are still empiric, and the application of even "standard" therapies is so varied that interinstitutional outcomes such as the incidence of chronic lung disease in the very-low-birth-weight infant are widely divergent.

The incidence of ventilator-induced chronic lung disease in the very-low-birth-weight infant has finally begun to slowly decrease according to the Vermont Oxford Network annual statistical survey of more than 600 NICUs. On the other hand, strategies to decrease prematurity have not worked and in recent years the incidence of premature birth has actually risen in the United States despite a national program to reduce this rate. Therefore, the number of newborns requiring respiratory support has continued to rise. Basic scientific research has begun to identify some of the molecular mediators of lung injury and offers promise of potential therapies. But for the clinician at the bedside, the keys to prevention of chronic lung disease are effective ventilatory devices, strategies for ventilatory assistance, and support protocols that will decrease barovolutrauma and allow appropriate growth of the immature lung. Thus, the initial premise of this text as a "how-to" manual of the mechanics for utilizing ventilatory assistance and its supportive components is no longer

valid. Survival is no longer the goal; survival without handicap must be our new paradigm.

In 1999, L.D. Hudson wrote that ". . . the concept of ventilatory-induced lung injury (VILI) has come of age" (*JAMA*). However, more than 250 years earlier, Fothergill recognized the potential for VILI from mechanical assistance of lung function: "Mouth to mouth resuscitation may be better than using a mechanical bellows to inflate the lung because . . . the lungs of one man may bear, without injury, as great as those of a man can exert, which by the bellows can not always be determined" (*J Philos Trans Roy Soc*, 1745). Therefore, the theme for this fifth edition remains "how best" to support the newborn's respiratory system to achieve optimal outcomes without sustaining damage from the known sequelae of ventilatory devices. Perhaps the best treatment is no treatment at all, that is, not to intervene when the infant is too immature or has no reasonable chance of intact survival. Or when intervention is chosen in the appropriately selected patient, to follow the "Columbia approach" of noninvasive respiratory assistance and attempt not to intubate or mechanically ventilate the infant. This is accomplished by early use of nasal continuous positive airway pressure (nCPAP), permissive hypercapnia, and a variety of other strategies that are discussed in the text. However, it should be pointed out that this approach is supported only by a number of uncontrolled and cohort studies, and no randomized trial has ever validated the benefits of nCPAP as the preferred method of support for the premature infant with respiratory distress syndrome. Moreover, although this approach has gained more acceptance and use for the larger premature infant (>1000 g), the extremely-low-birthweight newborn continues to require mechanical ventilation in most units. As a consequence, the population of infants receiving ventilatory assistance today is much different from even a decade ago. This population is made up of a group of term or postterm infants with relatively short duration control of breathing issues and a much larger group of extremely small infants who are ventilated often for extended periods of time and at great risk for developing chronic lung disease.

Assisted Ventilation of the Neonate attempts to follow evidence-based recommendations, but the reader will encounter empiric opinions where insufficient data exist. In this edition, all previous chapters have been updated to reflect the most recent data available. New chapters on ventilator-associated pneumonia, evidence-based quality improvement, human factors in the management of ventilators, and neonatal-assisted ventilation in under-resourced settings have been added. These chapters, along with revisions of the rest of the text, bring this subject current in a rapidly changing field.

Pathophysiology and pulmonary mechanics are discussed as integral to the mechanics of ventilatory assistance; the reader is referred to other textbooks for detailed descriptions of the pathologic conditions and radiographic findings of neonatal pulmonary disorders that lead to respiratory failure. As in previous editions, the authors have used brand names and given representative examples of specific devices and drugs when necessary to illustrate treatment protocols and approaches. However, these representations are not endorsements of these devices or drugs, and exclusion is not meant to be viewed as criticism.

Over the five editions and nearly 30-year span of this textbook, we have seen our specialty grow and have learned much about our capabilities and limitations. We hope each successive edition has reflected that growth and a maturation of the practitioners in this unique field of medicine. Our failures continue to frustrate us, and the temptation to adopt new and unproven therapies is great. However, we must continue to rely on evidence-based therapies and apply rigorous scientific principles to our research. More importantly, the tremendous variance in outcomes in the nearly 1000 NICUs in the United States gives impetus to the more uniform adoption of proven therapies and the application of quality improvement programs in neonatal respiratory care to narrow these discrepancies. It is hoped that this book will stimulate you and your colleagues to continue in these pursuits. As we wait for the solution(s) to prematurity, we should remember the wisdom of an old editorial. "The tedious argument about the virtues of respirators not invented over those readily available can be ended now that it is abundantly clear that the success of such apparatus depends on the skill with which it is used" (*Lancet* 2:1227,1965).

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1 Introduction to Assisted Ventilation

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Dramatic reductions in both neonatal and infant mortality rates have occurred during the past 50 years as a result of a variety of medical and surgical advances including better obstetric care, improved neonatal pharmacologic agents (particularly exogenous surfactants), more sophisticated respiratory support and monitoring devices, improvements in neonatal nutrition and laboratory micromethods, and enhanced surgical and cardiovascular diagnostic and operative techniques. The past few years in particular have witnessed a rapid evolution in the approach to providing assisted ventilation to premature neonates with respiratory failure. Consequently, unless there are congenital abnormalities of the lung such as pulmonary hypoplasia or congenital diaphragmatic hernia, few infants die in the newborn period from respiratory failure; instead, death is caused by the complications of prematurity such as infection, necrotizing enterocolitis (NEC), and intraventricular hemorrhage (IVH) or by pulmonary and other congenital anomalies—in both term and preterm infants. However, late deaths in infancy secondary to prematurity are often associated with the complications of ventilatory assistance known as *bronchopulmonary dysplasia (BPD)* or perhaps the more accurate term of *ventilator-induced lung injury (VILI)*.

Information related to the best methods of resuscitating and supporting newborns with respiratory failure has evolved rapidly in recent years. Both clinicians and investigators have been stimulated to evaluate a variety of approaches to managing these infants, including (1) specialized delivery room resuscitation teams who employ devices that limit pressure (Neopuff™) and pulse oximeters that measure oxygen saturation in the delivery room, (2) the administration of surfactant within the first few minutes of life, (3) use of continuous positive airway pressure (CPAP), nasal intermittent mandatory ventilation, and (4) a variety of microprocessor-based ventilators that allow for synchronized breaths and permit the operator to precisely control for both the volume and/or the pressure of each delivered breath. In addition many neonatal intensive care units (NICUs) now employ both high-frequency oscillator ventilators (HFOVs) and high-frequency jet ventilators (HFJVs) in the management of selected patients.

Despite these numerous additions to the neonatologist's armamentarium of medicines and therapeutic devices, it is still unclear in many clinical situations which therapy is the best approach and has the best chance of improving care and ultimately proving superior in preventing BPD and VILI in the long-term survivors. A prime example of this uncertainty is the question of whether to give surfactant in the first few minutes of life to an extremely-low-birth-weight newborn, apply nasal CPAP without surfactant, or intubate giving surfactant and then extubate to nasal CPAP? The potential benefits and risks of many of these therapeutic dilemmas are discussed in the subsequent chapters and will assist clinicians to better manage the patients in their care.

This chapter presents an introduction for clinicians involved in the management of newborns requiring assisted ventilatory support. A brief overview of the history of neonatal medicine with special emphasis on treating respiratory insufficiency hopefully provides the perspective needed to better appreciate the contributions improved neonatal resuscitation and neonatal assisted ventilation have made to the field of newborn care.

Definition and Purpose

Assisted ventilation can be defined as the movement of gas into and out of the lung by an external source connected directly to the patient. The external source may be a health care provider using mouth-to-mouth, mouth-to-mask, or a hand-operated resuscitation bag; the external source may be a mechanical device such as a continuous distending pressure device or a ventilator. Attachment of the device to the patient can be via a face mask, endotracheal tube, laryngeal mask airway, nasal prongs, or tracheostomy. Although not in general use today in modern intensive care nurseries, negative-pressure ventilation can be applied by an apparatus surrounding the infant's thorax. In the neonate, assisted ventilation is a modality for supporting pulmonary function until the patient can breathe adequately without help. In more recent years, with the increased survival of babies born at gestational ages approaching the limits of viability, infants are often requiring prolonged assisted ventilation for weeks or months and, in the case of some patients with severe chronic lung disease, years. The purpose of all mechanical ventilation devices is to facilitate alveolar ventilation and carbon dioxide removal, provide adequate tissue oxygenation, and reduce the work of breathing. This is accomplished through the use of a device that augments or replaces the bellows action of the respiratory musculature.

Mechanical ventilation of the neonate is a complex and often highly invasive procedure and must not be undertaken in a casual manner. Effective ventilation of the

diseased lung requires that the clinician understand normal pulmonary physiology as well as the pathophysiology of pulmonary diseases in the neonate. The clinician also must correlate the type of therapy to the stage of pulmonary growth and development and to the severity of the disease. The effect of assisted ventilation on other organ systems, particularly the heart and brain, must also be appreciated. In addition, the clinician must understand the basic mechanical principles of the specific ventilator in use and anticipate how the patient will respond to the changes in ventilator performance that are made by the operator. The beneficial effects of ventilatory therapy are dependent on a strong knowledge of these subjects, skill, and experience in management, combined with constant vigilance by medical, nursing, and respiratory personnel during treatment.

History of Neonatal Ventilation

And he went up, and lay upon the child, and put his mouth upon his mouth and his eyes upon his eyes, and his hands upon his hands; and he stretched himself upon the child and the flesh waxed warm.

II KINGS 4:34

From the earliest recorded description of mouth-to-mouth resuscitation in the Old Testament (one by Elijah, I Kings 17:17, and another in the preceding quoted passage by Elisa[1]), we have been fascinated with the idea of sustaining respiration by artificial means. The medical literature of the past several thousand years contains many references to early attempts to resuscitate. The Papyrus Ebers in 16th century BC Egypt gave the prognosis for a newborn infant at birth by making the observation that a crying infant is one that will likely survive, but that one with expiratory grunting will die.[2] Hippocrates (circa 400 BC) was the first investigator to record his experience with intubations of the trachea to support pulmonary ventilation.[3] His preliminary work was ignored for almost 2000 years, until Paracelsus (1493-1541) reported the use of bellows and an oral tube in this endeavor.[2] During the middle ages, the care of the neonate rested largely with illiterate midwives and barber surgeons, and the next significant advances in care were not recorded until 1513 when Eyucharius Rosslin's book first outlined standards for treating the newborn infant.[2]

The 16th and 17th Centuries

The scientific renaissance in the 16th and 17th centuries rekindled interest in the physiology of respiration and in techniques for tracheostomy and intubation. By 1667, simple forms of continuous and regular ventilation had been developed.[3] With these developments, a better understanding of the basic physiology of pulmonary ventilation emerged.

Various descriptions of neonatal resuscitation during this period can be found in the medical literature. Unfortunately, these guidelines were anecdotal and not always appropriate by today's standards. These reports came mainly from midwives who described many interventions for the depressed neonate such as physicians giving a small spoonful of wine into the infant's mouth in an attempt to stimulate respirations as well as some of the earliest descriptions of mouth-to-mouth resuscitation.[4]

The 19th Century

In the early 1800s, interest in resuscitation and mechanical ventilation of newborn infants flourished. In 1800, the first report describing nasotracheal intubation as an adjunct to mechanical ventilation was published by Fine in Geneva.[5] At about the same time, the principles for mechanical ventilation of adults were established; the rhythmic support of breathing was accomplished with mechanical devices, and on occasion, ventilatory support was carried out with tubes passed into the trachea.

In 1806, Vide Chaussier, a professor of obstetrics in the French Academy of Science, described his experiments with the intubation and mouth-to-mouth resuscitation of asphyxiated and stillborn infants.[6] The work of his successors led to the development in 1879 of the Aerophore Pulmonaire (Fig. 1-1), the first device specifically designed for the resuscitation and short-term ventilation of newborn infants.[3] This device was a simple rubber bulb connected to a tube. The tube was inserted into the upper portion of the infant's airway, and the bulb was alternately compressed and released to produce inspiration and passive expiration. Subsequent investigators refined these early attempts by designing devices that were used to ventilate laboratory animals.

Charles-Michel Billard (1800-1832) wrote one of the finest early medical texts dealing with clinical-pathologic correlations of pulmonary diseases in newborn infants. Dr. Billard's book, *Traite des Maladies des Enfants Nouveau-Nes et a la Mamelle*, was published in 1828.[7] His concern for the fetus and intrauterine injury is evident as he writes: "During intrauterine life man often suffers many affectations, the fatal consequences of which are brought with him into the world … children may be born healthy, sick, convalescent, or entirely recovered from former diseases."[7] His understanding of the difficulty newborns may have in establishing normal respiration at delivery is well illustrated in the following passage: "… the air sometimes passes freely into the lungs at the period of birth, but the sanguineous congestion which occurs immediately expels it or hinders it from penetrating in sufficient quantity to effect a complete establishment of life. There exists, as is well known, between the circulation and respiration, an intimate and reciprocal relation, which is evident during life, but more particularly so at the time of birth. . . . The symptoms of pulmonary engorgement in an infant are, in general, very obscure, and consequently difficult of observation; yet we may point out the following: the respiration is laboured; the thoracic parietes are not perfectly

Figure 1-1 ■ Aerophore Pulmonaire of Gairal. (From DePaul. Dictionnaire Encyclopédique, vol. XIII, 13th series.)

developed; the face is purple; the general color indicates a sanguineous plethora in all the organs; the cries are obscure, painful and short; percussion yields a dull sound."[7] It seems remarkable that these astute observations were made more than 180 years ago.

The advances made in the understanding of pulmonary physiology of the newborn and the devices designed to support a newborn's respiration undoubtedly were stimulated by the interest shown in general newborn care that emerged in the latter part of the 19th century and continued into the first part of the 20th century.[8] In France in 1880, Dr. Eteinne Tarnier, an obstetrician and leading figure in the European Infant Welfare Movement, appreciated the importance of keeping the premature infant warm and introduced a closed water-jacketed incubator. In 1884 he introduced and popularized gavage feedings for the "debile" and "weakling."[8] A few years later, his colleague Pierre Budin developed the principles of neonatal medicine and stressed the importance of weekly physician examinations of the newborn, maternal education, and sterilized milk. In 1892 Budin opened his "consultation for nurslings." The experience he gained in the care of premature infants resulted in a book on the subject. Budin was the first to dignify the newborn with a separate hospital chart in which weight, temperature, and breast milk intake were recorded and plotted daily. He also published survival data and established follow-up programs for his high-risk newborn patients.[8] As a result of these initiatives, he may well be regarded as the "father of neonatology." (How ironic he was an obstetrician.)

These advances were followed by the work of Dr. Ballantyne, an Edinburg obstetrician who emphasized the importance of prenatal care and recognized that syphilis, malaria, typhoid, tuberculosis, and maternal ingestion of toxins such as alcohol and opiates were detrimental to the development of the fetus.[8]

Better understanding of pulmonary physiology led to further refinements in ventilation. O'Dwyer[9] reported the first successful use of long-term positive-pressure ventilation in a series of 50 children with croup when he published the results of his studies in 1887 (Fig. 1-2). Shortly thereafter, Egon Braun and Alexander Graham Bell independently developed intermittent body-enclosing devices for the negative-pressure/positive-pressure resuscitation of newborns (Figure 1-3).[10,11]

Figure 1-2 ■ Fell-O'Dwyer apparatus for provision of intermittent positive-pressure ventilation. (From Northrup. M & S Rep Presbyterian Hospital, New York, 1896.)

The 20th Century

In the early 20th century in the United States, three principles of public health emerged that led to further improvements in newborn survival. (1) Saving of infant lives is best achieved by protection and education of mothers before and after pregnancy. (2) Infant mortality rate is the best available index of the overall health and welfare of a community. (3) Infant mortality is related to multiple factors, and multiple interventions are necessary to lower the rate.[8]

In the 1920s, obstetrics became a full-fledged surgical discipline and pediatricians assumed the care for all children. One of Budin's students, Courney, took advantage of the public fascination with premature infants and displayed them at the Chicago Exposition in 1914. A similar display featuring warming incubators was a popular venue at the World's Fair in 1939. Shortly thereafter, Dr. Julius Hess opened the first Premature Center at the Michael Reese Hospital in Chicago and other centers soon followed. Modern neonatology was born with the recognition that premature infants required particular attention with regard to temperature control, administration of fluids and nutrition, and protection from infection. In the 1930s and 1940s premature infants were given new stature, and it was acknowledged that their death was the greatest contributor to the infant mortality rate.[8]

The years following World War II were marked by soaring birth rates, the proliferation of labor and delivery

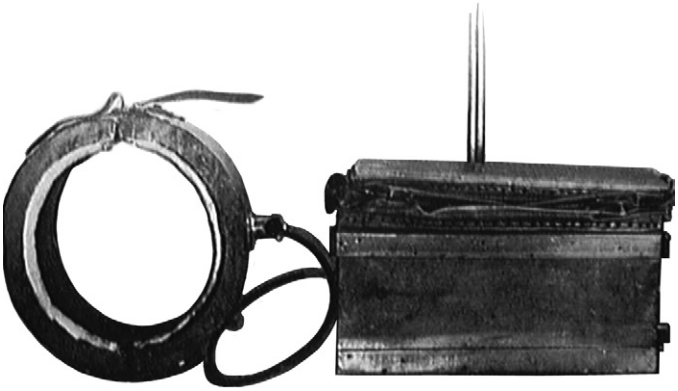

Figure 1-3 ■ Alexander Graham Bell's negative pressure ventilator, circa 1889. (From Stern L. et al., Canad, M.A.J., 1970)[3]

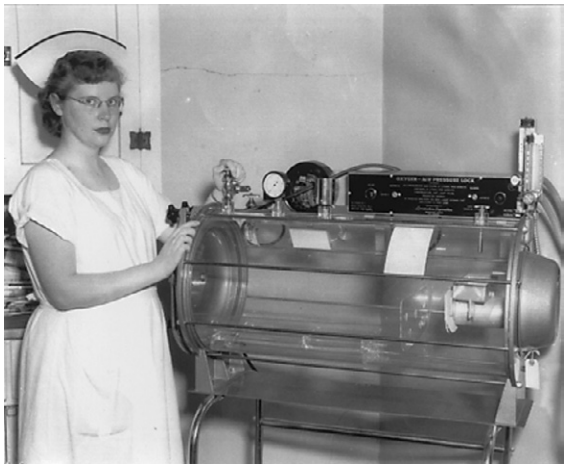

Figure 1-4 ■ Commercial Plexiglas version of the positive-pressure oxygen air lock. Arrival of the unit at the Dansville Memorial Hospital, Dansville, New York, June 1952. (Photo courtesy James Gross and the *Dansville Breeze*, June 26, 1952.)

services, the introduction of antibiotics, positive-pressure resuscitators, miniaturization of laboratory determinations, x-ray capability, and microtechnology that made intravenous therapy possible for neonatal patients. These advances and a host of other advances heralded the modern era of neonatal medicine.

Improvements in intermittent negative-pressure and positive-pressure ventilation devices in the early 20th century led to the development of a variety of techniques and machines for supporting ventilation in infants. In 1929, Drinker and Shaw[12] reported the development of a technique for producing constant thoracic traction to effect an increase in end-expiratory lung volume. In the early 1950s, Bloxsom[13] reported the use of a positive-pressure air lock for resuscitation of infants with respiratory distress in the delivery room. This device was similar to an iron lung; it alternately created positive and negative pressure in a tightly sealed cylindrical steel chamber that was infused with warmed humidified 60% oxygen.[14] Clear plastic versions of the air-lock quickly became commercially available in the United States in the early 1950s (Fig. 1-4). However, a study by Apgar and Kreiselman in 1953[15] on apneic dogs and another study by Townsend involving 150 premature infants[16] demonstrated that the device could not adequately support the apneic newborn. The linkage of oxygen administration and retinopathy of prematurity and a randomized controlled trial of the air-lock versus care in an Isolette® incubator at Johns Hopkins University[17] revealed no advantage to either study group and heralded the hasty decline in the use of Bloxsom's device.

In the late 1950s, body-tilting devices were designed that shifted the abdominal contents in order to create effective movements of the diaphragm. Phrenic nerve stimulation[18] and the use of intragastric oxygen[19] also were reported in the literature but had little clinical success. In the 1950s and early 1960s, many centers also used bag and face mask ventilation to support infants for relatively long periods of time. A synopsis of the major events in the development of neonatal resuscitation is shown as a timeline in Box 1-1.

The modern era of mechanical ventilation for infants can be dated back to the 1953 report of Donald and Lord,[20] who described their experience with a patient-cycled, servo-controlled respirator in the treatment of several newborn infants with respiratory distress. They claimed that three or possibly four infants were successfully treated with their apparatus.

In the decades following Donald and Lord's pioneering efforts, the field of neonatal ventilation made dramatic advances; however, the gains were accompanied by several temporary setbacks. Because of the epidemic of poliomyelitis in the 1950s, experience was gained with the use of the tank-type negative-pressure ventilators of the Drinker design.[21] The success of these machines with children encouraged physicians to try modifications of them on neonates, with some anecdotal success. However, initial efforts to apply intermittent positive-pressure ventilation (IPPV) to premature infants with respiratory distress syn-

Box 1-1 NEONATAL RESUSCITATION TIMELINE

1300 BC: Hebrew midwives use mouth-to-mouth breathing to resuscitate newborns.

200 BC-500 AD: Hebrew text (Talmud) states, "we may hold the young so that it should not fall on the ground, blow into its nostrils and put the teat into its mouth that it should suck."

98-138 AD: Greek physician Soranus describes evaluating neonates with system similar to present day APGAR scoring, evaluating muscle tone, reflex or irritability, and respiratory effort. He believed that asphyxiated or premature infants and those with multiple congenital anomalies were "not worth saving."

1667: Robert Hook presents to Royal Society of London his experience using fireside bellows attached to the trachea of dogs to provide continuous ventilation.

1774: Joseph Priestley produces oxygen but fails to recognize that it is related to respiration. Royal Humane Society advocates mouth-to mouth resuscitation for stillborn infants.

1733-1794: Lavoisier terms oxygen "vital air" and shows that respiration is an oxidative process that produces water and carbon dioxide.

1806: Vide Chaussier describes intubation and mouth-to-mouth resuscitation of asphyxiated newborns.

1834: James Blundell describes neonatal intubation.

1874: Open chest cardiac massage reported in adult.

1879: Report on the Aerophore Pulmonaire, a rubber bulb connected to a tube that is inserted into neonate's airway and then compressed and released to provide inspiration and passive expiration.

Late 1880s: Bonnair administers oxygen to premature "blue baby."

1949: Dr. Hess and Evelyn C. Lundeen, RN, publish *The Premature Infant: Medical and Nursing Care,* which ushers in the modern era of neonatal medicine.

1952: Virginia Apgar reports on system of neonatal assessment that bears her name.

1980s: American Heart Association and American Academy of Pediatrics recognize need to improve care of the compromised newborn and develop the Neonatal Educational Program (NEP), which in 1988 would become the Neonatal Resuscitation Program (NRP).

1998: Neonatal section formed in the International Liaison Committee on Resuscitation (ILCOR), which reviews evidence to develop guidelines for resuscitation every 5 years.

drome (RDS) were disappointing overall. Mortality was not demonstrably decreased, and the incidence of complications—particularly that of pulmonary air leaks—seemed to increase.[22] During this period, clinicians were hampered by the types of ventilators that were available and by the absence of proven standardized techniques for their use.

In accordance with the findings of Cournand et al.[23] in adult studies conducted in the late 1940s, standard ventilatory technique often required that inspiratory positive-pressure times be very short. Cournand et al. had demonstrated that prolongation of the inspiratory phase of the ventilator cycle in patients with normal lung compliance could result in impairment of thoracic venous return, a decrease in cardiac output, and the unacceptable depression of blood pressure. To minimize cardiovascular effects, they advocated that the inspiratory phase of a mechanical cycle be limited to one third of the entire cycle. Some ventilators manufactured in this period even were designed with the inspiratory-to-expiratory ratio fixed at 1 : 2.

Unfortunately, the findings of Cournand et al. were not applicable to patients with significant pulmonary parenchymal disease and with reduced lung compliance, such as premature infants with RDS. Neonates with pulmonary disease, which is generally characterized by increased chest wall compliance and terminal airway and alveolar collapse, did not generally respond to IPPV techniques that had worked well in adults and older children. Thus clinicians were initially disappointed with the outcome of neonates treated with assisted ventilation using these techniques.

The birth of a premature son to President John F. Kennedy and Jacqueline Kennedy on August 7, 1963, focused the world's attention on prematurity and the treatment of hyaline membrane disease (HMD), then the current appellation for RDS. Patrick Bouvier Kennedy was born by cesarean section at 34 weeks' gestation at Otis Air Force Base Hospital. He weighed 2.1 kg. and was transported to Boston's Massachusetts General Hospital, where he died at 39 hours of age (Fig. 1-5). The Kennedy baby was treated with the most advanced therapy of the time, hyperbaric oxygen,[24] but he died of progressive hypoxemia. In response to his death, *The New York Times* reported: "About all that can be done for a victim of hyaline membrane disease is to monitor the infant's blood chemistry and try to keep it near normal levels." The Kennedy tragedy, followed only 3 months later by the President's assassination, stimulated further interest and research in neonatal respiratory diseases and resulted in increased federal funding in these areas.


The New York Times.

NEW YORK, THURSDAY, AUGUST 8, 1963.

KENNEDY TO SEND TEST BAN TREATY TO SENATE TODAY

2d Son Born to Kennedys; Has Lung Illness

Child Transferred to Boston After Birth at Cape Hospital

President Kennedy arriving last night at the Children's Hospital Medical Center in Boston. At right is Dr. Leaden Sweeker, assistant in general director of the center.

Figure 1-5 ■ Front page of *The New York Times,* August 8, 1963. (Copyright © 1963 by The New York Times Co. Reprinted by permission.)

Partially in response to the Kennedy baby's death, several intensive care nurseries around the country (most notably at Yale, Vanderbilt, and the University of California in San Francisco) began programs focused on respiratory care of the premature neonate and the treatment of hyaline membrane disease. Initial success with ventilatory treatment of HMD was reported by Delivoria-Papadopoulos and colleagues[25] in Toronto, and as a result, modified adult ventilatory devices were soon in use in many medical centers across the United States. However, the initial anecdotal successes were also accompanied by the emergence of a new disease, bronchopulmonary dysplasia (BPD), first described in a seminal paper by Northway et al.[26] in 1967. Northway initially attributed this disease to the use of high inspired oxygen, but subsequent publications demonstrated that BPD was the result of intubation and positive-pressure ventilation as well as oxygen being given to infants over extended periods of time.

Breakthroughs in Ventilation

A major breakthrough in neonatal ventilation occurred in 1971 when Gregory et al.[27] reported on clinical trials with continuous positive airway pressure (CPAP) for the treatment of RDS. Recognizing that the major physiologic problem in RDS was the collapse of alveoli during expiration, they applied positive pressure to the airway via an endotracheal tube during both expiration and inspiration; dramatic improvement was achieved. Although infants receiving CPAP breathed spontaneously during the initial studies, later combinations of IPPV and CPAP in infants weighing less than 1500 g were not as successful.[27] Nonetheless, the concept of CPAP was a major advance. It was later modified by Bancalari et al.[28] for use in a constant distending negative-pressure chest cuirass and by Kattwinkel et al.,[29] who developed nasal prongs for the application of CPAP without the use of an endotracheal tube.

Meanwhile, Reynolds and Taghizadeh,[30,31] working independently in Great Britain, also recognized the unique pathophysiology of neonatal pulmonary disease. Having experienced difficulties with IPPV similar to those noted by clinicians in the United States, Reynolds and Taghizadeh suggested prolongation of the inspiratory phase of the ventilator cycle by delaying the opening of the exhalation valve. This "reversal" of the standard inspiratory-to-expiratory ratio, or "inflation hold," allowed sufficient time for the recruitment of atelectatic alveoli in RDS with lower inflating pressures and gas flows, which, in turn, decreased turbulence and limited the effect on venous return to the heart. The excellent results of Reynolds and Taghizadeh could not be duplicated uniformly in the United States, perhaps because their American colleagues used different ventilators.

Until the early 1970s, ventilators used in neonatal intensive care units (NICUs) were modifications of adult devices; these devices delivered intermittent gas flows, thus generating IPPV. The ventilator initiated every mechanical breath, and clinicians tried to eliminate the infants'

attempts to breathe between IPPV breaths ("fighting the ventilator"), which led to rebreathing of dead air. In 1971, a new prototype neonatal ventilator was developed by Kirby and colleagues.[32] This ventilator used continuous gas flow and a timing device to close the exhalation valve modeled after the Ayre's T-piece used in anesthesia (Fig. 1-6).[20,30,32] Using the T-piece concept, the ventilator provided continuous gas flow and allowed the patient to breathe spontaneously. Occlusion of the distal end of the T-piece diverted gas flow under pressure to the infant. In addition, partial occlusion of the distal end generated positive end-expiratory pressure. This combination of mechanical and spontaneous breathing under continuous gas flow was called *intermittent mandatory ventilation* (IMV).

IMV became the standard method of neonatal ventilation and has been incorporated into all infant ventilators since then. One of its advantages was the facilitation of weaning by progressive reduction in IMV rate, which allowed the patient to gradually increase spontaneous breathing against distending pressure. Clinicians no longer needed to paralyze or hyperventilate patients to prevent their "fighting the ventilator." Moreover, because patients continued to breathe spontaneously and lower cycling rates were used, mean intrapleural pressure was reduced and venous return was less compromised than with IPPV.[33]

From 1971 to the mid 1990s, myriad new ventilators specifically designed for neonates were manufactured and sold. The first generation of ventilators included the BABYbird I; the Bournes BP 200; and a volume ventilator, the Bournes LS 104/150. All operated on the IMV principle and were capable of incorporating CPAP into the respiratory cycle (known as *positive end-expiratory pressure* [PEEP] when used with IMV).[34]

The BABYbird I and the Bournes BP 200 used a solenoid-activated switch to occlude the exhalation limb of the gas circuit in order to deliver a breath. Pneumatic adjustments in the inspiratory-to-expiratory ratio and rate were controlled by inspiratory and expiratory times, which had to be timed with a stopwatch. A spring-loaded pressure manometer monitored peak inspiratory pressure and PEEP. These early mechanics created time delays within the ventilator, resulting in problems in obtaining short inspiratory times (less than 0.5 second).

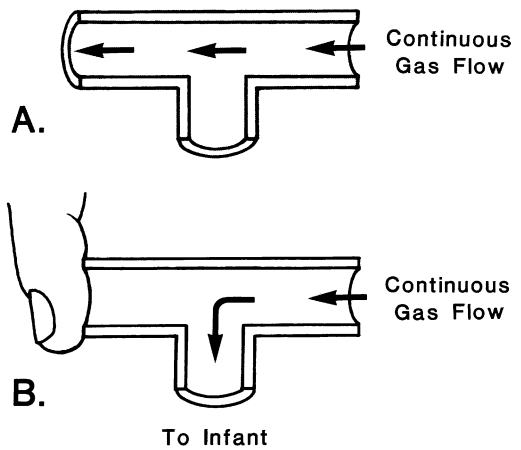

Figure 1-6 ■ Ayre's T-piece forms the mechanical basis of most neonatal ventilators currently in use. **A,** Continuous gas flow from which an infant can breathe spontaneously. **B,** Occlusion of one end of the T-piece diverts gas flow under pressure into an infant's lungs. The mechanical ventilator incorporates a pneumatically or electronically controlled time-cycling mechanism to occlude the expiratory limb of patient circuit. Between sequential mechanical breaths, the infant can still breathe spontaneously. The combination of mechanical and spontaneous breaths is intermittent mandatory ventilation. (From Kirby RR: Mechanical ventilation of the newborn. Perinatol Neonatol 5:47, 1981.)

In the next generation of neonatal ventilators, the incorporation of electronic controls, microprocessors, and microcircuitry allowed the addition of light-emitting diode (LED) monitors and provided clinicians with faster response times, greater sensitivity, and a wider range of ventilator parameter selection. These advances were incorporated into ventilators such as the Sechrist 100 and Bear Cub to decrease inspiratory times to as short as 0.1 second and to increase ventilatory rates to 150 breaths per minute. Monitors incorporating microprocessors measured inspiratory and expiratory times and calculated inspiratory-to-expiratory ratios and mean airway pressure. Ventilator strategies abounded, and controversy regarding the best (i.e., least harmful) method for assisting neonatal ventilation arose. High-frequency positive-pressure ventilation using conventional ventilators was proposed as a beneficial treatment of RDS.[35]

Meanwhile, extracorporeal membrane oxygenation (ECMO) and true high-frequency ventilation (HFV) were being developed at a number of major medical centers.[36,37] These techniques initially were offered as rescue therapy for infants who did not respond to conventional mechanical ventilation. The favorable physiologic characteristics of HFV led some investigators to promote its use as an initial treatment of respiratory failure, especially when caused by RDS in very-low-birth-weight infants.[38]

A third generation of neonatal ventilators began to appear in the early 1990s. Advances in microcircuitry and microprocessors, developed as a result of the space program, allowed new dimensions in the development of neonatal assisted ventilation. The use of synchronized IMV, assist/control mode ventilation, and pressure support ventilation—previously used in the ventilation of only older children and adults—became possible in neonates because of the very fast ventilatory response times. Although problems with sensing a patient's inspiratory effort sometimes limited the usefulness of these new modalities, the advances gave hope that ventilator complications could be limited and that the need for sedation or paralysis during ventilation could be decreased. Direct measurement of some pulmonary functions at the bedside became a reality and allowed the clinician to make ventilatory adjustments based on physiologic data rather than on a "hunch."

Over the last decade, an even newer generation of ventilators has been developed. These are microprocessor based with a wide array of technological features including several forms of patient triggering, volume targeting, and pressure support modes, and the ability to monitor many pulmonary functions at the bedside with ventilator graphics. As clinicians become more convinced that VILI is secondary to volutrauma more than barotrauma, the emphasis to control tidal volumes especially in the micropremie has resulted in a major change in the technique of ventilation. However, concurrent with these advances is an

increased complexity related to controlling the ventilator and thus more opportunity for operator error. Some ventilators are extremely versatile and can function for patients from extremely low birth weight (less than 1000 g) to 70-kg adults. Although these ventilators are appealing to administrators who have to purchase these expensive machines for many different categories of patients in their hospital, they add increased complexity and patient safety issues in caring for neonates.

Respiratory support in the present-day NICU continues to change as new science and new technology hopefully point the way to better outcomes with less morbidities, even for the smallest premature infants. Noninvasive respiratory support with the use of nasal CPAP has become a widely used technique to support premature infants with respiratory distress in the hope of avoiding the traumas of intubation and VILI. Using this approach as one potentially better practice, quality improvement programs to lower the rate of BPD have had mixed success. At the present time, noninvasive ventilation has been supported by a number of retrospective and cohort studies,[39] but no randomized clinical trial has validated its efficacy in reducing BPD.[40]

Surfactant Replacement Therapy

Perhaps the most important advance in treating RDS in the last 40 years has been the development of surfactant replacement therapy. The discovery by Avery and Mead[41] in 1959 that surfactant deficiency was the critical factor in neonatal RDS was the first step in a tremendous 40-year research effort that culminated in the licensing of two exogenous surfactant preparations in the United States in the early 1990s. (In 1990, the United States Food and Drug Administration approved exogenous surfactant for treatment of RDS, heralding a new era in the treatment of neonatal respiratory failure.) Surfactant replacement therapy has clearly been shown to improve lung function and mechanics in premature infants with RDS. Most studies have demonstrated decreased duration of assisted ventilation, lower fractions of inspired oxygen (F_{IO_2}), lower peak inflating pressures, and decreases in morbidity and mortality associated with its use in infants weighing from 600 to 1500 g.[42] Although originally developed for use in premature infants with RDS, exogenous surfactant therapy has been proposed for patients with other diseases (e.g., meconium aspiration syndrome, pneumonia) that cause neonatal respiratory failure.[43] It is now generally accepted that the earlier artificial surfactant is administered to infants at risk for developing RDS, the less severe the disease and the less time the patient spends on the ventilator.[44] However, the treatment of very low birth weight (VLBW) infants using nasal CPAP without surfactant is gaining increasing support. Nonetheless, it was obvious that a new era of treatment of neonatal pulmonary disease had arrived with the development of surfactants. The biochemistry and physiology of surfactant and surfactant replacement therapy are discussed in detail in Chapter 22.

Recent Advances and Outcomes

Assisted ventilation represents the hallmark of neonatal intensive care. Improvements in devices, the appearance of new techniques and better support systems, and the development of exogenous surfactant and other pharmacologic agents all have contributed to improving weight-specific survival rates for infants with neonatal respiratory failure. A report in the mid 1970s of all neonates ventilated from 1966 to 1969 proudly announced a survival rate of 33%.[45] A study looking at the outcome of infants born in the United States in the 1990s reports survival rates of 0% to 21% for infants born at 22 weeks' gestation, 5% to 46% for infants born at 23 weeks' gestation, 40% to 59% for infants born at 24 weeks' gestation, 60% to 82% for infants born at 25 weeks' gestation, and 75% to 93% for infants born at 26 weeks' gestation.[46]

However, in recent years the emphasis has shifted from merely survival to survival without significant sequelae, especially in regard to normal growth and development. A recent article published by Tyson et al.[47] in 2008 detailed a study of survival and morbidity at 18 to 22 months in infants born between 22 and 25 weeks' gestation. The study concluded that 49% died, 61% died or had profound impairment, and 73% died or had *some* impairment. In each of the gestational age groups between 22 and 25 weeks, the mean resources use per survivor, as measured by total ventilator days and total number of hospital days, decreased with advancing gestational age and was less for females compared to their male cohorts. The same trend was also found in the survivors without profound impairment.

It is generally recognized that survival rates for infants born at 32 weeks' gestation afforded modern neonatal intensive care are essentially the same as those of infants born at term. The decade-long increase in prematurity rates in the United States has mainly been fueled by the increase in the late premature infants. It is disturbing to note that recent data on the late preterm infant have shown that even mild prematurity has a significant effect on cognitive function, with a statistically increased number of these infants having difficulties in school-related tasks.[48] Nevertheless, it is evident that the number of neonates requiring mechanical ventilation has been reduced over the last decade. Better obstetric and maternal anesthetic care, the administration of maternal corticosteroids, and improved neonatal resuscitation all contribute to healthier infants being admitted to the NICU. Larger premature infants with respiratory distress may require shorter periods of ventilation or only CPAP. The character of the NICU in the United States has changed, with many more babies receiving only noninvasive ventilation. Moreover, most of the babies on mechanical ventilation are much smaller and more immature than those who use to be ventilated before the new millennium. Today's ventilated neonates often require mechanical assistance for extended periods of time and require diligent attention to prevention of infection (including ventilator-associated pneumonia), nutrition, and other medical, developmental, and psychosocial support needs.

Unfortunately, complications associated with infants born at the lowest extremes of viability (bronchopulmonary dysplasia, blindness, and neuro-developmental disability) remain significant. The data on the incidence of major disabilities are much more difficult to analyze; these topics are dealt with in detail in subsequent chapters.

Certainly, the treatment of neonatal respiratory failure has improved dramatically over the last four decades, and many exciting developments are on the horizon. Better ventilators, improvement of surfactant formulation, and advances in monitoring equipment can be expected in the coming years. The goal of future care is the application of effective therapy without iatrogenic consequences. Even the use of 100% oxygen in the delivery room for resuscitation is being questioned, and the recent *Neonatal Resuscitation Program* manual permits the use of lower concentrations of oxygen or even room air during the initial phases of neonatal resuscitation.[49]

Despite some encouraging statistics, the United States still has one of the highest infant mortality rates of the industrialized world and much work is left to be done to increase survival and decrease morbidity of very-low-birth-weight and extremely-low-birth-weight neonates. This effort should include not only better methods of insuring that all pregnant women receive high-quality prenatal care but also programs directed at the indirect risk factors of prematurity, such as providing increased services to mothers of low socioeconomic status, preventing teenage pregnancy, decreasing alcohol, drug, and tobacco abuse in pregnancy, and in general providing early educational programs that promote good health care practices to women of conceptual age.

Five W's of Assisted Ventilation

Who: Which infants are candidates for ventilation? Who is an inappropriate candidate? What are the ethical and legal considerations?
Where: Which hospitals should undertake neonatal ventilatory assistance? What equipment and personnel are necessary?
When: When is a patient in respiratory failure? What are the causes of inadequate ventilation?
Why: Do the neurologic and physical outcomes of babies who are ventilated justify the expense, use of resources, and effort? Does the gestational age matter? What are the financial ramifications?
What: What are the types and classifications of ventilators?

Who and Why: Which Infants Are Candidates for Ventilation? The Ethics of Providing Ventilatory Support

The provision, omission, or withdrawal of ventilatory support is paramount in any discussion regarding the ethical issues of intensive medical care. It is often difficult to draw the line in regard to when care is indicated or when it would be futile. In neonatology these discussions generally surround babies in three categories: (1) those at the margins of viability in terms of extremely low birth weight or immature gestational age; (2) babies with potentially lethal congenital anomalies; and (3) babies with severe brain damage from such insults as grade 4 intraventricular hemorrhage or severe perinatal asphyxia. These ethical discussions occasionally spill over into the legal arena in the form of court interventions for the provision or denial of medical care and/or medical malpractice actions.

In recent years, the provision of ventilation has followed the ethical guidelines provided by the principles established in the Neonatal Resuscitation Program.[49] Because delivery room decisions often have to be made relatively quickly, most clinicians will err on the side of intervention until more information is known about the baby and until the family can be consulted. A major principle in this regard is that stopping ventilatory support is ethically equivalent to not starting it in the first place.

Concerning limits of viability, new data are giving some credence to the belief that under certain circumstances, care may be offered to preterm infants as early as 22 weeks' gestation.[50] It appears that singleton, female preterm infants have a 1-week survival advantage over comparable male infants from 23 to 25 weeks' gestation. Other factors that affect outcome include steroid administration to the mother, singleton or multiple gestation, and gestational age and estimated weight.[47] This data should be presented to parents when determining the advisability of resuscitation and continued ventilatory support at the margins of viability. Informed parental choice should guide the practice of delivery room resuscitation and ventilation in these circumstances unless the newborn is significantly different than the baby expected based on prenatal information. However, there are questions regarding how well parents comprehend the data they are given during often emotional prenatal counseling when they are being asked to participate in these decisions.

In general, infants with lethal anomalies would not be offered assisted ventilation once the diagnosis is known. However, often diagnoses are not made prenatally and diagnosis in the delivery room can be difficult. Moreover, certain conditions once considered lethal are now amenable to therapy (e.g., hypoplastic left heart syndrome, asphyxiating thoracic dystrophy), and ventilatory assistance may be offered until a complete discussion is held with the parents regarding the lesion, its potential treatment, and the chances for a successful outcome. In addition, the prognosis for infants with severe perinatal asphyxia has recently been altered with the provision of whole body or head cooling immediately after birth. These factors must be taken into account before withdrawing support from an affected newborn. A full discussion of the ethical issues of providing ventilatory assistance can be found in Chapter 5.

Where: Which Hospitals Should Ventilate Newborns?

Approximately 6000 hospitals in the United States deliver more than 4.2 million babies each year. About 1065 of these hospitals have neonatal intensive care units (NICUs). The National Center for Health Statistics defines an NICU as a "hospital facility or unit staffed and equipped to provide continuous mechanical ventilatory support for more than 24 hours." The complex techniques involved in the treatment of respiratory failure of the newborn require an NICU staffed by specially trained nurses; a geographically accessible full-time staff of physicians composed of neonatologists, the full complement of pediatric subspecialists, and 24-hour-per-day, 7-day-per-week, in-house coverage by staff physicians (i.e., neonatologists/hospitalists); pediatric house officers; and/or neonatal nurse practitioners.

Forty years ago the vast majority of neonatal intensive care was provided in large teaching hospitals or large community hospitals. Today sophisticated neonatal care is provided in many tertiary medical centers, as well as in many smaller hospitals that may not fulfill the expectations of a major academic center as implied by Downes[51] in 1971. The proliferation of NICUs in hospitals with relatively small delivery services or limited ancillary services that provide care for infants with severe prematurity or complex neonatal conditions is a consequence of the "deregionalization of perinatal care." Often smaller institutions will have neonatology coverage, but limited or no availability of subspecialists such as pediatric cardiologists, pediatric ophthalmologists, or pediatric surgeons. This has necessitated the use of telemedicine for the transmission of echocardiograms and other technology such as Retcams for the diagnosis of retinopathy of prematurity. Moreover, neonatal transport systems must be capable of transporting the "sickest" infants to NICUs in which the full array of pediatric subspecialists, experienced NICU nurses, respiratory therapists, and laboratory and diagnostic services is available to support these patients.

Despite the movement of neonatal services away from larger medical centers to smaller facilities (deregionalization), several professional organizations and governmental agencies have attempted to preserve the regionalized approach to perinatal care. A comprehensive report by the Committee on Perinatal Health[52] and the follow-up publication of the March of Dimes, *Toward Improving the Outcome of Pregnancy: The 90s and Beyond*,[53] promoted the concept of designating certain hospitals for the care of high-risk newborns based on each hospital's ability to provide a certain level of care. Such regionalization programs were advanced under three assumptions: that the regionalization of prenatal care (1) increased the availability of medical services; (2) decreased morbidity and mortality; and (3) decreased costs. Hospitals were traditionally designated in terms of three levels of prenatal care.[52]

Level I: Hospitals that provide services primarily for uncomplicated maternity and newborn patients.

Level II: Large urban and suburban hospitals at which the majority of deliveries occur. Because they have a highly trained staff and modern equipment, these facilities are capable of treating most perinatal complications.

Level III: Hospitals that serve a delivery population of at least 8000 to 12,000 births annually and are capable of treating all types of maternal-fetal and neonatal illnesses. A level III hospital also is responsible for the education of medical providers, transport of critically ill neonates or mothers, and evaluation of the overall quality of perinatal care in its region. Typically level III centers are designated as the perinatal center for a region.

With the expansion of neonatal care into many community hospitals, the requirements of level III hospitals have been altered in many regions. In some states, centers providing ECMO and/or heart surgery and transplantation adopted the term *level IV centers* or *regional level III centers*. These centers also became responsible for continuing education in their region and, in some cases, regionalized transport systems and quality assurance reviews as well.

In 2004, the American Academy of Pediatrics (AAP) published an expanded system for the classification of levels for neonatal care, which is now included in the *Guidelines for Perinatal Care*.[54] Level I care remained the same at the basic level. Level II care was divided into levels *IIA* and *IIB*; *IIA* was similar to previous descriptions of care and a level *IIB* facility would require additional capability to care for infants requiring CPAP and up to 24 hours of ventilatory care. Level III care was divided into three levels: A, B, and C.

Level IIIA

Provides care for infants greater than 1000 g birth weight and 28 weeks' gestation
Provides "sustained" mechanical ventilation
Performs minor surgical procedures

Level IIIB

Includes level IIIA capabilities plus the following:
- Advanced respiratory support such as inhaled nitric oxide and high-frequency ventilation
- Advanced imaging with available interpretation on "an urgent basis"
- Prompt access to full range of medical and surgical subspecialists

Level IIIC

Includes IIIB capabilities plus the following:
- Extracorporeal life support
- Open heart surgical capability

Many states have replaced the numerical designations with more descriptive terms to facilitate regionalization within the state, promote inter-facility cooperation and transfer agreements, serve as resource for determining certificates of need for creation of new facilities, and act as a basis for payments to the hospital for newborn care. Despite these attempts, tremendous diversity in the nomenclature and classification of NICUs still remains all around the country.

Blackmon, Barfield, and Stark[55] in late 2009 published the first comprehensive article that clarifies the variations in definitions, criteria, and regulatory status of neonatal services provided by hospitals in the United States. They obtained data from all 50 states and the District of Columbia related to levels of neonatal service provided throughout the country. As one might expect, this review confirmed a report published by the American Academy of Pediatrics (AAP) Section of Prenatal Pediatrics in 2000 that concluded a great deal of variation was found among states and the then 880 units that identified themselves as Level II/subspecialty or Level III/specialty NICUs.[56]

Blackmon et al.[55] summarized their findings as follows:

- Published definitions of neonatal services levels vary widely among states in specific terminology, criteria, and regulatory status.
- Many states have expanded the monographs *Toward Improving the Outcome of Pregnancy (TIOP I and II)* to three levels of perinatal care services stratification.

- Most states have enforcement mechanisms for compliance available through various state agencies despite diverse sources of the published definitions.
- Consistent definitions would be informative to all constituencies, allow fair comparison of clinical outcomes among institutions, and support state Maternal and Child Health (MCH) programs in perinatal health care systems development and quality improvement.
- Existing AAP policy statements and guidelines could serve as a resource for fostering consistency among states regarding definitions and designations of levels of perinatal care services.

This article underscores the conclusion that the lack of uniformity in defining neonatal services among states and the great variation in regulatory status of existing definitions are potential obstacles to providing the appropriate care for those infants at greatest risk for poor perinatal outcomes.

There is widespread consensus among neonatologists and other providers of neonatal care that adopting the proposals of Blackmon et. al. would be a major step in improving the quality of maternal and neonatal services in our country.

Applying the AAP guidelines, prolonged (greater than 24-hour) assisted ventilation should be limited to level III units and subspecialty NICUs. However, for many reasons, the deregionalization of care has fostered a proliferation in the number of NICUs,[57] all of which want to offer a full array of neonatal services, including assisted ventilation. Although many IIIA units ventilate infants according to these guidelines, the lack of subspeciality availability and expertise, especially in imaging interpretation, may affect the achievement of optimal outcomes.

Weight-specific outcomes for ventilated babies vary greatly among hospitals. Large variances exist among level III hospitals in respect to survival and especially morbidities of ventilated very-low-birth-weight (VLBW) infants. Data from the Vermont Oxford Network (VON) of over 600 hospitals noted an average incidence for BPD of 34% in 2007 for this population. However, the VON database reported a varying incidence of BPD from 5% to 65% in level III hospitals caring for babies whose birth weight is 400 to 1500 g.[58] Similar large variances are seen in almost all outcome categories and cannot be accounted for by differences in the neonatal population being served. Third-party payors and other governmental agencies have noted these variances and taken steps to improve outcomes and decrease variances among similar hospitals caring for comparable groups of babies. Some attempts to improve outcomes by limiting care to certain hospitals have resulted in the formation of industry and insurance company advisory groups such as the Leapfrog Group that, among other issues, has tried to mobilize health care purchasers to reward improvements in patient safety and consumer value in health care.

The tremendous growth in the number of NICUs in community hospitals has occurred for a number of reasons. The growing number of neonatologists graduating from more than 100 fellowship training programs in the United States has increased the availability of such physicians to community hospitals. Experience in some well-prepared and well-staffed community hospitals has demonstrated survival results with ventilated babies that are similar to those reported by university centers.[59] However, morbidity outcomes in these comparisons are not reported. Neonatal care is a highly visible activity that generates good public relations; thus community hospitals, which operate in a competitive environment, wish to demonstrate to their potential consumers that all services can be provided. Obstetricians not wishing to transfer high-risk expectant mothers to other facilities have put pressure on hospital administrators to hire neonatologists at level II and community level III centers.[60] Moreover, if indigent patients are excluded (or at least limited), NICUs can be highly profitable for individual hospitals and private practicing physicians.

Medico-legal considerations have undoubtedly caused many obstetricians to demand hospital administrators provide delivery room coverage by neonatologists, pediatric hospitalists, or nurse practitioners for cesarean sections or unexpected high-risk deliveries. However, in response to the changing patterns of reimbursement that started in the 1990s, there may be a shift away from the concept of deregionalization because small hospitals that provide expensive neonatal care in a limited number of intensive care beds are finding it difficult to compete with larger institutions because of low census and high staffing costs.

Providers in level I hospitals argue that if they transfer all sick newborns to level II and level III centers, they will lose the skills necessary for the management of neonatal respiratory emergencies.[60] Moreover, on occasion, no beds are available at the perinatal center or conditions preclude transport. Under such circumstances, the level I and II hospitals must ventilate infants until transport can be arranged. This dilemma does not have an easy solution, but the following basic principles may apply:

1. All hospitals with delivery services should have resources for adequate resuscitation to include intubation and the maintenance of assisted ventilation for up to 8 hours.
2. No infant should be more than 4 hours away from neonatal intensive care with appropriate transport.
3. Every infant should have access to optimal respiratory care, regardless of financial or geographic considerations.

The skills necessary to successfully carry out prolonged assisted ventilation cannot be learned easily, nor can they be maintained with limited numbers of ventilatory cases. All personnel (physicians, nurses, and respiratory therapists) must be extensively trained for all aspects of ventilatory assistance so that optimal outcome can be achieved.

Data collected as far back as 1980 confirmed that hospitals ventilating fewer than 50 babies per year demonstrated twice the mortality of level III larger centers in the same area (all level III hospitals at that time ventilated more than 50 babies per year). These data have been validated by more recent studies that documented enhanced survival and fewer morbidities for infants cared for in level III perinatal centers.[61,62] More recently, Phibbs et al.[63] concluded that mortality rates among VLBW infants varied according to both the volume of patients and the level of care at the delivery hospital. In hospitals with less than 100

VLBW cases per year, the odds ratio for death ranged from 1.19 to 2.72 more than hospitals with greater than 100 cases per year. The researchers concluded that mortality among VLBW infants was lowest for deliveries that occurred in hospitals with NICUs that had both a high level of care and a high volume of such patients.

The responsibility for improved pregnancy outcome rests with obstetricians, as well as with pediatricians and neonatologists. Responsible prenatal health care professionals should encourage the transport of a high-risk mother and her unborn fetus to a level III center for the delivery and subsequent care of the neonate. Studies comparing VLBW infants (less than 1500 g) born outside level III centers with those born in level III hospitals have shown shorter hospital stays,[64] lower costs per survivor,[64] and reduced morbidity and mortality[63,65,66] for the inborn infants. These differences are accentuated when patients require assisted ventilation. Spitzer et al.[67] evaluated out born and inborn infants with RDS and found that inborn infants had significantly lower mean maximal FIO_2, decreased duration of required O_2 administration, lower peak inspiratory pressure, and shorter duration of IPPV.

The qualifications of personnel and types of equipment necessary to maintain infants on assisted ventilation are the subjects of considerable discussion. Guidelines have been written and debated throughout the country. A modified rating system initially devised by Indyk and Cohen[68] (Table 1-1) describes some of the necessary qualifications of units that are to undertake intensive care measures such as mechanical ventilation. Although the scoring system has long since been abandoned, evaluation of the ventilatory capability of an institution can start by reviewing this table and determining how the unit measures up. The most important aspect of prolonged ventilatory care, however, is the continuous presence of skilled personnel. A person able to perform endotracheal intubation, chest tube placement, and cardiopulmonary resuscitation must be in the hospital at all times.[69] Complications such as dislodgment of the endotracheal tube or pulmonary air leaks occur suddenly, often without warning, and require immediate correction. Often a patient cannot wait for a physician to be summoned from the office or home. Assigning the responsibility for such emergencies to untrained or uncertified staff nurses, respiratory therapists, or inexperienced emergency room physicians is not justified at the present time, when more appropriate resources are available.

Further information regarding what personnel and equipment requirements a hospital should satisfy if it is to

TABLE 1-1 Modified Indyk-Cohen (INCO) Rating System for Neonatal Intensive Care Units that Ventilate Newborns[52]

Category	2 points	1 point	0 points
Nursing ratio (Nurses:patients) for ventilated infants	1:1	1:2	1:3 or less
Nursing education	Full time in-service coordinator; formal courses given frequently	Infrequent formal courses	Apprentice program
Director of unit	Full time neonatologist with no other responsibilities	Part-time neonatologist	Pediatrician
Respiratory care	Respiratory therapist(s) assigned exclusively to unit	Respiratory therapist in hospital at all times	Less than full-time coverage
Availability of surgical coverage	Pediatric surgeon immediately available	24-hour availability of general surgeon	Less than full-time coverage
In-house personnel responsibilities (gases, radiography, ventilation)	Physician or nurse practitioner in unit on 24-hour basis; can run ventilators, read radiographs, interpret gases	Nurse or respiratory therapist for this function with physician outside hospital	No formal plan
Enthusiasm and awareness of new ideas	Up-to-date, studies ongoing, quality improvement programs	Aware, not innovative, no research, not measuring outcomes	No awareness or activity
Availability and types of monitoring equipment	Virtually unlimited including pulse oximetry, capnography, and pulmonary functions	Standard monitoring without pulmonary function availability	Complete monitoring package not available for all patients
Availability of subspecialists (pediatric neurologist, cardiologist, radiologist)	24-hour availability of all specialists	Some specialists available	No pediatric subspecialist coverage
Data collection and analysis	Computerized records, data analysis, quality improvement program	Some statistical collection	No collection and follow-up
Laboratory services (blood gases)	Available in unit	Available within 15 minutes	Takes longer than 15 minutes
Radiography	Portable machine in unit; computerized files available in clinical area; pediatric radiologist	Machine available from central services; general radiologist	Slow response of portable x-ray
Transport	Two-way transport with dedicated team	One-way transport from referring hospital	No special neonatal transport protocol
Ancillary services	Dedicated pharmacist, nutritionist and social worker	Lacking one service dedicated to unit	Lacking two or more services

Units performing prolonged ventilation should achieve score of ≥25 points.
Modified from Indyk L, Cohen S.[52]

provide a certain level of perinatal and neonatal care can be found in the most recent *Guidelines for Perinatal Care,* sixth edition,[54] published by The American College of Obstetricians and Gynecologists and the American Academy of Pediatrics in 2007.

Transport systems are equipped and staffed to be capable of stabilizing infants in referring hospitals and moving them to health care centers safely. Hospital, community, and physician pride or economic considerations should not prevent the provision of optimal care to all infants.

When: Causes of Respiratory Failure and Indications for Ventilation

Although there are many reasons for beginning assisted ventilation in neonates, the most common is respiratory failure. In any infant, this condition may take one of two forms. The first is apnea, a condition in which mechanical ventilation is necessary because a patient does not breathe. If the lungs are normal, the cause most often is related to the control of respiration by the central nervous system. Potential causes include apnea of prematurity, asphyxia, intracranial hemorrhage, and drug overdose.

In the second form of respiratory failure, the mechanism of pulmonary gas exchange has been compromised. The cause most often is a primary lung disease (e.g., RDS) or an airway disease. In these instances, physiologic alterations in gas exchange cause acidosis, hypercapnia, and hypoxemia. If organ damage or death is to be prevented, mechanical assistance is required.

The classic constellation of findings in respiratory failure consists of an acute increase in the partial pressure of arterial carbon dioxide ($PaCO_2$) and a decrease in pH. The presence of hypoxemia by itself does not indicate respiratory failure, as illustrated by patients with cyanotic congenital heart disease. Respiratory failure may be caused by the failure of organ systems other than the central nervous system and the lungs (Table 1-2). When the lungs are primarily responsible, however, it is important to make a simplistic distinction between two physiologic types of lung disease: atelectatic disease and obstructive disease (Table 1-3).

An atelectatic disease is characterized by decreased lung volume and decreased functional residual capacity. Examples are RDS and pneumonia. Increased lung volumes and increased functional residual capacity, as seen in aspiration syndromes and bronchopulmonary dysplasia (BPD), characterize an obstructive disease. In many pulmonary conditions, both types of disease exist (e.g., RDS in combination with pulmonary air leaks). Even though the physiologic distinction is not absolute, it may be important for the clinician to make such a distinction before he or she addresses the criteria for the initiation of assisted ventilation, the choice of ventilator, or the parameters of ventilator control.

The physician can make a diagnosis of respiratory failure guided by both clinical manifestations and the results of blood gas analysis. Clinically, the physician should look for the following signs:

1. Increase in respiratory rate
2. Decrease in respiratory rate accompanied by increasing effort or increasing retractions
3. Prolonged apnea with cyanosis, bradycardia, or both
4. Cyanosis not relieved by O_2 administration
5. Hypotension, pallor, and decrease in peripheral perfusion
6. Tachycardia (leading to bradycardia)
7. Gasping, and the use of accessory respiratory muscles
8. Periodic breathing with prolonged respiratory pauses

TABLE 1-2 Causes of Respiratory Failure

Problem Area	Possible Causes
Pulmonary	Respiratory distress syndrome
	Aspiration syndromes
	Pneumonia
	Pulmonary hemorrhage
	Pulmonary alveolar proteinosis
	Wilson-Mikity syndrome
	Bronchopulmonary dysplasia
	Pulmonary insufficiency of prematurity
	Pneumothorax
	Tumor
	Diaphragmatic hernia
	Chylothorax
	Congenital malformations (lobar emphysema, cystic adenomatoid malformation, lymphangiectasis)
Airway	Laryngomalacia
	Choanal atresia
	Pierre Robin syndrome
	Micrognathia
	Nasopharyngeal tumor
	Subglottic stenosis
Abnormalities of muscles of respiration	Phrenic nerve palsy
	Spinalcord injury
	Myasthenia gravis
	Werdnig-Hoffmann syndrome
Central problems	Apnea of prematurity
	Drugs: morphine, magnesium sulfate, mepivacaine, meperidine
	Seizures
	Birth asphyxia
	Hypoxic encephalopathy
	Intracranial hemorrhage
	Ondine's curse
	Rapid eye movement sleep
Miscellaneous	Congestive heart failure
	Persistent fetal circulation
	Postoperative anesthesia/sedation
	Tetanus neonatorum
	Extreme immaturity
	Shock
	Sepsis
	Hypoglycemia
	Electrolyte abnormalities
	Acid-base imbalance
	Infant botulism
	Hydrops fetalis

The Silverman-Anderson[70] retraction score has also been helpful in evaluating respiratory distress (Fig. 1-7). A score of 7 or greater indicates impending respiratory failure. Although the score is not frequently used today, it is a consistent, fairly reproducible and logical way of communicating the severity of respiratory symptoms between caretakers such as nurses or physicians who are responsible for the baby during sequential periods of time. Moreover, in resource limited settings, the score may be used in lieu of repeated blood gas analysis.

TABLE 1-3 Theoretical Classification of Neonatal Pulmonary Disorders

	Atelectatic	Obstructive
Example	Respiratory distress syndrome	Meconium aspiration syndrome
Physiology	↓ Lung volume	↑ Lung volume
	↓ Compliance	↓ Compliance
	↓ Functional residual capacity	↑ Functional residual capacity
	Normal airway resistance	↑ Airway resistance
	Normal time constant	↑ Time constant
Clinical appearance	Severe retractions; pectus excavatum	↑ Anteroposterior diameter
	Prematurity—common	Term or post term—common
Management	Early positive-pressure ventilation	Avoid positive-pressure ventilation
	Correct hypoventilation	Avoid overventilation
	Pulmonary air leaks: <10%	Pulmonary air leaks: ≥20%
	Persistent pulmonary hypertension—rare	Persistent pulmonary hypertension—common

↓, Decreased; ↑, increased.

Blood gas analysis can be used to identify candidates for ventilatory assistance and mechanical ventilation. The selection criteria differs from center to center. Moreover, the benchmark criteria has been subject to change as the techniques of ventilatory support have changed over recent years. On the one hand, the improved ability to use assisted ventilation resulting in enhanced outcomes and decreased complications has resulted in less rigid indications for initiation of mechanical support. For example, the indications of Gregory et al.[27] for CPAP administration in 1971 was a Pa_{O_2} less than 50 mm Hg in 100% O_2. Today, many centers would begin CPAP or assisted ventilation in extremely-low-birth-weight infants (less than 1000 g) at birth or in infants with atelectatic disease who cannot maintain Pa_{O_2} greater than 50 mm Hg in 40% to 60% F_{IO_2}. Although there is general consensus that Pa_{O_2} less than 50 mm Hg is unsatisfactory, there is considerable debate on what maximal inspired O_2 should be used before CPAP or mechanical ventilation is initiated. The early application of CPAP or positive end-expiratory pressure (PEEP) has become common therapy in premature infants in order to develop or maintain a functional residual capacity in the face of possible surfactant deficiency. When positive pressure with end-expiratory pressure is not started at birth, initiation of ventilatory support at an inspired oxygen level of 40% to 60% is chosen for two reasons. First, O_2 toxicity to the lungs increases with higher inspired O_2 concentration, and "early" respiratory assistance may allow the use of lower oxygen concentrations and decrease the total duration of oxygen therapy.[71,72]

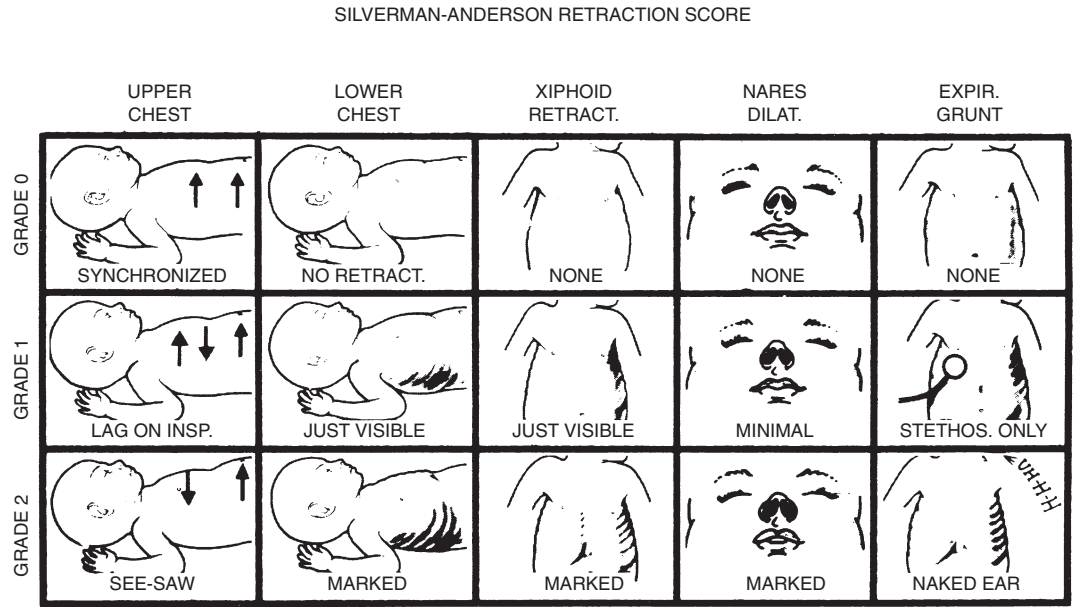

Figure 1-7 ■ Index designed to provide continuous evaluation of an infant's respiratory status. An index of respiratory distress is determined by grading each of five arbitrary criteria: chest lag, intercostal retraction, xiphoid retraction, nares dilatation, and expiratory grunt. The "retraction score" is computed by adding the values (0, 1, or 2) assigned to each factor that best describes the infant's condition at the time of a single observation. A score of zero indicates the absence of respiratory distress; a score of 10 indicates severe respiratory distress. *DILAT,* dilatation; *EXPIR,* expiratory; *INSP,* inspiration; *RETRACT,* retraction; *STETHOS,* stethoscope. (Adapted from Silverman WE, Andersen DH: Controlled clinical trial of effects of water mist on obstructive respiratory signs, death rate, and necroscopy findings among premature infants. Pediatrics 171:1,1956, with permission of Pediatrics.)

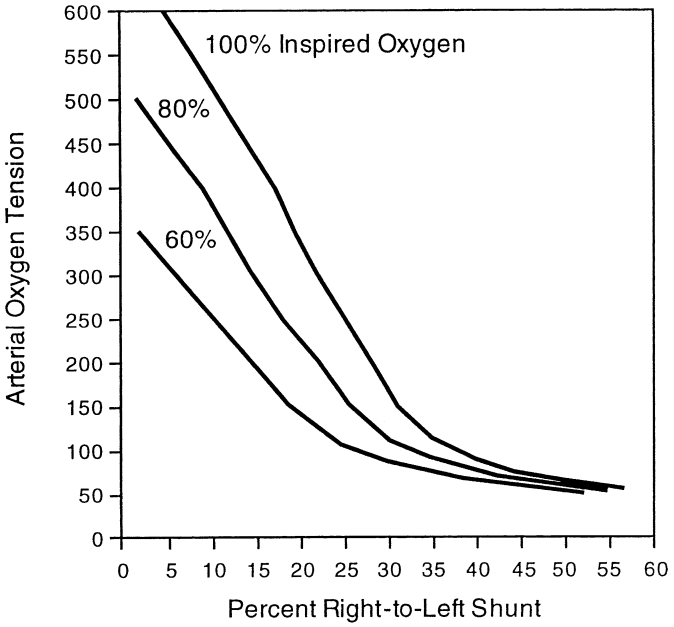

Figure 1-8 ■ Graph for estimating the shunt at different inspired O_2 mixtures. Calculations were based on an assumed hemoglobin concentration of 16 g per 100 mL, arteriovenous difference of 4 vol %, respiratory quotient of 0.8, and $PaCO_2$ of 40 mm Hg. The graph was constructed with the aid of a Severinghaus nomogram.

Second, in most infants with respiratory failure, intrapulmonary and intracardiac right-to-left shunting are the primary causes of hypoxemia. If the shunt is greater than 30%, an increase in FIO_2 from 60% to 100% should have very little effect on PaO_2 (Fig. 1-8).[73]

The CO_2 criteria for initiation of mechanical support has also seen significant change over the last decade. Previous admonitions to avoid respiratory acidosis have been replaced with the concept of "permissive hypercapnia," allowing PCO_2 levels to be as high as 70 mm Hg or higher as long as the pH remains above 7.20 and there is no organ system dysfunction.

The infant's gestational age, postnatal age, weight, and disease are factors that should be considered in the determination of criteria for respiratory failure, especially when that is defined by blood gas analysis. Generally, a pH less than 7.25, PaO_2 less than 50 mm Hg, and $PaCO_2$ greater than 60 mm Hg in 60% O_2 indicate the need for some form of respiratory assistance. This may be accomplished by noninvasive support such as nasal CPAP without the need for intubation and mechanical ventilation unless there is significant apnea. It should be remembered that the normal intrauterine umbilical artery pH after labor and a vaginal delivery is approximately 7.25.[74] Thus blood gases obtained immediately after vaginal birth must be interpreted with awareness of the normal physiologic adaptation process.

Previously clinicians have recommended that the $PaCO_2$ criteria for ventilatory assistance should be lowered to values greater than 50 mm Hg for VLBW infants because respiratory acidosis may increase the incidence of intraventricular hemorrhage.[75] A contrary view is held by many neonatologists and promoted by the group at Columbia University, where pH is allowed to decrease to 7.25 or lower and $PaCO_2$ to increase to 55 to 65 mm Hg (permissive hypercapnia), resulting in a marked decrease in BPD, similar mortality rates, and no apparent increase in intraventricular hemorrhage or neurologic sequelae.[39] This concept is discussed more fully in Chapters 8 and 15. CPAP failure, and thus the need for mechanical ventilation, is indicated in acute disease by the presence of $PaCO_2$ greater than 60 to 65 mm Hg, pH less than 7.20 in 60% to 100% O_2 while administering a distending pressure of 8 to 10 cm H_2O (depending on the CPAP system).

Criteria should also be modified by the pathophysiology of the disease process. In atelectatic disease with decreased lung volume (e.g., RDS), CPAP or IMV may be initiated early to increase lung volume, provide alveolar stabilization, and increase functional residual capacity. In such diseases, many clinicians initiate CPAP at birth.[39,76] However, in obstructive disease (e.g., aspiration syndrome), an attempt is made to avoid positive pressure and provide ambient O_2 up to high concentrations before intubation is considered. The incidence of pulmonary air leaks can be high when infants with obstructive lung disease are ventilated.[77] Although each case should be evaluated individually, a scoring system may be used to select infants with pulmonary disease based on the results of blood gas analysis. (Table 1-4). Indications for assisted ventilation are (1) a score of 4 or greater, (2) PaO_2 less than 50 mm Hg in 60% O_2 in the absence of cyanotic heart disease, or (3) CPAP failure (i.e., CPAP of 8-10 cm H_2O at 100% FIO_2).

Decisions to institute assisted ventilation should be made after the risks and benefits have been evaluated; they should not be based on blood gas criteria alone. For example, significant compensated hypercapnia in a patient with severe BPD would not warrant intubation, whereas significant uncompensated hypercapnia in acute early RDS would generally be treated with some form of positive pressure (CPAP or IMV). Even in the presence of near-normal blood gas values, certain conditions may necessitate ventilator support. A trend of deterioration in an extremely-low-birth-weight infant may indicate the need for respiratory assistance, even though severe hypercapnia and acidosis are not yet present. In addition, repeated episodes of prolonged apnea unresponsive to other measures (i.e., methylxanthine administration, cutaneous stimulation) and associated with bradycardia or cyanosis

TABLE 1-4 Blood Gas Scoring System for Initiating Assisted Ventilation in Acute Neonatal Disease*†

	POINTS			
	0	**1**	**2**	**3**
PaO_2 (mm Hg)	>60	50-60	<50‡	<50‡
pH	>7.30	7.20-7.29	7.1-7.19	<7.1
$PaCO_2$ (mm Hg)	<50	50-60	61-70	>70

*A score of 4 or more indicates need for CPAP or IMV.
†Ambient oxygen failure → CPAP
CPAP failure (CPAP 10 cm H_2O and 100% FIO_2) → IMV
‡May indicate need for CPAP or IMV by itself, if cyanotic heart disease is not present.
CPAP, Continuous positive airway pressure; *IMV*, intermittent mandatory ventilation.

should be treated with high flow nasal cannulae, CPAP, or assisted ventilation. Many infants may be placed on ventilatory assistance early in the course of progressive atelectatic disease to reduce the work of breathing and, theoretically, to conserve surfactant by alveolar stabilization before absolute criteria are met. VLBW infants may be intubated and placed on assisted ventilation before criteria are met so that exogenous surfactant therapy can be initiated immediately after birth. Furthermore, clinical judgment and the experience of the clinician may dictate when intubation and mechanical ventilation are initiated. The criteria for the initiation of artificial surfactant therapy are discussed in detail in Chapter 22.

What: Types and Classification of Mechanical Ventilators

The classification of ventilators can be confusing because it may be based on the pressure relationship to the patient, the cycling mode, the power source, or the ventilatory rate (Box 1-2). The following approach, although somewhat simplistic, should serve as an introduction to the later discussions on specific ventilators, techniques, and ventilatory strategies.

Mechanical ventilation can be achieved through the use of intermittent negative-pressure or positive-pressure devices. Negative-pressure ventilators are mainly of historical interest and represent only a small percentage of machines currently in use in the United States. Negative-pressure respirators can provide assisted ventilation without the need for endotracheal intubation; thus trauma to the airway is avoided and the risk of infection is reduced. They can also provide effective continuous negative pressure.[78] The only commercially available equipment for newborns, the Isolette Respirator (Airshields, Inc., Hatboro, PA, USA), is no longer manufactured. In the early 1990s, this form of ventilation experienced a minor resurgence of interest because of reported success in the ventilation of infants with persistent pulmonary hypertension who met ECMO cannulation criteria.[79] The Isolette Respirator has not been proven effective in the ventilation of VLBW infants, who represent the largest group of the NICU population. Comparison of the advantages and disadvantages of negative-pressure ventilators is presented in Table 1-5.

Modes of mechanical ventilation can be classified by three factors: (1) how each breath is initiated, (2) how gas flow is controlled during breath delivery, and (3) how the breath is terminated. In controlled ventilation, breaths are initiated by a timing device without regard to the patient's respiratory efforts. Synchronized or patient-triggered ventilation occurs when breaths are initiated by the patient and then assisted or augmented by the ventilator (see Chapter 12); gas flow during the breath may be controlled by pressure (the amount of pressure set on the ventilator to deliver the breath) or by volume (the set volume delivered per breath). The termination of each breath (i.e., the cycling mode) is often used to classify positive-pressure devices.

Box 1-2 CLASSIFICATION OF NEONATAL VENTILATORS

- By pressure relationship to patient (positive or negative)
- By cycling mode (at termination of inspiration)
- By power source
- By rate

TABLE 1-5 Negative-Pressure Ventilators

Advantages	Disadvantages
Less pulmonary O_2 toxicity (bronchopulmonary dysplasia)	High cost
Doubles as an incubator	Patient inaccessible for routine procedures and resuscitation
Decrease in pulmonary infections	Cooling of infants
Decrease in atelectasis	Neck abrasions
Decrease in pulmonary air leaks	Monitoring of pulmonary status based on blood gas analysis is more difficult
Decrease in airway trauma	Patient usually removed for radiography
May be effective in persistent pulmonary hypertension of the newborn	Decreased airway patency in neurologically depressed infants
	Compression of trunk during inspiration decreases effectiveness
	Not effective for very-low-birth-weight infants (<1500 g)

There are six basic types of cycling[80]:

1. *Volume cycling:* Inspiration ends when a certain volume is reached
2. *Pressure cycling:* Inspiration ends when a preset pressure is reached
3. *Time cycling:* Inspiration ends when a preset time is reached
4. *Flow cycling:* Inspiration ends when flow has reached a critical low level
5. *Mixed cycling:* Two or more independent cycling mechanisms are present in the same ventilator
6. *High-frequency ventilation:* Ventilator is capable of cycling at rates greater than 150 breaths per minute

The vast majority of positive-pressure neonatal ventilators fall under the first three categories. Chapter 9 discusses pressure-cycled and time-cycled ventilators, and Chapter 10 addresses volume-cycled ventilators.

A surge of interest that began in the 1980s has led to the development of a new class of ventilators that cannot be classified based on conventional mechanical ventilation criteria. Because of respiratory complications, including oxygen toxicity, barotrauma, and cardiovascular compromise, high-frequency ventilation (HFV) has been tried as an alternative to conventional mechanical ventilation when the latter has failed. HFV now is being used in many centers in the United States, either as a rescue device when conventional mechanical ventilation fails or occasionally as the primary device to treat RDS in VLBW infants. Currently there are three major types of HFV: (1) high-frequency positive-pressure ventilation, which is produced by conventional or modified conventional mechanical ventilators operating at rapid rates; (2) high-frequency jet ventilation, which is produced by ventilators that deliver a high-velocity jet of O_2 or gas directly into the airway; and (3) high-frequency oscillation, which moves air back and forth at the airway opening and produces a minimum of

bulk gas flow. HFV is not a specific type of ventilator but rather a pattern of ventilation that uses very high rates such that tidal volumes are less than or equal to the patient's anatomic dead space.[81] This mode of ventilation is discussed in more detail in Chapter 11.

In pressure-cycled, time-cycled, and volume-cycled ventilation, compliance varies pressure and volume as independent variables. Compliance equals that unit of volume change produced by a unit of pressure change ($cm^3/cm\ H_2O$). In volume-cycled ventilation, identical volumes delivered to two infants generate greater pressure in the infant with poorer compliance. In pressure-cycled ventilation, identical peak inspiratory pressures delivered to two infants result in greater tidal volumes in the infant with better compliance; also, the infant with poor compliance has a shorter inspiratory time. If time-cycled ventilators are not pressure limited, the volume of gas delivered to the infant is determined by inspiratory time and gas flow. Long inspiratory times and high gas flows generate increased volumes and pressures. In the case of identical inspiratory times and gas flow in two infants, the infant with the poorer compliance receives less volume and greater pressure, as shown in Figure 1-9.[82] Physiologic principles of mechanical ventilation are discussed in Chapter 2.

Devices can be added to the ventilator that prevent excessive pressure or volume as the compliance of an infant's lung changes. A pressure-limiting device regulates the maximal pressure by means of a pop-off valve. A volume-limiting device allows the ventilator to deliver less (but never more) than a specified amount. In all three types of positive-pressure ventilators, tidal volume is determined by lung compliance and, if present, a pressure-limiting device.

Ventilators also can be classified according to the manner in which they control ventilation, often termed the *ventilator mode*. To start inspiration, the machine can be triggered by the patient (assistor type), by the ventilator only (controller type), or by both the patient and the ventilator (assistor-controller type). In assistor-controller ventilators, a device allows the patient to initiate some respirations; however, it also has a predetermined frequency of IMV that can be used as backup. In neonatal ventilators, the assistor device must be extremely sensitive to the slightest inspiratory effort. IMV, with or without an assistor device, has become an important aspect of neonatal ventilation, especially during weaning from respiratory support. Standard neonatal ventilators have incorporated synchronized IMV, pressure support, or both in their cycling modes. Synchronized IMV generates breaths that do not stack on top of or combine with the patient's spontaneous breaths while maintaining a preset rate as a background for periods of patient apnea. Pressure support ventilation provides a preset gas flow in which each breath is completely spontaneous (i.e., it is patient triggered). These modes of ventilation are discussed in Chapter 12. Novel modes of synchronized ventilation include proportional assist ventilation that regulates inspiratory pressure in proportion to patient effort and is useful in infants with poor lung compliance and high airway resistance. Another experimental mode is neurally adjusted ventilator assist that uses the patient's own respiratory effort transmitted from bipolar electrodes mounted on a feeding tube in the esophagus to drive the ventilator.

The power source for the ventilator can be either pneumatic (i.e., gas powered) or electrical. Other devices can be added to the ventilator for flow pattern and exhalation classification. The delivery of PEEP is widely used in neonatal ventilation for maintaining CPAP and improving oxygenation. With a PEEP device, the patient is allowed to exhale, but the expiratory pressure never reaches zero; thus functional residual capacity is increased, and the patient is able to retain a large amount of gas in the alveoli.

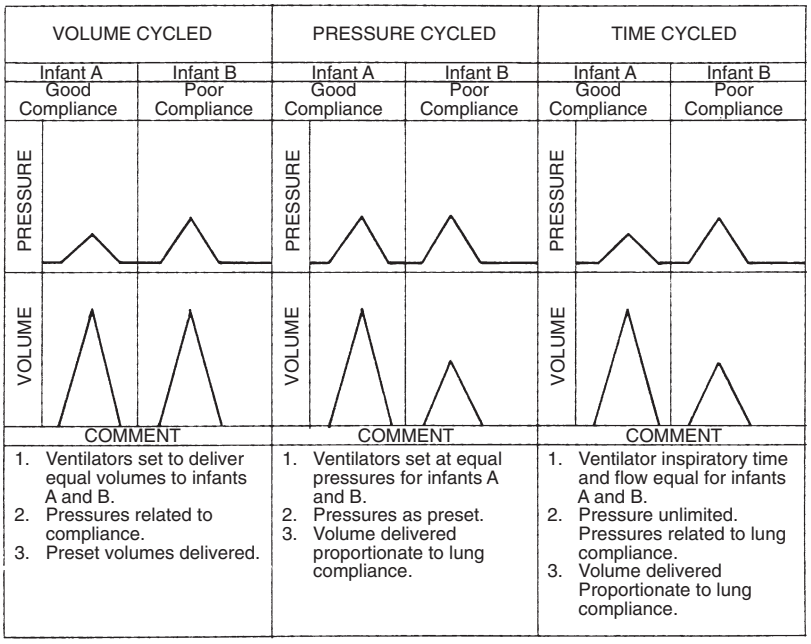

Figure 1-9 ■ Diagrammatic pressure and volume curves generated in infants with different compliance on volume-cycled, pressure-cycled, and time-cycled ventilators. (From Gottschalk SK, King B, Schuth CR: Basic concepts in positive pressure ventilation of the newborn. Perinatol Neonatol 4:15, 1980.)

Dozens of conventional neonatal ventilators are commercially available. None of them is perfect for the complete management of every type of respiratory disease. Many of the newer ventilators are quite complex and often can be used for patients from the extremely-low-birth-weight neonate to adults. This adds complexity to the ventilator, issues of proper use and operator knowledge of the controls, and obvious safety issues. Human factors when interacting with such a complex device are becoming a significant concern as the complexity of the devices increases. At a minimum, a satisfactory neonatal ventilator should fulfill the following requirements:

1. All modes of ventilation should be possible, including IMV, CPAP, PEEP, and some form of synchronized IMV, assistor-controller ventilation, or pressure support ventilation.
2. The ventilator should have simple controls and be easy to operate.
3. The ventilator should be reliable (i.e., have few mechanical failures).
4. The machine should be relatively quiet, small, and "inexpensive."
5. The conventional ventilator should offer a wide range of respiratory rates up to 150 breaths per minute.
6. Fi_{O2} concentrations should be adjustable and accurate (from 21% to 100%).
7. The ventilator should possess a low compliance system both inside and outside.
8. The conventional ventilator should accurately deliver a wide range of tidal volumes (2-100 mL).
9. The ventilator should have a quick response time.
10. The device should have an alarm system(s) (visual and audible) to warn about mechanical failures or patient disconnects.
11. The system should offer user-variable flow rates that remain constant at a set flow.
12. The ventilator should be able to adequately humidify and heat inspired gas (60% humidity at 37° C).
13. Variable-pressure or volume-limiting devices should be available.
14. The device should offer a wide range of pressure or volume capacities.
15. The ventilator should have the capacity to digitally and/or graphically read out a variety of pulmonary function parameters.

Appendix 1 compares commonly used ventilators classified by pressure characteristic, cycling mode, power source, and rate and also lists the principles of operation, advantages, and disadvantages.

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2 Physiologic Principles

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Knowledge of the unique physiology and pathophysiology of the respiratory system of newborn infants forms the foundation of individualized care that optimizes pulmonary and neurodevelopmental outcomes in our vulnerable patients. It is the responsibility of those who care for critically ill infants to have a sound understanding of respiratory physiology, especially the functional limitations and the special vulnerabilities of the immature lung. The first tenet of the Hippocratic Oath states, "Primum non nocere" ("First do no harm"). That admonition cannot be followed without adequate knowledge of physiology. In daily practice, we are faced with the difficult task of supporting adequate gas exchange in an immature respiratory system, using powerful tools that by their very nature can inhibit ongoing developmental processes, often resulting in alterations in end-organ form and function.

In our efforts to provide ventilatory support, the infant's lungs and airways are subjected to forces that lead to acute and chronic tissue injury. This results in alterations in the way the lungs develop and the way they respond to subsequent noxious stimuli. Injury leads to alterations in lung development, which result in alterations in lung function as the infant's body attempts to heal and continue to develop. Superimposed on this is the fact that the ongoing development of the respiratory system is hampered by the healing process itself.

This complexity makes caring for infants with respiratory failure both interesting and challenging. To effectively provide support for these patients, the clinician must have an understanding not only of respiratory physiology but also of respiratory system development, growth, and healing.

Although the lung has a variety of functions, some of which include the immunologic and endocrine systems, the focus of this chapter is its primary function, that of gas exchange.

Basic Biochemistry of Respiration: Oxygen and Energy

The energy production required for a newborn infant to sustain his or her metabolic functions depends upon the availability of oxygen and its subsequent metabolism. During the breakdown of carbohydrates, oxygen is consumed and carbon dioxide and water are produced. The energy derived from this process is generated as electrons, which are transferred from electron donors to electron acceptors. Oxygen has a high electron affinity and therefore is a good electron acceptor. The energy produced during this process is stored as high-energy phosphate bonds, primarily in the form of adenosine triphosphate (ATP). Enzyme systems within the mitochondria couple the transfer of energy to oxidation in a process known as *oxidative phosphorylation*.[1]

For oxidative phosphorylation to occur, an adequate amount of oxygen must be available to the mitochondria. The transfer of oxygen from the air outside the infant to the mitochondria, within the infant's cells, involves a series of steps: (1) convection of fresh air into the lung, (2) diffusion of oxygen into the blood, (3) convective flow of oxygenated blood to the tissues, (4) diffusion of oxygen into the cells, and finally, (5) diffusion into the mitochondria. The driving force for the diffusion processes is an oxygen pressure gradient, which, together with the convective processes of ventilation and perfusion, results in a cascade of oxygen tensions from the air outside the body to intracellular mitochondria ( ). The lungs of the newborn infant transfer oxygen to the blood by diffusion, driven by the oxygen partial pressure gradient. For gas exchange to occur efficiently, the infant's lungs must remain expanded, the lungs must be both ventilated and perfused, and the ambient partial pressure of oxygen in the air must be greater than the partial pressure of the oxygen in the blood.. The efficiency of the newborn infant's respiratory system is determined by both structural and functional constraints; therefore, the clinician must be mindful of both aspects when caring for the infant.

The infant's cells require energy in order to function. This energy is obtained from high-energy phosphate bonds (e.g., ATP) formed during oxidative phosphorylation. Only a small amount of ATP is stored within the cells. Muscle cells contain an additional store of ATP, but to meet metabolic needs beyond those that can be provided for by the stored ATP, new ATP must be made by phosphorylation of adenosine diphosphate (ADP). This can be done anaerobically through glycolysis, but this is an inefficient process and leads to the formation of lactic acid. Long-term energy demands must be met aerobically, through ongoing oxidative phosphorylation within the mitochondria, which is a much more efficient process that results in the formation of carbon dioxide and water.

*Acknowledgement: We wish to acknowledge gratefully the important contribution of Brian Wood, MD, who was the author of this chapter in the previous editions of this textbook..

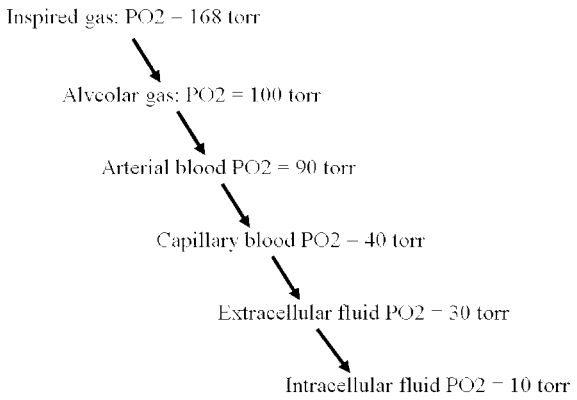

Figure 2-1 Transfer of oxygen from outside air to intracellular mitochondria via an oxygen pressure gradient: Oxygen tension at different levels of the O_2 transport Chain.

There is a hierarchy of how energy is used by the infant. During periods of high-energy demand, tissues initially draw upon the limited stores of ATP, then use glycolysis to make more ATP from adenosine diphosphate (ADP), and then use oxidative phosphorylation to supply the infant's ongoing energy requirements. Oxidative phosphorylation and oxygen consumption are so closely linked to the newborn infant's energy requirements that total oxygen consumption is a reasonably good measure of the total energy needs of the infant. When the infant's metabolic workload is in excess of that which can be sustained by oxidative phosphorylation (aerobic metabolism), the tissues will revert to anaerobic glycolysis to produce ATP. This anaerobic metabolism results in the formation of lactic acid, which accumulates in the blood and causes a decrease in pH (acidosis/acidemia). Lactic acid is therefore an important marker of inadequate tissue oxygen delivery.

Ontogeny Recapitulates Phylogeny: A Brief Overview of Developmental Anatomy

Lung Development

The tracheobronchial airway system begins as a ventral outpouching of the primitive foregut, which leads to the formation of the embryonic lung bud. The lung bud subsequently divides and branches, penetrating the mesenchyma and progressing toward the periphery. Lung development is divided into five phases. The demarcation between these phases is somewhat arbitrary with some overlap between them. A variety of physical, hormonal, and other factors impact the pace of lung development and maturation. Adequate distending pressure of fetal lung fluid and normal fetal breathing movements are some of the more prominent factors known to affect lung growth and development.

Phases of Lung Development

- Embryonic phase (weeks 3-6)
- Pseudoglandular phase (weeks 6-16)
- Canalicular phase (weeks 16-26)
- Terminal sac phase (weeks 26-36)
- Alveolar phase (week 36-3 years)

Embryonic Phase (Weeks 3-6): Development of Proximal Airways

The lung bud arises from the foregut 21 to 26 days after fertilization.

Aberrant development during the embryonic phase may result in the following:

- Tracheal agenesis
- Tracheal stenosis
- Tracheoesophageal fistula
- Pulmonary sequestration (if an accessory lung bud develops during this period)

Pseudoglandular Phase (Weeks 6-16): Development of Lower Conducting Airways

During this phase the first 20 generations of conducting airways develop. The first 8 generations (the bronchi) ultimately acquire cartilaginous walls. Generations 9 to 20 comprise the nonrespiratory bronchioles. Lymph vessels and bronchial capillaries accompany the airways as they grow and develop.

Aberrant development during the pseudoglandular phase may result in the following:

- Bronchogenic cysts
- Congenital lobar emphysema
- Congenital diaphragmatic hernia

Canalicular Phase (Weeks 16-26): Formation of Gas-Exchanging Units or Acini

The formation of respiratory bronchioles (generations 21-23) occurs during the canalicular phase. The relative proportion of parenchymal connective tissue diminishes. The development of pulmonary capillaries occurs. Gas exchange depends upon adequacy of acinus-capillary coupling.

Terminal Sac Phase (Weeks 26-36): Refinement of Acini

The rudimentary primary saccules subdivide by formation of secondary crests into smaller saccules and alveoli during the terminal sac phase, thus greatly increasing the surface area available for gas exchange. The interstitium continues to thin out, decreasing the distance for diffusion. Capillary invasion leads to an increase in alveolar–blood barrier surface area. The development and maturation of the surfactant system occurs during this phase.

Birth and initiation of spontaneous or mechanical ventilation during the terminal sac phase may result in the following:

- Pulmonary insufficiency of prematurity (due to reduced surface area, increased diffusion distance, and unfavorable lung mechanics)
- Respiratory distress syndrome (due to surfactant deficiency and/or inactivation)
- Pulmonary interstitial emphysema (due to tissue stretching by uneven aeration, excessive inflating pressure and increased interstitium that traps air in the perivascular sheath)
- Impairment of secondary crest formation and capillary development, leading to alveolar simplification, decreased surface area for gas exchange and variable increase in interstitial cellularity and/or fibroproliferation (bronchopulmonary dysplasia [BPD]).

Alveolar Phase (Week 36-3 Years): Alveolar Proliferation and Development

Saccules become alveoli as a result of the thinning of the acinar walls, dissipation of interstitium, and invagination of alveoli by pulmonary capillaries with secondary crest formation during the alveolar phase. The alveoli attain a polyhedral shape.

Mechanics

The respiratory system is composed of millions of air sacs that are connected to the outside air via airways. The lung behaves like a balloon that is held in an expanded state by the intact thorax and will deflate if the integrity of the system becomes compromised. The interior of the lung is partitioned so as to provide a large surface area to facilitate efficient gas diffusion. The lung is expanded by forces generated by the diaphragm and the intercostal muscles. It recoils secondary to elastic and surface tension forces. This facilitates the inflow and outflow of respiratory gases required to allow the air volume contained within the lung to be ventilated. During inspiration the diaphragm contracts. The diaphragm is a dome-shaped muscle at rest. As it contracts, the diaphragm flattens, and the volume of the chest cavity is enlarged. This causes the intrapleural pressure to decrease and results in gas flow into the lung.[3] During unlabored breathing, the intercostal and accessory muscles serve primarily to stabilize the rib cage as the diaphragm contracts, countering the forces resulting from the decrease in intrapleural pressure during inspiration. This limits the extent to which the infant's chest wall is deformed inward during inspiration.

Although the premature infant's chest is very compliant, the rib cage offers some structural support, serves as an attachment point for the respiratory muscles, and limits lung deflation at end-expiration. The elastic elements of the respiratory system—the connective tissue—are stretched during inspiration and recoil during expiration. The air-liquid interface in the terminal air spaces and respiratory bronchioles generates surface tension that opposes lung expansion and promotes lung deflation. The conducting airways, which connect the gas exchange units to the outside air, provide greater resistance during exhalation than during inspiration, because during inspiration, the tethering elements of the surrounding lung tissue increase airway diameter, relative to expiration. The respiratory system is designed to be adaptable to a wide range of workloads; however, in the newborn infant, several structural and functional limitations make the newborn susceptible to respiratory failure.

Differences between the shape of a newborn infant's chest and that of an adult put the infant at a mechanical disadvantage. Unlike the adult's thorax, which is ellipsoid in shape, the infant's thorax is more cylindrical and the ribs are more horizontal, rather than oblique. Because of these anatomic differences, the intercostal muscles in infants have a shorter course and provide less mechanical advantage for elevating the ribs and increasing intrathoracic volume during inspiration than do those of adults. Also, because the insertion of the infant's diaphragm is more horizontal than in the adult, the lower ribs tend to move inward rather than upward during inspiration. The compliant chest wall of the infant exacerbates this inward deflection with inspiration. This is particularly evident during rapid eye movement (REM) sleep, when phasic changes in intercostal muscle tone are inhibited. Therefore, instead of stabilizing the rib cage during inspiration, the intercostal muscles are relaxed. This results in inefficient respiratory effort, which may be manifested clinically by intercostal and substernal retractions associated with abdominal breathing, especially when lung compliance is decreased. The endurance capacity of the diaphragm is determined primarily by muscle mass and the oxidative capacity of muscle fibers. Infants have low muscle mass and a low percentage of type 1 (slow twitch) muscle fibers compared to adults.[4] To sustain the work of breathing, the diaphragm must be provided with a continuous supply of oxygen. The infant with respiratory distress is thus prone to respiratory muscle fatigue leading to respiratory failure.

During expiration the main driving force is elastic recoil, which depends on the surface tension produced by the air-liquid interface, the elastic elements of lung tissue, and the bony development of the rib cage. Expiration is largely passive. The abdominal muscles can aid in exhalation by active contraction if required, but they make little contribution during unlabored breathing. Because the chest wall of premature infants is compliant, it offers little resistance against expansion upon inspiration and little opposition against collapse upon expiration.

This collapse at end-expiration can lead to atelectasis. In premature infants the largest contributor to elastic recoil is surface tension. Pulmonary surfactant serves to reduce surface tension and stabilize the terminal airways. In circumstances in which surfactant is deficient, the terminal air spaces have a tendency to collapse leading to diffuse atelectasis. Distending airway pressure in the form of positive end-expiratory pressure (PEEP), or continuous positive airway pressure (CPAP) may be applied to the infant's airway to counter the tendency toward collapse and the development of atelectasis. The application of airway distending pressure also serves to stabilize the chest wall.

Lung compliance and airway resistance are related to lung size. The smaller the lung, the lower the compliance and the greater the resistance. If, however, lung compliance is corrected to lung volume (specific compliance), the values are nearly identical for term infants and adults.[5] In term infants, immediately after delivery, specific compliance is low but normalizes as fetal lung fluid is absorbed and a normal functional residual capacity (FRC) is established. In premature infants, specific compliance remains low, due in part to diffuse microatelectasis and failure to achieve a normal FRC, because the lung recoil forces are incompletely opposed by the excessively compliant chest wall.

The resistance within lung tissue during inflation and deflation is called *viscous resistance*. Viscous resistance is elevated in the newborn. In immature small lungs, there are relatively fewer terminal air spaces and relatively more stroma (cells and interstitial fluid). This is manifested by a low ratio of lung volume to lung weight. Although in absolute terms airway resistance is high in the newborn

infant, when corrected to lung volume (specific conductance, which is the reciprocal of resistance per unit lung volume), the relative resistance is lower than in adults. It is important to remember that because of the small diameter of the airways in the lungs of the newborn infant, even a modest further narrowing will result in a marked increase in resistance. That the newborn's bronchial tree is short and the inspiratory flow velocities are low are teleologic advantages for the newborn because both of these factors decrease airway resistance.

Overcoming the elastic and resistive forces during ventilation requires energy expenditure and accounts for the work of breathing. The normal work of breathing is essentially the same for newborns and adults when corrected for metabolic rates.[5] When the work of breathing increases in response to various disease states, the newborn is at a decided disadvantage. The newborn infant lacks the strength and endurance to cope with a significant increase in ventilatory workload. A large increase in ventilatory workload can lead to respiratory failure.

Elastic and resistive forces of the chest, lungs, abdomen, airways, and ventilator circuit oppose the forces exerted by the respiratory muscles and/or ventilator. The terms *elastic recoil, flow resistance, viscous resistance,* and *work of breathing* are used to describe these forces. Such forces may also be described as *dissipative* and *nondissipative* forces. The latter refers to the fact that the work needed to overcome elastic recoil is stored like the energy in a coiled spring and will be returned to the system upon exhalation. Resistive and frictional forces, on the other hand, are lost and converted to heat (dissipated). The terms *elasticity, compliance,* and *conductance* characterize the properties of the thorax, lungs, and airways. The static pressure-volume curve illustrates the relationships between these forces at different levels of lung expansion. Dynamic pressure-volume loops illustrate the pressure-volume relationship during inspiration and expiration ( ).

Elastic recoil refers to the tendency of stretched objects to return to their original shape. When the inspiratory muscles relax during exhalation, the elastic elements of the chest wall, diaphragm, and lungs, which were stretched during inspiration, recoil to their original shapes. These elastic elements behave like springs ( ). The surface tension forces at the air-liquid interfaces in the distal bronchioles and terminal airways decrease the surface area of the air-liquid interfaces ( ).

At some point, the forces that tend to collapse are counterbalanced by those that resist further collapse. The point at which these opposing forces balance is called the *resting state of the respiratory system* and corresponds with FRC (; see also). Because the chest wall of the newborn infant is compliant, it offers little opposition to collapse at end-expiration. Thus the newborn, especially the premature newborn, has a relatively low FRC and thoracic gas volume, even when the newborn does not suffer from primary surfactant deficiency. Clinically, this manifests as a mild degree of diffuse microatelectasis and is referred to as *pulmonary insufficiency of prematurity.* This low FRC and the relative underdevelopment of the conducting airway's structural support explain the tendency for early airway closure and collapse with resultant gas trapping in premature infants.

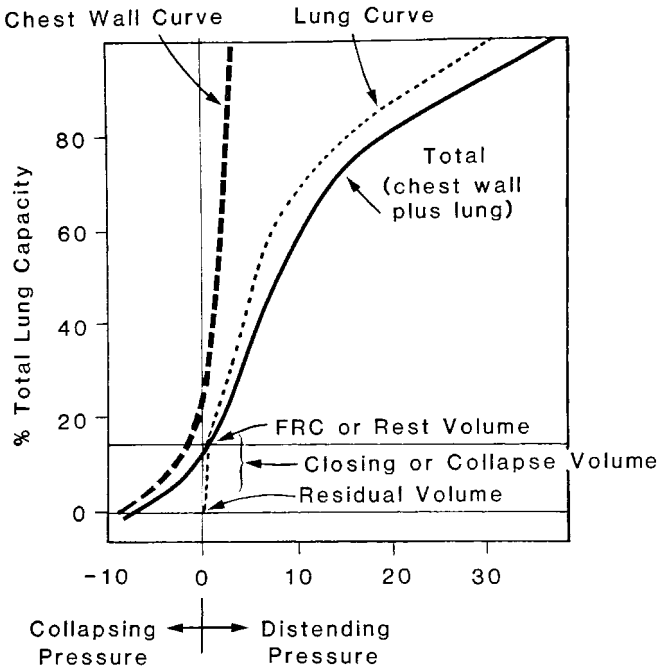

Figure 2-2 Static pressure-volume curves for the chest wall, the lung, and sum of the two for a normal newborn infant. Functional residual capacity (FRC) or rest volume (less than 20% of total lung capacity) is the point at which collapsing and distending pressures balance out to zero pressure. The lung would empty to residual volume if enough collapsing pressure (forced expiration) was generated to overcome chest wall elastic recoil in the opposite direction. The premature infant has an even steeper chest wall compliance curve than that shown here, whereas his or her lung compliance curve tends to be flatter and shifted to the right, depending on the degree of surfactant deficiency.

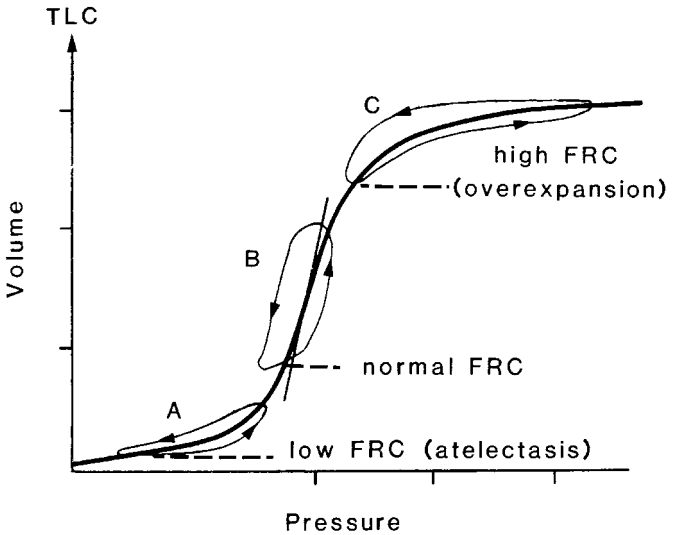

Figure 2-3 Extended compliance or lung expansion curve with "flattened" areas (*A* and *C*) at both ends. Area *A* represents the situation in disease states leading to atelectasis or lung collapse. Area *C* represents the situation in an overexpanded lung, as occurs in diseases involving significant air trapping (e.g., meconium aspiration) or in the excessive application of distending pressure during assisted ventilation. *FRC,* Functional residual capacity.

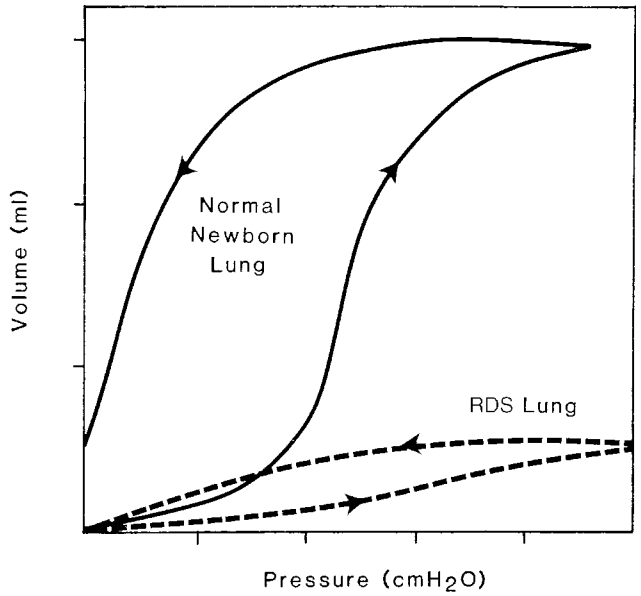

Figure 2-4 Comparison of the pressure-volume curve of a normal infant (*solid line*) with that of a newborn with respiratory distress syn drome (*dotted line*). Note that very little hysteresis (i.e., the difference between the inspiratory and expiratory limbs) is observed in the respira tory distress syndrome curve because of the lack of surfactant for stabilization of the alveoli after inflation. The wide hysteresis of the normal infant's lung curve reflects changes (reduction) in surface tension once the alveoli are opened and stabilized. *RDS*, Respiratory distress syndrome.

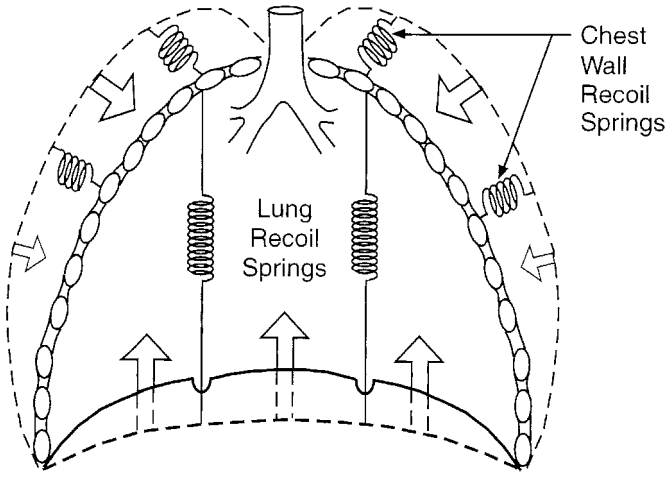

Figure 2-5 Elastic recoil is the tendency of elements in the chest wall and lungs that are stretched during inspiration to snap back or recoil (*arrows*) to their original state at the end of expiration. At this point (functional residual capacity or rest volume), the "springs" are relaxed and the structure of the rib cage allows no further collapse. Opposing forces of the chest wall and elastic recoil balance out, and intrathoracic and airway pressures become equal (this further defines functional residual capacity or rest volume; see also).

The respiratory system's resting volume is very close to the closing volume of the lung (the volume at which dependent lung regions cease to ventilate because the airways leading to them have collapsed). In newborns, closing volume may occur even above FRC (see).[6] Gas trapping related to airway closure has been demonstrated experimentally by showing situations in which the thoracic gas volume is greater than the FRC. For this to occur, the total gas volume measured in the chest at end-expiration is greater than the amount of gas that is in communication with the upper airway (FRC).

The main contributor to lung elastic recoil in the newborn is surface tension. The pressure required to counteract the tendency of the bronchioles and terminal air spaces to collapse is described by the Laplace relationship:

$$P = \frac{2\,ST}{r}$$

Simply stated, this relationship illustrates that the pressure (*P*) needed to stabilize the system is directly proportional to twice the surface tension (*2 ST*) and inversely proportional to the radius of curvature (*r*). In infants, the

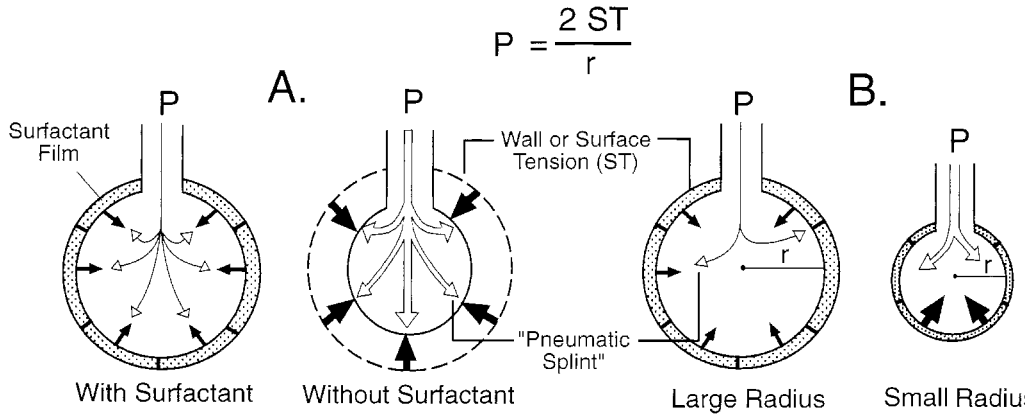

Figure 2-6 Diagrammatic illustration of the Laplace relationship and the effects of surfactant film (**A**) and alveolar radius (**B**) on wall or surface tension. The degree (reflected in the size of the open arrows) of airway or intra-alveolar pressure (*P*) needed to counteract the tendency of alveoli to collapse (represented by the solid arrows) is directly proportional to double the wall or surface tension (*ST*) and inversely proportional to the size of the radius (*r*). Distending airway pressure applied during assisted ventilation can be likened to a "pneumatic splint."

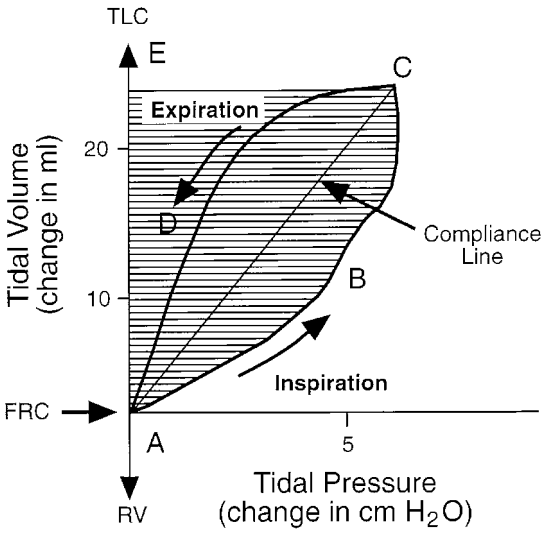

Figure 2-7 Pressure-volume loop showing the compliance line (*AC*, joining points of no flow); work done in overcoming elastic resistance (*ACEA*), which incorporates the frictional resistance encountered during expiration (*ACDA*); work done in overcoming frictional resistance during inspiration (*ABCA*); and total work done during the respiratory cycle (*ABCEA*, or the entire shaded area).

relationship should be modified, because, unlike in a soap bubble, there is an air-liquid interface on only one side of the terminal lung unit, so P = ST/r probably describes the situation more accurately in the lung.

In reality, alveoli are not spherical but polyhedral and share their walls with adjacent alveolar structures, making strict application of Laplace's law suspect. Nonetheless, the basic concept of the law does apply to both terminal air sacs and small airways, and it provides a crucial framework for the understanding of respiratory physiology. The surface tension in the lung is primarily governed by the presence or absence of surfactant. Surfactant is a surface-active material released by type II pneumocytes. It is composed mainly of dipalmitoyl phosphatidylcholine, but contains other essential components, such as surfactant-associated proteins A, B, C, and D as well.

Surfactant has a variety of unique properties that enable it to decrease surface tension at end-expiration and thereby prevent further lung deflation below resting volume and allow an increase in surface tension upon lung expansion that facilitates elastic recoil at end-inspiration. In addition, surfactant reduces surface tension when lung volume is decreased.[7] A reduction in the quantity of surfactant results in an increase in surface tension and necessitates the application of more distending pressure to counter the tendency of the bronchioles and terminal air spaces to collapse (see *A*).

As can be seen from the Laplace relationship, the larger the radius of curvature of the terminal bronchioles or air spaces, the less pressure is needed to hold them open or to expand them further (see *B*). The smaller the radius of curvature (e.g., in premature infants), the more pressure is required to hold the airways open. Surfactant helps this situation throughout the respiratory cycle. As the radii of the air-liquid interfaces become smaller during exhalation, the effectiveness of surfactant in reducing surface tension increases; as the radii become larger, its effectiveness decreases.

Respiratory distress syndrome (RDS) imposes a significant amount of energy expenditure on the newborn infant who must generate high negative intrapleural pressures in order to expand and stabilize their distal airways and alveoli (see). In untreated RDS, each breath requires significant energy expenditure because lung volumes achieved with the high opening pressures during inspiration are rapidly lost as the surfactant-deficient lung collapses to its original resting volume during expiration. The burden imposed by this large work of breathing may quickly outstrip the infant's ability to maintain this level of output and lead to respiratory failure.

The infant with RDS may need relatively high inflation pressure to open atelectatic alveoli, and provision of adequate end-expiratory pressure will help keep the lung open. However, once the lung is expanded, the radii of the bronchioles and terminal air spaces are larger and therefore, less pressure is required to hold them open or to expand them further. Attention should be paid to tidal volume and overall lung volume after initial alveolar recruitment to avoid overdistention and volutrauma, which are major factors in the development of bronchopulmonary dysplasia (BPD).[8] Failure to reduce inspiratory and distending pressures appropriately and thus avoid lung overdistention once normal lung volume has been achieved may lead to air leak complications such as pulmonary interstitial emphysema (PIE) and pneumothorax (see Chapter 21).

Compliance

Compliance is a measure of the change in volume resulting from a given change in pressure:

$$C_L = \Delta V/\Delta P$$

where C is lung compliance, ΔV is change in volume, and ΔP is change in pressure.

Static Compliance

When measured under static conditions, compliance reflects only the elastic properties of the lung. Static compliance is the reciprocal of elastance, the tendency to recoil toward its original dimensions upon removal of the distending pressure required to stretch the system. Static compliance is measured by determining the transpulmonary pressure change after inflating the lungs with a known volume of gas. Transpulmonary pressure is the pressure difference between alveolar pressure and pleural pressure. It is approximated by measuring pressure at the airway opening and in the esophagus. To generate a pressure-volume curve, pressure measurements are made during static conditions after each incremental volume of gas is introduced into the lungs (see *Lung Curve* in). If one measures the difference between pleural pressures (esophageal) and atmospheric pressures (transthoracic) at different levels of lung expansion, the plotted curve will be a chest wall compliance curve (see *Chest Wall Curve* in). This kind of plot shows the elastic properties of the chest wall. In the newborn, the chest wall is very compliant; thus large volume changes are achieved with small pressure changes. Taking the lung and chest wall compli-

ance curves together gives the total respiratory system compliance (see the *Total* curve in).

Dynamic Compliance

If one measures compliance during continuous breathing, the result is called *dynamic compliance*. Dynamic compliance reflects not only the elastic properties of the lungs but, to some extent, also the resistive component. It measures the change in pressure from the end of exhalation to the end of inspiration for a given volume and is based on the assumption that at zero flow the pressure difference reflects compliance. The steeper the slope of the curve connecting the points of zero flow, the greater the compliance. Dynamic compliance is the compliance that is generally measured in the clinical setting, but its interpretation can be problematic.[9]

At the fairly rapid respiratory rates common in infants, the instant of zero flow may not coincide with the point of lowest pressure. This is because dynamic compliance is rate dependent. For this reason, dynamic compliance may underestimate static compliance, especially in infants who are breathing rapidly and those with obstructive airway disease. Two additional factors further complicate the interpretation of compliance measurements. In premature infants, REM sleep is associated with paradoxical chest wall motion, so pressure changes recorded from the esophagus may correlate poorly with intrathoracic or pleural pressure changes. Chest wall distortion generally results in underestimation of esophageal pressure changes.[10] Also, because lung compliance is related to lung volume, measured compliance is greatly affected by the initial lung volume above which the compliance measurement is made. Ideally, comparisons should be normalized to the degree of lung expansion, for example, to FRC. Lung compliance divided by FRC is called *specific lung compliance*.

Dynamic pressure-volume relationships can be examined by simultaneous recording of pressure and volume changes. The pressure-volume loop allows one to quantify the work done to overcome airway resistance and to determine lung compliance (see and). shows a static lung compliance curve upon which three pressure-volume loops are superimposed. Each of the loops shows a complete respiratory cycle, but each is taken at a different lung volume. The overall compliance curve is sigmoidal. At the lower end of the curve (at low lung volume), the compliance is low, that is, there is a small change in volume for a large change in pressure (see , region *A*). This correlates with underinflation. Pressure is required to open up terminal airways and atelectatic terminal air spaces before gas can move into the lung. The lung volume is starting below critical opening pressure. At the center of the curve, the compliance is high; there is a large change in volume for a small change in pressure. This is where normal tidal breathing should occur (see , region *B*). This is the position of maximum efficiency in a mechanical sense, the best ventilation/perfusion matching and lowest pulmonary vascular resistance. At the upper end of the curve (at high lung volume), the compliance is low; again, there is a small change in volume for a large change in pressure (see , region *C*). This correlates with a lung that already is overinflated. Applying additional pressure yields little in terms of additional volume but may contribute significantly to airway injury and compromises venous return because of increased transmission of pressure to the pleural space. This is the result of the chest wall compliance rapidly falling with excessive lung inflation. Thus it is important to understand that compliance is reduced at both high and low lung volumes. Low lung volumes are seen in surfactant deficiency states (e.g., RDS), whereas high lung volumes are seen in obstructive lung diseases, such as BPD. Reductions in both specific compliance and thoracic gas volume have been measured in infants with RDS.[11,]

The rapid respiratory rates of premature infants with surfactant deficiency can compensate for chest wall instability to a certain extent, because the short expiratory time results in gas trapping that tends to normalize their FRC. They also use expiratory grunting as a method of expiratory braking to help maintain FRC. In infants with RDS treated in the pre-surfactant era, serial measurements of FRC and compliance have been shown to be sensitive indicators of illness severity.[13]

Dynamic lung compliance has been shown to decrease as the clinical course worsens and to improve as the recovery phase begins. When mechanical ventilation is used in infants with noncompliant lungs resulting from surfactant deficiency, elevated distending pressures may be required initially to establish a reasonable FRC. shows the pressure-volume loop of a normal infant and that of an infant with RDS. A higher pressure is required to establish an appropriate lung volume in the infant with RDS than in the normal infant. However, this lung volume will be lost if the airway pressure is allowed to return to zero without the application of positive end-expiratory pressure (PEEP). Mechanical ventilation without PEEP leads to surfactant inactivation resulting in worsening lung compliance, and the repeated cycling of the terminal airways from below critical opening pressure leads to cellular injury and inflammation (atelectotrauma). This results in alveolar collapse, atelectasis, interstitial edema, and elaboration of inflammatory mediators.

Once atelectasis occurs, lung compliance deteriorates, surfactant turnover is increased and ventilation/perfusion mismatch with increased intrapulmonary right-to-left shunting develops. A higher distending pressure and higher concentrations of inspired oxygen (F_{IO_2}) will be required to maintain lung volume and adequate gas exchange, resulting in further injury. Early establishment of an appropriate FRC, administration of surfactant, use of CPAP or PEEP to avoid the repeated collapse and reopening of small airways (atelectatrauma), avoidance of overinflation caused by using supraphysiologic tidal volumes (volutrauma), and avoidance of use of more oxygen than is required (oxidative injury) all are important in achieving the best possible outcome and long-term health of patients.[14]

The level of PEEP at which static lung compliance is maximized has been termed *best*, or *optimum, PEEP*. This is the level of PEEP at which O_2 transport (cardiac output and O_2 content) is greatest. If the level of PEEP is raised above the optimal level, dynamic compliance decreases rather thanincreases.[15] Additionally, venous return and cardiac output are compromised by excessive PEEP. One hypothesis for this reduction in dynamic lung compliance

is that some alveoli become overexpanded because of the increase in pressure, which puts them on the "flat" part of the compliance curve (see region *C* in). Therefore, despite the additional pressure delivered, little additional volume is obtained. The contribution of this "population" of over-expanded alveoli may be sufficient to reduce the total lung compliance. It has been shown that dynamic lung compliance was reduced in patients with congenital diaphragmatic hernia (CDH) even though some of the infants had normal thoracic gas volumes.[11] The reduction in dynamic lung compliance in patients with CDH is attributed to overdistention of the hypoplastic lung into the "empty" hemithorax after surgical repair of the defect. Because CDH infants have a reduced number of alveoli, they develop areas of pulmonary emphysema that persist at least into early childhood.[16]

Based on available evidence, it seems prudent to avoid rapid reexpansion of the lungs in the treatment of CDH. Clinicians must be alert to any sudden improvement in lung compliance in infants receiving assisted ventilation (i.e., immediately after administration of surfactant or recruitment of lung volume). If inspiratory pressure is not reduced as compliance improves, cardiovascular compromise may develop because proportionately more pressure is transmitted to the mediastinal structures as lung compliance improves. The distending pressure that was appropriate prior to the compliance change may become excessive and lead to alveolar overexpansion and ultimately air leak.[17] The use of volume-targeted ventilation would be ideal in these circumstances, because in this mode the ventilator will decrease the inspiratory pressure as lung compliance improves to maintain a set tidal volume.[18]

Because the chest wall is compliant in the premature infant, use of paralytic agents to reduce chest wall impedance is rarely necessary. Little pressure is required to expand the chest wall of a premature infant (see *Chest Wall Curve* in). In studies investigating the use of paralytic agents in premature infants at risk for pneumothoraces, no change in lung compliance or resistance was demonstrated after 24 or 48 hours of paralysis, and many of the infants studied required more rather than less ventilator support after paralysis.[19,]

In the past, paralysis was often used in larger infants who were "fighting the ventilator" or were actively expiring against it despite the use of sedation and/or analgesia.[19] It should be noted that poor gas exchange (inadequate support) is usually the cause, rather than the result of the infant "fighting" the ventilator, and heavy sedation or paralysis masks this important clinical sign. The use of synchronized mechanical ventilation modes such as assist/control will obviate the need to paralyze or heavily sedate infants because the baby will then be breathing in synchrony with the ventilator.

During positive-pressure ventilation, the relative compliance of the chest wall and the lungs determines the amount of pressure transmitted to the pleural space. Increased intrapleural pressure leads to impedance of venous return and decreased cardiac output, a well documented but largely ignored complication of positive-pressure ventilation. The relationship is described by the following equation:

$$P_{PL} = Paw \times (C_L / C_L + C_{CW})$$

where P_{PL} is pleural pressure, *Paw* is mean airway pressure, C_L is compliance of the lungs, and C_{CW} is compliance of the chest wall.

Thus it can be seen that in situations of good lung compliance but poor chest wall compliance, transmission of pressure to the pleural space and hemodynamic impairment are increased. This situation commonly arises in cases of increased intraabdominal pressure with upward pressure on the diaphragm, as may be seen in infants with necrotizing enterocolitis, or after surgical reduction of viscera that had developed outside the abdominal cavity, that is, large omphalocele, gastroschisis, or CDH.

Resistance

Resistance is the result of friction. Viscous resistance is the resistance generated by tissue elements moving past one another. Airway resistance is the resistance that occurs between moving molecules in the gas stream and between these moving molecules and the wall of the respiratory system (e.g., trachea, bronchi, bronchioles). The clinician must be aware of both types of resistance, as well as the resistance to flow as gas passes through the ventilator circuit and the endotracheal tube. In infants, viscous resistance may account for as much as 40% of total pulmonary resistance. The relatively high viscous resistance in the newborn is due to relatively high tissue density (i.e., a low ratio of lung volume to lung weight) and the higher amount of pulmonary interstitial fluid. This increase in pulmonary interstitial fluid is especially prevalent after cesarean section delivery and in conditions such as transient tachypnea of the newborn or delayed absorption of fetal lung fluid.

A reduction in tissue and airway resistance has been shown after administration of furosemide. Airway resistance (R) is defined as the pressure gradient (P1 – P2) required to move gas through the airways at a constant flow rate ($\dot{V}$ or volume per unit of time). The standard formula is as follows:

$$R = (P1 - P2)/\dot{V}$$

Airway resistance is determined by flow velocity, length of the conducting airways, viscosity and density of the gases, and especially the inside diameter of the airways. This is true for both laminar and turbulent flow conditions.

Although in absolute terms airway resistance is elevated in the newborn infant, when corrected to lung volume (specific conductance, which is the reciprocal of resistance per unit lung volume), the relative resistance is lower than in adults. It is important to remember that because of the small diameter of the airways in the lungs of the newborn infant, even a modest narrowing will result in a marked increase in resistance.

Resistance to flow depends on whether flow is laminar or turbulent. Turbulent flow results in inefficient use of energy, because the turbulence leads to flow in random directions, unlike with laminar flow, where molecules move in an orderly fashion parallel to the wall of the tube. Therefore, pressure gradient necessary to drive a given flow is always greater for turbulent flow, but cannot be easily calculated. The Reynolds number is used as an index to

determine whether flow is laminar or turbulent. It is a unitless number that is defined as follows:

$$Re = 2\,r \cdot v \cdot d/\eta$$

where r is radius, v is velocity, d is density, and η is viscosity. If the Reynolds number is greater than 2000, then turbulent flow is very likely. According to this equation, turbulent flow is likely if the tube has a large radius, a high velocity, a high density, or a low viscosity.

When flow is laminar, resistance to flow of gas through a tube is described by Poiseuille's law:

$$R \propto L \times \eta/r^4$$

where R is resistance, L is length of the tube, η is viscosity of the gas and r is the radius. In the following paragraphs we will consider each factor in more detail.

Flow Rate

Average values for airway resistance in normal, spontaneously breathing newborn infants are between 20 and 30 cm H_2O/L/sec, and these values can increase dramatically in disease states. Nasal airway resistance makes up approximately two thirds of total upper airway resistance; the glottis and larynx contribute less than 10%; and the trachea and first four or five generations of bronchi account for the remainder ( ). Average peak inspiratory and expiratory flow rates in spontaneously breathing term infants are approximately 2.9 and 2.2 L/min, respectively. Maximal peak inspiratory and expiratory flow rates average about 9.7 and 6.4 L/min, respectively.[30] The range of flow rates generated by spontaneously breathing newborns (including term and premature infants) is approximately 0.6 to 9.9 L/min. Turbulent flow is produced in standard infant endotracheal tubes whenever flow rates exceed approximately 3 L/min through 2.5-mm internal diameter (ID) tubes or 7.5 L/min through 3.0-mm ID tubes.[31] Flow rates that exceed these critical levels produce disproportionately large increases in airway resistance. For example, increasing the rate of flow through a 2.5-mm ID endotracheal tube from 5 to 10 L/min raises airway resistance from 32 to 84 cm H_2O/L/sec, more than twice its original value.[31]

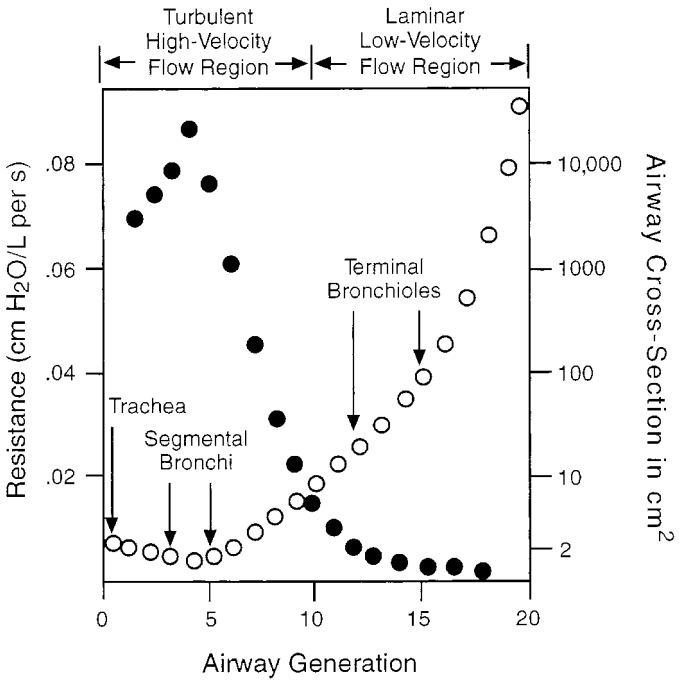

Figure 2-8 Airway resistance to gas flow (*solid circles*) is inversely proportional to the total cross-sectional area of the airways (*open circles*). Approximately 80% of airway resistance is encountered in the first few generations of bronchi, where total cross-sectional area is the least. Pressure decreases exponentially in regions of high-velocity turbulent flow, whereas pressure decreases more linearly in regions of low-velocity laminar flow further out in the periphery. (Reprinted and adapted by permission of the publisher from The Pathway for Oxygen: Structure and Function in the Mammalian Respiratory System by Edward R. Weibel, pp. 285-286, 295, Cambridge, Mass. Copyright © 1984 by the President and Fellows of Harvard College.)

Flow conditions are likely to be at least partially turbulent ("transitional") when ventilator flow rates exceed 5 L/min in infants intubated with 2.5-mm ID endotracheal tubes or when rates exceed 10 L/min in infants with 3.0-mm ID endotracheal tubes. With turbulent flow, resistance increases exponentially. The resistance produced by infant endotracheal tubes is equal to or higher than that in the upper airway of a normal newborn infant breathing spontaneously. The increased resistance due to the endotracheal tube poses little problem as long as the infant receives appropriate pressure support from the ventilator, because the machine can generate the additional pressure needed to overcome the resistance of the endotracheal tube. However, when the infant is being weaned from the ventilator or if the infant is disconnected from the ventilator with the endotracheal tube still in place, the infant may not be capable of generating sufficient effort to overcome the increase in upper airway resistance created by the endotracheal tube. LeSouef et al.[33] measured a significant reduction in respiratory system expiratory resistance after extubation in premature newborn infants recovering from a variety of respiratory illnesses, including RDS, pneumonia, and transient tachypnea of the newborn.

Airway or Tube Length

Resistance is linearly proportional to tube length. The shorter the tube, the lower the resistance; therefore it is good practice to cut endotracheal tubes (ETT) to the shortest practical length. Shortening a 2.5-mm ID ETT from 14.8 cm (full length) to half its length is feasible, because the depth of insertion in a small preemie is usually about 6 cm. This would reduce resistance of the tube to half. Cutting the tube to 4.8 cm reduces the flow resistance in vitro to essentially that of a full-length tube of the next size (3.0-mm ID ETT). These relationships are consistent for the range of flows generated by spontaneously breathing newborns.[34]

Airway or Tube Diameter

In a single-tube system, the radius of the tube is the most significant determinant of resistance. As previously described, Poiseuille's law states that resistance is inversely proportional to the fourth power of the radius. Therefore, reduction in the radius by half results in a 16-fold increase in resistance and thus the pressure drop required to maintain a given flow. It is important to fully appreciate that resistance to flow increases exponentially as ETT diameter

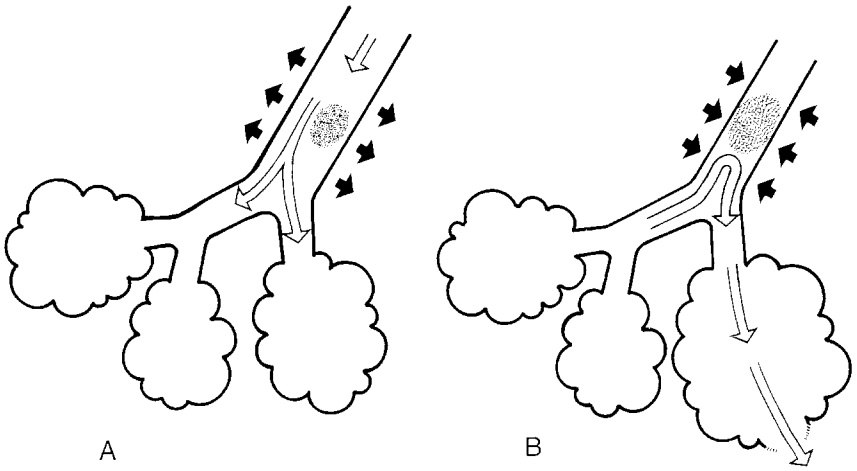

Figure 2-9 Air trapping behind particulate matter (e.g., meconium) in an airway, which leads to alveolar overexpansion and rupture. This illustrates the so-called *ball-valve mechanism*, in which tidal gas passes the particulate matter on inspiration, when the airways naturally dilate (**A**), but does not exit on expiration, when the airways naturally constrict (**B**). (From Harris TR, Herrick BR: Pneumothorax in the Newborn. Tucson, AZ, Biomedical Communications, Arizona Health Sciences Center, 1978.)

decreases. This is one of the reasons extremely low-birth-weight infants are difficult to wean from mechanical ventilation. In a multiple tube system, like the human lung, resistance depends on the total cross-sectional area of all of the tubes. Although the individual bronchi decrease in diameter as they extend toward the periphery, the total cross-sectional area of the airway (see) increases exponentially.[35]

Because resistance increases to the fourth power as the airway is narrowed, even mild airway constriction can cause significant increases in resistance to flow. This effect is exaggerated in newborn infants compared to adults because of the narrowness of the infant's airways. Resistance during inspiration is less than resistance during expiration because the airways dilate upon inspiration ( ). This is true even though gas flow during inspiration usually is greater than that during expiration, because as we saw above, the relationship between resistance and flow is linear, whereas that of radius is geometric. There is an inverse, nonlinear relationship between airway resistance and lung volume, because airway size increases as FRC increases. Lung volume recruitment therefore reduces resistance to airflow. Any process that causes a reduction in lung volume, such as atelectasis or restriction of expansion, results in increased airway resistance. At extremely low volumes, resistance approaches infinity because the airways begin to close as residual volume is approached (see).

Consistent with the above physiologic principles, the preponderance of evidence indicates that application of PEEP and CPAP decreases airway resistance. Endotracheal tube resistance is of considerable clinical importance. It has been shown that successful extubation is accomplished more often in infants coming directly off intermittent mandatory ventilation (IMV) than after a 6-hour preextubation trial of endotracheal CPAP. Nasal CPAP circuit design, specifically its resistance and the means by which nasal CPAP is attached to the patient are the most important determinants of CPAP success or failure.[39]

Viscosity and Density

Gas viscosity is negligible, relative to viscosity of fluids. However, gas density can be of clinical significance. The relationship between airway resistance and the density of the gas in turbulent flow is directly proportional and linear. Decreasing the density of the gas by two thirds, such as occurs when heliox, a mixture of 80% helium and 20% O_2 is administered, reduces airway resistance to one third compared to that when room air is breathed. Heliox can be useful for reducing upper airway resistance (and work of breathing) in patients with obstructive disorders such as laryngeal edema, tracheal stenosis, and BPD.[40] Gas density is influenced by barometric pressure, so airway resistance is slightly decreased at high altitudes, although this has little clinical significance.

Work of Breathing

Breathing requires the expenditure of energy. For gas to be moved into the lungs, force must be exerted to overcome the elastic and resistive forces of the respiratory system. This is mathematically expressed by the following equation:

$$\text{Work of breathing} = \text{Pressure (force)} \times \text{Volume (displacement)}$$

where pressure is the force exerted and the volume is the displacement. Work of breathing is the integrated product of the two, or simply the area under the pressure-volume curve (see).

Work of breathing is the force generated to overcome the frictional resistance and static elastic forces that oppose lung expansion and gas flow into and out of the lungs. The workload depends on the elastic properties of the lung and chest wall, airway resistance, V , and respiratory rate. Approximately two thirds of the work of spontaneous breathing is the effort to overcome the static elastic forces of the lungs and thorax (tissue elasticity and compliance). Approximately one third of the total work is applied to overcoming the frictional resistance produced by the movement of gas and tissue components (air flow and viscous).[41]

In healthy infants exhalation is passive. A portion of the energy generated by the inspiratory muscles is stored (as potential energy) in the lungs' elastic components; this energy is returned during exhalation, hence it is also referred to as *nondissipative work*, in contrast to the

frictional forces that are lost or dissipated as heat. If the energy required to overcome resistance to flow during expiration exceeds the amount of elastic energy stored during the previous inspiration, work must be done not only during inspiration but also during expiration; thus exhalation is no longer entirely passive.

In infants, energy expenditure correlates with oxygen consumption. Resting oxygen consumption is elevated in infants with RDS and BPD. Mechanical ventilation reduces oxygen consumption by decreasing the infant's work of breathing.[13,43] Work of breathing is illustrated in a dynamic pressure-volume loop (see). Pressure changes during breathing can be measured with an intraesophageal catheter or balloon, and volume changes can be measured simultaneously with a pneumotachograph. During inspiration (ascending limb of the loop) and expiration (descending limb of the loop), both elastic and frictional resistance must be overcome by work. If only elastic resistance needed to be overcome, the breathing pattern would follow the compliance line; however, because airway resistance and tissue viscous resistance must also be overcome, a loop is formed (hysteresis). The areas ABCA and ACDA in represent the inspiratory work and the expiratory work, respectively, performed to overcome frictional resistance. The area ABCEA represents the total work of breathing during a single breath.

The diaphragm is responsible for the majority of the workload of respiration. The most important determinant of the diaphragm's ability to generate force is its initial position, the length of its muscle fibers at the beginning of a contraction. The longer and more curved the muscle fibers of the diaphragm, the greater the force the diaphragm can generate. In situations in which the lung is hyperinflated (overdistended), the diaphragm is flattened and thus at a mechanical disadvantage.

The application of PEEP or CPAP (continuous distending pressure [CDP]) may reduce the work of breathing for an infant whose breathing is on the initial flat part of the compliance curve secondary to atelectasis (see region *A* in). In this situation, CDP should reduce the work of breathing by increasing FRC and bringing breathing to a higher level on the pressure-volume curve where the compliance is higher (see region *B* in). Reductions in respiratory work with the application of CDP have been shown in newborns recovering from RDS[44] and in babies after surgery for congenital heart disease.[37]

If the lung already is overinflated, increasing CDP will not result in a decrease in the work of breathing (see region *C* in). The one exception here is when lung overinflation is the result of airway collapse, as can be seen in infants with BPD. In this unique situation, higher CDP will maintain airway patency and relieve air trapping, reducing lung volume to a more normal level. Alveolar overdistention caused by any reason is often accompanied by an increase in $PaCO_2$ (indicating decreased alveolar ventilation) and a decrease in Pa_{O_2}, despite an increase in FRC.[36,45]

Time Constant

The time constant of a patient's respiratory system is a measure of how quickly his or her lungs can inflate or deflate, that is, how long it takes for alveolar and proximal airway pressures to equilibrate. Passive exhalation depends on the elastic recoil of the lungs and chest wall. Because the major force opposing exhalation is airway resistance, the expiratory time constant (Kt) of the respiratory system is directly related to both lung compliance (C_L), which is the inverse of elastic recoil, and airway resistance (Raw):

$$Kt = C_L \times Raw$$

The time constants of the respiratory system are analogous to those of electrical circuits. One time constant of the respiratory system is defined as the time it takes the alveoli (capacitor) to discharge 63% of its tidal volume (V); (electrical charge) through the airways (resistor) to the mouth or ventilator (electrical) circuit. By the end of three time constants, 95% of the V is discharged. When this model is applied to a normal newborn with a compliance of 0.005 L/cm H_2O and a resistance of 30 cm H_2O/L/sec, one time constant = 0.15 second and three time constants = 0.45 second.[46] In other words, 95% of the last V should be emptied from the lung within 0.45 second of when exhalation begins in a spontaneously breathing infant. In a newborn infant receiving assisted ventilation, the exhalation valve of the ventilator would have to be open for at least that length of time to avoid air-trapping. Inspiratory time constants are roughly half as long as expiratory, largely because airway diameter increased during inspiration. This relationship between inspiratory and expiratory time constants accounts for the normal 1:2 inspiratory/expiratory (I:E) ratio with spontaneous breathing.

The concept of time constants is key to understanding the interactions between the elastic and resistive forces and how the mechanical properties of the respiratory system work together to modulate the volume and distribution of ventilation. A working knowledge of time constants is essential for choosing the safest and most effective ventilator settings for an individual patient at a particular point in the course of a specific disease process that necessitates the use of assisted ventilation. It must be recognized that compliance and resistance change over time and therefore, the optimal settings need to be reevaluated frequently.

Patients are at risk for incomplete emptying of previously inspired breath when their lung condition involves an increase in airway resistance with no or only a modest reduction in lung compliance. They also are at risk when the pattern of assisted ventilation does not allow sufficient time for exhalation, that is, the lungs have an abnormally long time constant, or there is a mismatch between the time constant of the respiratory system (time constant of the patient + that of the endotracheal tube + that of the ventilator circuit) and the expiratory time setting on the ventilator. In these situations, the end result is gas trapping. This gas trapping is accompanied by an increase in lung volume and a build-up of pressure in the alveoli and distal airways referred to as *inadvertent PEEP* or *auto PEEP*.[47]

Important clinical and radiographic signs of gas trapping and inadvertent PEEP include (1) radiographic evidence of overexpansion (e.g., increased anteroposterior diameter of the thorax, flattened diaphragm below the ninth posterior ribs, intercostal pleural bulging); (2)

decreased chest wall movement during assisted ventilation; (3) hypercapnia that does not respond to an increase in ventilator rate (or even worsens); and (4) signs of cardiovascular compromise, such as mottled skin color, a decrease in arterial blood pressure, an increase in central venous pressure, or the development of metabolic acidosis. Such late signs of air trapping should never occur today, because all modern ventilators give us the ability to monitor flow waveforms, which allow us to graphically see whether or not expiration has been completed before the next breath begins.

Time constants are also a function of patient size, because total compliance is proportional to size. The much shorter time constants of an infant are reflected in the more rapid normal respiratory rate, compared to adults. To keep the concept simple, remember that whales and elephants have very large lungs and very long time constants; hence they breathe very slowly. Mice and hummingbirds have tiny lungs with extremely short time constants and have a very rapid respiratory rate to match. Everything else being equal, large infants have longer time constants than "micropreemies." Any decrease in compliance makes time constant shorter, therefore tachypnea is the usual clinical sign of any condition leading to decreased compliance.

Extremely low-birth-weight infants with RDS have decreased compliance but initially normal airway resistance. This means that the time constants are extremely short. Equilibration of the airway and alveolar pressures occurs very quickly (i.e., early in the inspiratory cycle). Reynolds[48] estimated that the time constant in RDS may be as short as 0.05 second. This means that 95% of the pressure applied to the airway is delivered to the alveoli within 0.15 second, a value consistent with clinical observation. Short time constants make rapid rate conventional ventilation feasible in these infants and makes them ideal candidates for high-frequency ventilation.

Term infants with meconium aspiration or older growing preterm infants with BPD have elevated airway resistance and correspondingly longer time constants; therefore they are most at risk of inadvertent PEEP. They should be ventilated with slower respiratory rates and longer inspiratory and, especially, expiratory times. Evidence of air trapping should be actively sought by examining ventilator waveforms, before clinical signs of CO_2 retention and hemodynamic impairment develop. It should be noted that proximal airway PEEP level does not indicate the level of alveolar PEEP, nor does it demonstrate the occurrence of alveolar gas trapping. Even under conditions of zero proximal airway PEEP, alveolar PEEP levels and the degree of gas trapping may be dangerously high if the baby has compliant lungs, increased airway resistance, or both (i.e., a prolonged time constant).[49]

Although it is useful clinically to think of the infant's respiratory system as having a single compliance and a single resistance, we know this is not really the case. The resistance and compliance values we obtain from pulmonary function measurements are essentially weighted averages for the respiratory system. There are populations of respiratory subunits with a range of discrete compliance and resistance values, whereas what we measure at the airway are averaged values for those populations of subunits.

Gas Transport

Mechanisms of Gas Transport

Ventilation or gas transport involves the movement of gas by convection or bulk flow through the conducting airways and then by molecular diffusion into the alveoli and pulmonary capillaries. This makes possible gas exchange (oxygen [O_2] uptake and carbon dioxide [CO_2] elimination) that matches the minute-by-minute metabolic needs of the patient. The driving force for gas flow is the difference in pressure at the origin and destination of the gases; for diffusion, it is the difference in the concentrations between gases in contiguous spaces. Gas flows down a pressure gradient and diffuses down a concentration gradient. The predominant mechanism of gas transport by convection is bulk flow, whereas the predominant mechanism of gas transport by diffusion is Brownian motion.

Ventilation of the alveoli is an intermittent process that occurs only during inspiration, whereas gas exchange between alveoli and pulmonary capillaries occurs throughout the respiratory cycle. This is possible because a portion of gas remains in the lungs at the end of exhalation (FRC); the remaining gas provides a source for ongoing gas exchange and maintains approximately equal O_2 and CO_2 tensions in both the alveoli and the blood returning from the lungs.

During spontaneous breathing, inspiration is achieved through active contraction of the respiratory muscles. A negative pressure is produced in the interpleural space, a portion of which is transmitted via the parietal and visceral pleura through the pulmonary interstitial space to the lower airways and alveoli. A pressure gradient between the outside atmospheric pressure and the airway and alveoli pressures results in gas flowing down the pressure gradient into the lungs ( ). Interpleural pressure is more negative than alveolar pressure, which is more negative than mouth and atmospheric pressures.

When an infant receives negative-pressure ventilation, pressure is decreased around the infant's chest and abdomen to supplement the negative-pressure gradient used to move gas into the lungs, mimicking the normal physiologic function. During positive-pressure ventilation, the upper airway of the infant ( ) is connected to a device that generates a positive-pressure gradient down which gas can flow during inspiration. The pressure in the ventilator circuit and in the upper airway is greater than alveolar pressure, which is greater than interpleural pressure, which is greater than atmospheric pressure. The negative intrathoracic pressure during spontaneous or negative pressure respiration facilitates venous return to the heart. Positive pressure ventilation alters this physiology and inevitably leads to some degree of impedance of venous return, adversely affecting cardiac output.

The amount of gas inspired in a single spontaneous breath or delivered through an endotracheal tube during a single cycle of the ventilator is called the *tidal volume* (V). V in milliliters (mL) multiplied by the number of breaths per minute or respirator frequency (f) is called *minute ventilation* (V_E):

$$V_E = V_T \times f$$

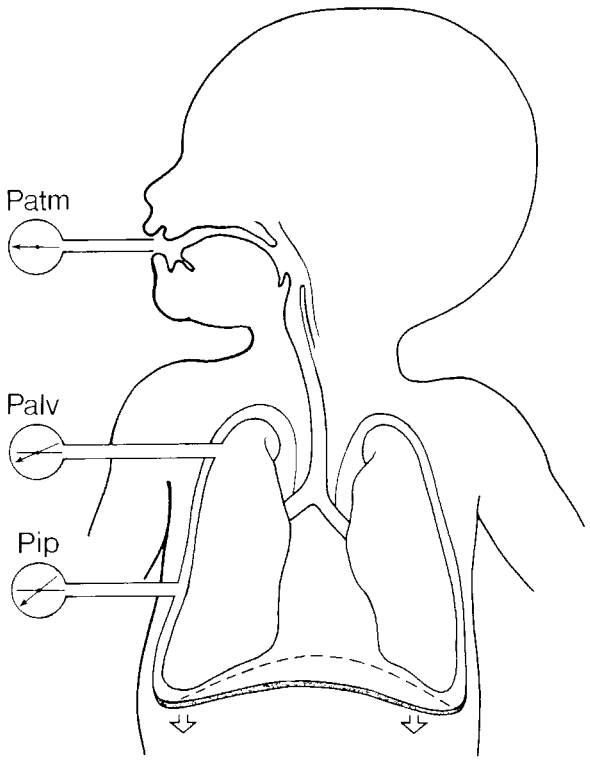

Figure 2-10 Negative-pressure gradient produced upon inspiration by the descent of the diaphragm in a spontaneously breathing infant. Pressures are measured in the interpleural space (*Pip*), in the alveoli (*Palv*), and at opening of mouth or atmosphere (*Patm*). Pip < Palv < Patm.

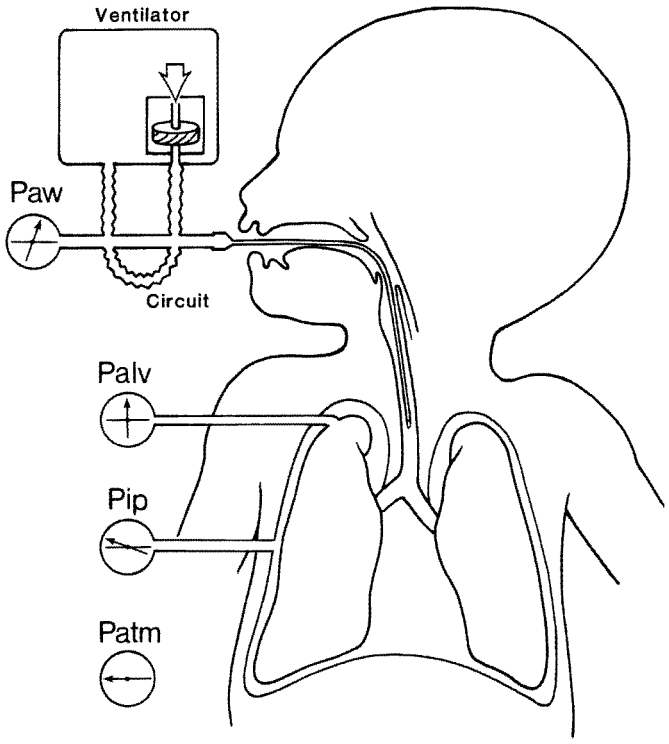

Figure 2-11 Positive-pressure gradient produced by a ventilator. Pressures are measured in the airway (*Paw*) and as shown in . Paw > Palv > Pip > Patm. Abbreviations as in .

The portion of the incoming V that fails to arrive at the level of the respiratory bronchioles and alveoli but instead remains in the conducting airways occupies the space known as the *anatomic dead space*. Another portion of V may be delivered to unperfused alveoli. Because gas exchange does not take place in these units, the volume that they constitute is called *alveolar dead space*. Together, anatomic dead space and alveolar dead space make up *total* or *physiologic dead space* (VDS). The ratio of dead space to tidal volume (VDS/V) defines *wasted ventilation*, which reflects the proportion of tidal gas delivered that is not involved in actual gas exchange. In general, rapid shallow breathing is inefficient due to high dead space to tidal volume ratio.

A number of mechanisms of gas transport other than bulk convection and molecular diffusion have been described, particularly as they relate to high-frequency ventilation. They include axial convection, radial diffusive mixing, coaxial flow, viscous shear, asymmetrical velocity profiles, and pendelluft effect.[50]

The concept of anatomic dead space is a useful one and does apply under conditions of relatively low flow velocities. It assumes that the fresh gas and exhaled gas move as solid blocks without any mixing However, in small infants with their rapid respiratory rates and small airways, the concept begins to break down. Nearly 100 years ago, Henderson et al.[51] noted that during rapid shallow breathing or panting in dogs, adequate gas exchange was maintained even though the volume of gas contained in each "breath" was less than that of the anatomic dead space. They hypothesized that low-volume inspiratory pulses of gas moved down the center of the airway as axial spikes and that these spikes dissipated at the end of each "breath" ( ). The faster the inspiratory pulse, the further it penetrated down the conducting airway and the larger the boundary of mixing between the molecules of the

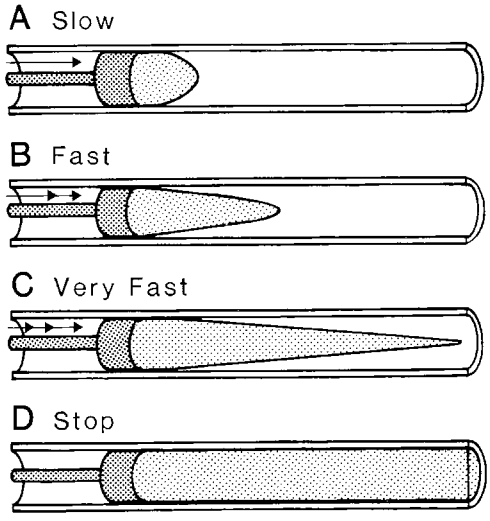

Figure 2-12 Spike theory of panting or high-frequency ventilation. **A-C,** The quicker or more "energy dense" the puff (or inspiratory pulse), the sharper the spike and the further it extends into the airway. **D,** If the pulse is suddenly stopped at end-inspiration, mixing occurs instantaneously. (Modified from Henderson Y, Chillingworth FP, Whitney JL: The respiratory dead space. Am J Physiol 38:1, 1915.)

incoming gas (with high O_2 and low CO_2) and the outgoing gas (with high CO_2 and low O_2).

During this kind of breathing, both convection and molecular diffusion are enhanced or facilitated. The provision of a greater interface or boundary area between inspiratory and expiratory gases with their different O_2 and CO_2 partial pressures is known as *radial diffusive mixing*. During high-frequency ventilation (HFV), with each inspiration, gas molecules near the center of the airway flow further than those adjacent to the walls of the airway, because the gas traveling down the center of the airway is exposed to less resistance. *A*, illustrates the velocity profiles using vectors that demonstrate the intra-airway flow patterns of gas molecules in a representation of the airway during inspiration. At the end of the inspiratory phase, the contour of the leading edge of the inspired gas is cone-shaped (*B*), having a larger diffusion interface with the preexisting gas than would be present if the leading edge was disk shaped. During exhalation, the velocity profiles are more uniform across the entire lumen rather than being cone shaped (*C*). The pulse of gas originally occupying the lumen of the airway is displaced to the right (i.e., toward the patient's alveoli), and an equal volume of gas is displaced to the left (*D*). This occurs even though the net displacement of the piston during a cycle of HFOV is zero.

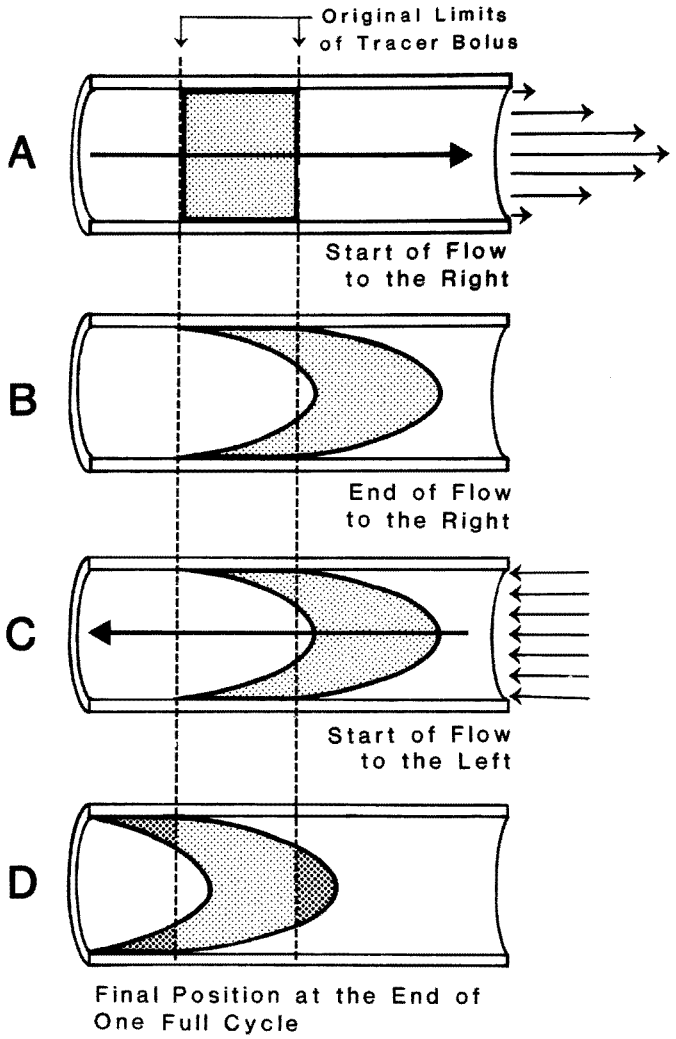

Figure 2-13 Viscous shear and inspiratory-to-expiratory velocity profiles associated with respiratory cycling. **A,** During inspiration or movement toward the right, the gas molecules of a cylindrical tracer bolus that are situated near the center of the tube travel further and faster than the gas molecules near the wall, as represented by the velocity profiles arrows at the right. **B,** At the end of the inspiratory half of the respiratory cycle, a paraboloid front has formed. **C,** During exhalation or movement toward the left, the velocity profiles are essentially uniform across the lumen. **D,** The end result after a complete respiratory cycle (with zero net directional flow) is displacement of axial gas to the right and wall gas to the left. (Modified with permission from Haselton FR, Scherer PW: Bronchial bifurcations and respiratory mass transport. Science 208:69, 1980. Copyright © 1990 by the American Association for the Advancement of Science.)

Although these mechanisms have mostly been recognized to be operative with HFV, recent evidence suggests that they are present even at conventional respiratory rates in small preterm infants with narrow endotracheal tubes.[53,54] The back-and-forth currents of gas through lung units with unequal time constants are called *pendelluft*.[50,55] This gas flow is produced because of local differences in airway resistance and lung compliance that are accentuated under conditions of high-velocity flow. This leads to regional differences in rates of inflation and deflation. "Fast units" with short time constants inflate and deflate more rapidly, emptying out into the conducting airways to be "inhaled" by "slow units" still in the process of filling ( ). Pendelluf thus improves gas mixing and exchange.

Carbon dioxide diffuses more easily across the alveolar/capillary wall, an essential characteristic given the relatively low concentration gradient between the alveoli and capillary blood. The effectiveness of CO_2 removal is primarily determined by the effectiveness of ventilation, that is, the process by which CO_2 that has diffused into the alveoli is removed, so that the maximal diffusion gradient is maintained. The movement of any gas across a semipermeable membrane is governed by Fick's equation for diffusion:

$$dQ/dt = k \times A \times dC/dl$$

where dQ/dt is the rate of diffusion in mL/min, k is the diffusion coefficient of the gas, A is the area available for diffusion, dC is the concentration difference of molecules across the membrane and dl is the length of the diffusion pathway. It is evident from the above that atelectasis, which will reduce the area available for gas exchange, and pulmonary edema, which will increase the diffusion pathway, will both reduce the effectiveness of CO_2 removal. Alveolar minute ventilation is, of course, the most critical element, because it maintains the concentration gradient that drives diffusion.

Oxygenation

Oxygen transport to the tissues depends on the oxygen-carrying capacity of the blood and the rate of blood flow. The amount of oxygen in arterial blood is called *oxygen content* (CaO_2).

$$CaO_2 = (1.34 \times Hb \times SaO_2) + (0.003 \times PaO_2)$$

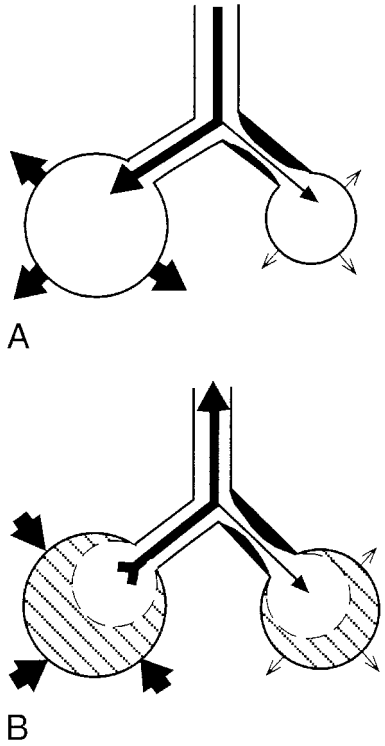

Figure 2-14 Effects of different time constants on the uneven distribution of ventilation and the production of "pendelluft." **A,** On inspiration, the fast unit receives the majority of ventilation, whereas the slow unit fills slowly (owing to local increase in airway resistance). **B,** At the beginning of expiration, the slow unit may still be filling and actually "inspires" from the exhaling fast unit. These effects are accentuated at higher frequencies, with gas "pedaling" back and forth between neighboring units with inhomogeneity of time constants. (Modified from Otis AB, McKerrow CB, Bartlett RA, et al: Mechanical factors in distribution of pulmonary ventilation. *J Appl Physiol* 8:427, 1956.)

where *Hb* is hemoglobin concentration and SaO_2 is arterial oxygen saturation. Oxygen is contained in the blood in two forms: (1) a small quantity dissolved in the plasma and (2) a much larger quantity bound to hemoglobin. The total O_2 content of the blood is the sum of these two quantities. The contribution of hemoglobin to oxygen content is described in the first term of the equation, which states that each gram of hemoglobin will bind 1.34 mL O_2 when fully saturated with oxygen. The second term of the equation describes the contribution of oxygen dissolved in the plasma.

The dissolved portion of O_2 in blood is linearly related to Po_2, such that an increase in Po_2 is accompanied by an increase in O_2 content. Oxygen content increases 0.003 mL per 100 mL of blood with every 1 mm Hg increase in Po_2. For an infant breathing 21% O_2, the dissolved portion of the blood's O_2 content is only about 2% of the total. However, for a healthy patient breathing 100% O_2, with a very high Pao_2 of 500 mm Hg (not normally recommended because of the dangers of hyperoxia), the dissolved portion of the blood's O_2 content can be as much as 10% of the total. Oxygen binds reversibly to hemoglobin. Each hemoglobin molecule can bind up to four molecules of O_2. The hemoglobin-bound portion of O_2 content is nonlinear with respect to Po_2. This relationship is illustrated by the oxyhemoglobin dissociation curve, which is sigmoid in shape ( ).

The amount of O_2 that binds to hemoglobin increases quickly at low Po_2 values but begins to level off at Po_2 values greater than 40 mm Hg. After Po_2 exceeds 90 to 100 mm Hg, the curve flattens. Once the hemoglobin is saturated, further increases in Po_2 do not increase the content of bound oxygen. The total amount of O_2 carried by hemoglobin depends on the hemoglobin concentration of the blood and the bloods' oxygen saturation. Several factors affect hemoglobin's affinity for oxygen. These factors include the (1) percentages of fetal and adult hemoglobin present in the patient's blood; (2) amount of 2,3-diphosphoglycerate; (3) pH; and (4) temperature. A greater percentage of fetal hemoglobin (as seen in premature infants), a decrease in 2,3-diphosphoglycerate content (as occurs in premature infants with RDS), alkalization of pH (e.g., after infusion of bicarbonate), a reduction in Pco_2 (secondary to hyperventilation), and a decrease of body temperature (as occurs during open heart surgery or therapeutic hypothermia for neuroprotection) all increase the O_2 affinity of hemoglobin (shift the oxyhemoglobin dissociation curve to the left without changing its shape). This means that the same level of hemoglobin saturation can be achieved at lower Po_2 values. In contrast, increased production of 2,3-diphosphoglycerate (as occurs in healthy newborns shortly after birth or with adaptation to high altitudes), a reduction of the percentage of fetal hemoglobin (e.g., after transfusion of adult donor blood to a newborn infant), a more acidic pH, CO_2 retention, and febrile illness each results in a reduction in O_2 affinity

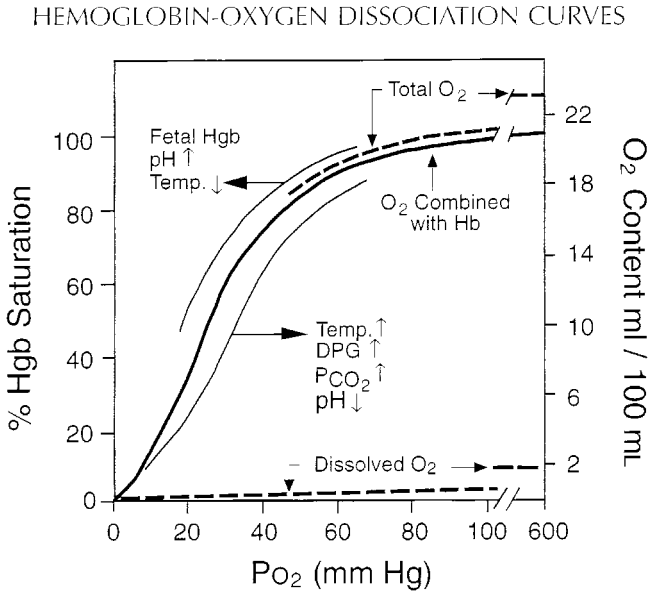

Figure 2-15 Nonlinear or S-shaped oxyhemoglobin curve and the linear or straight-line dissolved oxygen (O_2) relationships between O_2 saturation (Sao_2) and O_2 tension (Po_2). Total blood O_2 content is shown with division into a portion combined with hemoglobin and a portion physically dissolved at various levels of Po_2. Also shown are the major factors that change the O_2 affinity of hemoglobin and thus shift the oxyhemoglobin dissociation curve to either the left or the right (see also Appendix 10). (Modified from West JB: Respiratory Physiology: The Essentials, 2nd ed. Baltimore, Williams & Wilkins, 1979, pp. 71, 73.)

(shift of the oxyhemoglobin dissociation curve to the right) (see).

Some shifts in the oxyhemoglobin dissociation curve promote O_2 uptake in the lungs, O_2 release at the tissue level, or both. For example, when pulmonary arterial blood (which is rich in CO_2 and poor in O_2) passes through the lung's capillaries, it releases its CO_2; this raises local pH, which increases O_2 affinity. This allows more of the incoming O_2 to be bound to hemoglobin while plasma P_{O_2} is kept low, thus maximizing the concentration gradient down which O_2 diffuses from the alveoli into the pulmonary capillary plasma. Also, when systemic arterial blood (which is rich in O_2 and poor in CO_2) enters the tissue capillaries, it picks up CO_2 (which is in high concentration in the tissues). As a result, pH and O_2 affinity are lowered; this allows the hemoglobin to release its O_2 without significantly decreasing P_{O_2} and thus helps to maintain the concentration gradient down which O_2 diffuses into the tissues.[56]

Sa_{O_2} as monitored clinically with pulse oximetry (Sp_{O_2}) shows the percentage of hemoglobin in arterial blood that is saturated with O_2 and therefore more closely reflects blood oxygen content than does Pa_{O_2}, especially in the newborn infant with predominantly fetal hemoglobin. The greater affinity of fetal hemoglobin for oxygen, together with the relative polycythemia normally seen in newborns, allows the fetus to maintain adequate tissue oxygen delivery in the relatively hypoxemic environment in utero. The Pa_{O_2} and Sa_{O_2} in the healthy fetus are only about 25 mm Hg and 60%, respectively. This is, of course, why normal newborn infants emerge from the womb quite cyanotic. It has been demonstrated that Sp_{O_2} in the healthy newborn infant increases gradually after birth and does not normally reach 90% until 5 to 10 minutes of life.[57]

Rapid increases in Pa_{O_2}, such as occur when delivery room resuscitation is carried out with 100% oxygen, appears to result in a variety of adverse consequences, including delayed onset of spontaneous breathing and increased mortality.[58] The normal range of Sa_{O_2} in newborn infants is different from that in adults; instead of Sa_{O_2} levels of 95% or greater in adults, Sa_{O_2} levels of 85% to 92% appear to be adequate for newborns, and higher values may predispose the antioxidant-deficient preterm infant to the dangers of hyperoxia. It has been shown that the O_2 demands of most extremely premature infants can be met by maintaining Pa_{O_2} levels just above 50 mm Hg or Sa_{O_2} levels just above 88%.[59] There is currently insufficient evidence to recommend a definite range of optimal Sp_{O_2} values, but there is mounting evidence that complications of prematurity in which damage from reactive oxygen species is implicated can be reduced by the use of lower Sp_{O_2} targets in the range of 85% to 92%.[60,61]

Tissue oxygen delivery depends not only on blood oxygen content but also on cardiac output and tissue perfusion. Positive-pressure ventilation impedes venous return to various degrees and therefore can adversely affect cardiac output and pulmonary blood flow. These important cardiorespiratory interactions are often not fully appreciated, but nevertheless deserve close attention during mechanical ventilation.

The partial pressure of O_2 in arterial blood (Pa_{O_2}) is the tension or partial pressure of O_2 physically dissolved in the arterial blood plasma and is expressed in millimeters of mercury (mm Hg), or torr. This oxygen is in equilibrium with the oxygen that is bound to hemoglobin, which as we saw earlier constitutes the bulk of the total. Pa_{O_2} measured directly as part of blood gas analysis. Pa_{O_2} is a useful indicator of the degree of O_2 uptake through the lungs. The fraction of inspired O_2 (F_{IO_2}) is the proportion of O_2 in the inspired gas. F_{IO_2} is measured directly with an O_2 analyzer and is expressed as a percentage (e.g., 60% O_2) or, preferably, in decimal form (e.g., 0.60 O_2). The F_{IO_2} in room air is approximately 0.21. The partial pressure of O_2 in alveolar gas (P_{AO_2}) is the tension of O_2 present in the alveoli.

Alveolar gas typically contains oxygen, nitrogen, CO_2, and water vapor. P_{AO_2} represents the amount of O_2 available for diffusion into the pulmonary capillary blood. The partial pressure of CO_2 in the alveoli, or P_{ACO_2}, is nearly identical to the amount of CO_2 physically dissolved in the arterial blood, or Pa_{CO_2}. The partial pressure of water vapor at 100% relative humidity at body temperature and normal atmospheric pressure is 47 mm Hg. One additional correction factor must be used. This is called the *respiratory quotient* (RQ), which is the ratio of CO_2 excretion to O_2 uptake. The respiratory quotient ranges from approximately 0.8 to slightly greater than 1.0, depending on diet. To calculate the partial pressure of O_2 in alveolar gas or P_{AO_2}, we use the alveolar gas equation:

$$P_{AO_2} = [(\text{Barometric pressure} - \text{Partial pressure of water vapor}) \times F_{IO_2}] - P_{ACO_2}/RQ$$

At sea level, with normal Pa_{CO_2} of 40 mm Hg and respiratory quotient of 0.8, the alveolar gas equation for breathing room air is as follows:

$$P_{AO_2} = [(760 - 47) \times 0.21] - 40/0.8$$

P_{AO_2} is approximately $150 - 50 = 100$.

A high-carbohydrate diet raises the respiratory quotient, thus increasing CO_2 production. It is important to remember that P_{ACO_2} is decreased by hyperventilation and that the decrease in P_{ACO_2} is matched by an equal increase in P_{AO_2}. Barometric pressure varies with weather conditions and altitude. To demonstrate the effect of altitude on the absolute amount of oxygen available at the alveolar level, let us consider an infant with P_{ACO_2} of 40 mm Hg and respiratory quotient of 0.8 who is breathing room air in Denver, Colorado, which is located 5280 feet above sea level and has an average barometric pressure of approximately 600 mm Hg. Subtracting 42 mm Hg (the partial pressure of water vapor is also reduced proportionally at altitude) from 600 mm Hg yields 558 mm Hg, which, when multiplied by 0.21, gives a value of around 117 mm Hg. After subtracting the dividend of 40 mm Hg/0.8, or 50 mm Hg, from 117 mm Hg, a P_{AO_2} value in Denver of only 67 mm Hg is obtained (instead of the approximately 100 mm Hg that would be expected at sea level). Therefore, the infant has about one third less available oxygen in the alveoli when breathing room air in Denver compared to when breathing room air at sea level. The alveolar gas equation is useful in calculating a variety of indexes of oxygenation, as well as, for example, the F_{IO_2} need of an infant with compromised gas exchange who must travel to a home at higher altitude or in a commercial

aircraft, cabin pressurized to 7000 or 8000 feet above sea level.

Some important values derived from blood gas measurements are useful as clinical indicators of disease severity and are commonly used as criteria for initiation of invasive or costly therapies. They include the following:

1. Arterial-alveolar O_2 tension ratio (Pa_{O_2}/PA_{O_2}, or the a/A ratio). The a/A ratio should be close to one in a healthy infant. Ratio of less than 0.3 indicates severe compromise of oxygen transfer.
2. Alveolar-arterial O_2 gradient or difference ($AaDO_2 = PA_{O_2} - Pa_{O_2}$) In healthy infants $AaDO_2$ is less than 20 in room air. Calculating $AaDO_2$ allows the clinician to estimate disease severity and estimate appropriate FI_{O_2} change when PaO_2 is high.
3. Oxygenation index $(Paw \times FI_{O_2} \times 100)/Pa_{O_2}$

The oxygenation index factors in the pressure cost of achieving a certain level of oxygenation in the form of Paw. An oxygenation index greater than 15 signifies severe respiratory compromise. An oxygenation index of 40 or more on multiple occasions historically indicated a mortality risk approaching 80% and continues to be used as an indication for extracorporeal membrane oxygenation (ECMO) in most ECMO centers.

Effects of Altering Ventilator Settings on Oxygenation

Oxygen uptake through the lungs can be increased by (1) increasing PA_{O_2} via increasing the FI_{O_2} (increasing the concentration gradient); (2) optimizing lung volume (optimizing ventilation-to-perfusion (V/Q) matching and increasing the surface area for gas exchange); (3) maximizing pulmonary blood flow (preventing blood from flowing right-to-left through extrapulmonary shunts). There are functionally two ventilator changes available to the clinician:

1. Alter FI_{O_2}
2. Alter mean airway pressure (Paw)

is a graphic representation of the factors that affect proximal airway pressure for conventional mechanical ventilation. It has been demonstrated that, regardless of how the increase in Paw is achieved, it has a roughly equivalent effect on oxygenation.[63] Although increasing each of these variables will increase Paw, the relative safety and effectiveness of these maneuvers has not been systematically evaluated. Prolongation of the inspiratory time to the point of inverse I:E ratio is potentially the most dangerous measure and is rarely used today. Higher frequency and higher peak inspiratory pressure (PIP) both may result in inadvertent hyperventilation, which is also undesirable. The rate of upstroke has a relatively minor impact. In practice, increasing PEEP appears to be the safest and most effective way to achieve optimal Paw, in part because normally, the greatest proportion of the respiratory cycle is the expiratory phase.

Control variables for high-frequency jet ventilators (HFJVs) are similar to those for conventional ventilation. However, it should be noted that the I:E ratio of HFJV is very short (typically 1:6 or even less); therefore, to maintain adequate Paw, the PEEP typically needs to be raised by 2 to 4 cm H_2O from the baseline on conventional ventilation. When reducing pressure amplitude in response to improving ventilation, it should be kept in mind that Paw comes down as PIP is lowered; therefore, it is necessary to raise the PEEP slightly to maintain Paw.[64]

The control variables for HFOV allow for direct and independent adjustment of Paw and pressure amplitude. This separates the two chief gas exchange functions and makes it relatively easy to understand that ventilation is controlled by pressure amplitude (set as "power") and oxygenation is controlled by Paw and FI_{O_2}.[65]

Although general principles and guidelines for ventilator management can be developed, it is important to recognize that individual infants may at times respond differently under apparently similar circumstances. Therefore, individualized care based on these principles is the best approach. To optimize care, the clinician should formulate a hypothesis based on a physiologic rationale, make a ventilator change, and observe the response. This provides the clinician with feedback that either confirms

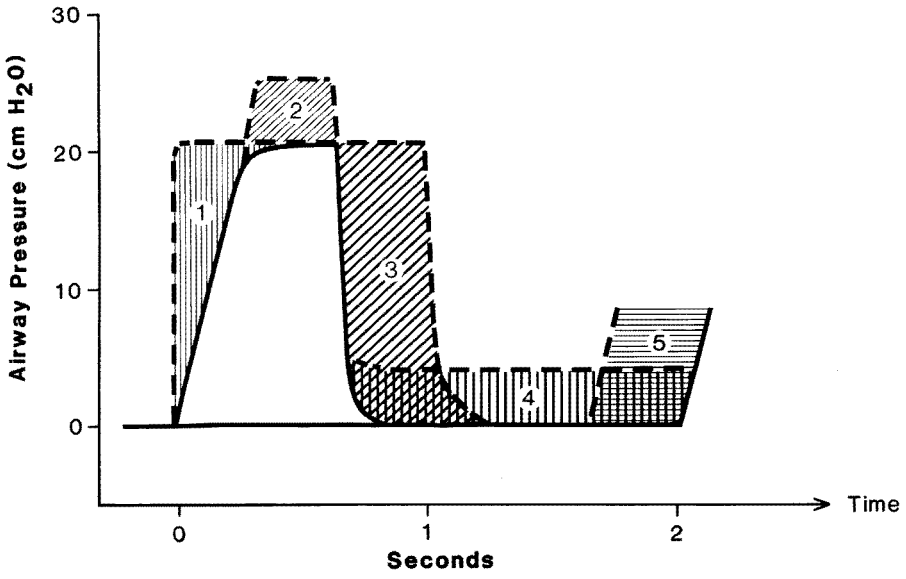

Figure 2-16 Five different ways to increase mean airway pressure: (1) increase inspiratory flow rate, producing a square-wave inspiratory pattern; (2) increase peak inspiratory pressure; (3) reverse the inspiratory-to-expiratory ratio or prolong the I-time without changing the rate; (4) increase positive end-expiratory pressure; and (5) increase ventilatory rate by reducing expiratory time without changing the I-time. (Modified from Reynolds EOR: Pressure waveform and ventilator settings for mechanical ventilation in severe hyaline membrane disease. Int Anesthesiol Clin 12:259, 1974.)

or refutes the hypothesis. The response of biologic systems is never entirely predictable and occur against a background of continuing change in the infant's condition. Additionally, there are complex interactions between the various organ systems. Otherwise appropriate ventilator changes may have adverse hemodynamic effects. Opening of a ductus arteriosus may alter hemodynamics and lung compliance, the infant's own respiratory effort may change because of neurologic alterations, and so on. In addition, it is important to keep in mind that, because ventilators are powerful tools, they can cause significant damage even under the best of circumstances, but especially if they are not used judiciously. We must learn from experience (our own and that of others) and apply that knowledge when making ventilator setting changes during assisted ventilation of the newborn.

Ventilation

For gas exchange to occur efficiently, ventilation and perfusion must be well matched. Gas is distributed through the lung via the airways. The volume of gas moved into and out of the lung with each normal breath is the *tidal volume* (V). The largest volume that can be inhaled after a full exhalation is the *vital capacity*. The volume of gas that remains in the lung after a normal expiration is the *functional residual capacity* (FRC). The volume that remains in the lung after a maximal expiration is the *residual volume*. Residual volume and vital capacity together are the *total lung capacity*. The product of tidal volume and breathing frequency is the *minute volume*. As previously discussed, only a portion of the minute volume actually reaches the alveoli. The volume of the conducting airways is called the *anatomic dead space*.

As respiratory rate and/or V are increased, minute ventilation increases. When V is increased, alveolar ventilation increases even more than minute ventilation because the anatomic dead space remains constant. In contrast, with increases in respiratory rate, alveolar minute ventilation and total minute ventilation increase proportionally. Despite the fact that increasing V has greater impact on alveolar minute ventilation, increasing V may not always be the optimal choice, because excessive V has been shown to be the most important determinant of lung injury, and increasing V appears to be more injurious to the lung than a faster rate.[66,67] The dimensions of the airway system influence ventilation. With progressive dichotomous branching moving toward the lungs' periphery, the overall cross-sectional area of the airways increases, so airflow velocity decreases, as does resistance.

With each breath, inspired gas is distributed by bulk flow to the distal airways, depending on the length of the conducting airways and the rate of flow through them. Gas flow rates are determined by local differences in driving pressure, flow resistance, tissue elasticity, and compliance. For spontaneous breathing, the driving pressure is the interpleural pressure swings generated during inspiration; during assisted ventilation, the transpulmonary pressure swings are produced by the forces exerted by the ventilator (see and). In practice, with synchronized (assisted) ventilation, the negative inspiratory effort of the infant and the positive pressure generated by the ventilator are additive and together form the *transpulmonary pressure* that determines the tidal volume. It should be noted that in routine ventilator-based pulmonary mechanics measurement, only the ventilator contribution to the transpulmonary pressure is measured, ignoring the infant's contribution. Therefore, in actively breathing infants, ventilator-based lung mechanics measurements are not accurate.

In the healthy lung, gravity-dependent differences in interpleural or transpulmonary pressure are responsible for most of the regional differences in ventilation. In the sick lung, local differences in compliance and airway resistance (time constants) are the major contributors to uneven distribution of ventilation. Bryan et al.[68] showed that the dependent lung regions in normal subjects have a greater regional volume expansion ratio (change in volume per unit of preinspiratory volume) than do the nondependent regions of lung. When a patient is upright, the basal regions of the lung are ventilated to a greater extent than are the apical regions. When a patient is supine, the basal and apical regions are ventilated to a similar extent, but the posterior (lowermost) regions are ventilated to a greater extent than the anterior regions (uppermost).

It is important to remember, however, that at the end of a normal exhalation (at FRC), the volume in the uppermost regions of the lung is greater than that of the dependent regions ( ). This may appear contradictory, but these differences can be explained on the basis of regional interpleural pressure differences ( ). Interpleural pressure at end-expiration is more negative in the uppermost portions than in the dependent portions of the lung. Converting the interpleural pressures to transpulmonary pressures, one can plot a pressure-volume curve (*lower*

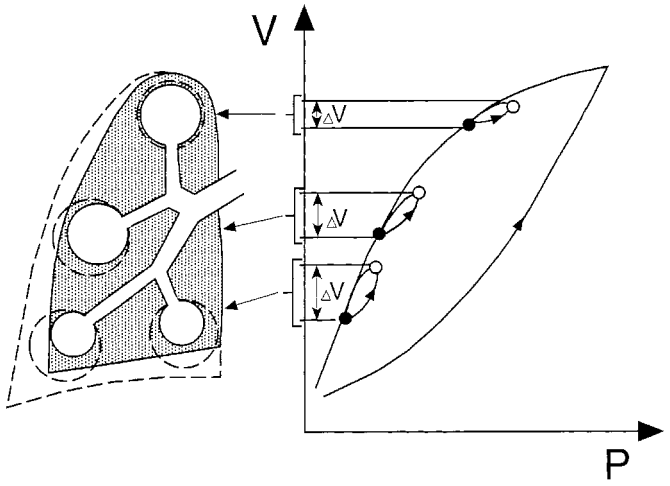

Figure 2-17 Although the upper parts of the lung are more expanded or hold a greater volume at end-expiration or the functional residual capacity level of expansion than do the lower parts, the latter show greater volume changes (i.e., ventilation changes) than do the former during tidal breathing. This occurs because the lower parts are situated on a steeper portion of the compliance or pressure-volume curve and achieve a greater ΔV per unit of ΔP. (Reprinted and adapted by permis sion of the publisher, from *The pathway for oxygen: structure and function in the mammalian respiratory system* by Edward R. Weibel, pp. 285-286, 295, Cambridge, Mass. Copyright © 1984 by the President and Fellows of Harvard College.)

right of). When the lungs are inflated starting from FRC, the dependent lung units will receive proportionately more of the inspired gas, and the nondependent units will receive proportionally less as the height above the dependent units increases. The basilar units are stretched proportionately more than the higher units because they are operating on a steeper slope of the volume-pressure curve. Compliance increases progressively from the highest portion of the lung to the most dependent portion or from high starting lung volumes to lower volumes. At the beginning of a gradual inflation from FRC, the more dependent lung regions operate on a steeper part of the compliance curve than the less dependent regions, so ventilation is greater in the dependent regions. However, because of the small size of newborn infants, the gravity-dependent regional differences are not nearly as large as they are in adults.

Lung units that contain collapsed airways require large pressure changes before the airways open to permit gas transfer. These units are not ventilated as well as units in which the airways are patent from the start. Units with high resistance are ventilated poorly regardless of their position, because these units have low compliance for any given transpulmonary pressure. In newborn infants, airway closure may be present in the resting V range, unlike older individuals in whom pleural surface pressure at FRC is substantially subatmospheric throughout the lung, thus preventing airway closure while the lung is at operational volume.[69] Starting inspiration from a lung volume that is below FRC or rest volume actually reverses the pattern of the distribution of ventilation.[70] If inspiration is started from a low level of lung volume, interpleural pressures are less negative overall (because elastic recoil is minimal at these low lung volumes) and even may be positive in the more dependent regions of the lung.

When regional interpleural pressure exceeds (is more positive than) airway pressure, then airway closure occurs and no gas enters that segment for the first portion of inspiration or until regional interpleural pressure decreases to below airway pressure further along into inspiration. Thus ventilation is reduced in dependent regions and is redirected to the upper lung regions, making them the better-ventilated areas; this is a reversal of the usual pattern.

During assisted ventilation, inflation at end-inspiration is uniform, as evidenced by the observation of alveoli of equal size throughout the lung.[71] At end-expiration or FRC level, however, alveoli in the uppermost regions of the lung are found to have a volume fourfold that of alveoli at the base. Moderate levels of PEEP increase FRC more in dependent regions than in upper regions of the lung because the former are less well expanded initially and are at a lower and more favorable point on their compliance curve. If significant basilar atelectasis preexists, the addition of PEEP or CPAP should help the most in the more dependent areas, opening them for improved regional ventilation. All forms of continuous distending pressure favor uniformity of ventilation because they expand airways and thus lower resistance and because they prevent airway closure and gas trapping during forced exhalation.

Gravitational effects on the distribution of ventilation have been exploited in adult patients with or without ventilatory assistance who have unilateral lung disease or who have undergone thoracotomy.[73] Improved gas exchange in these patients can be accomplished if they are positioned with their "good" side down. This technique increases ventilation to the dependent lung regions, which also receive relatively greater blood flow, resulting in better V/Q matching in the good lung. Body position affects ventilation and gas exchange in infants in the opposite way.

When infants with unilateral lung disease are placed in the lateral decubitus position, the uppermost "good" lung receives a greater portion of ventilation than the dependent lung. This may be the case for infants with restrictive

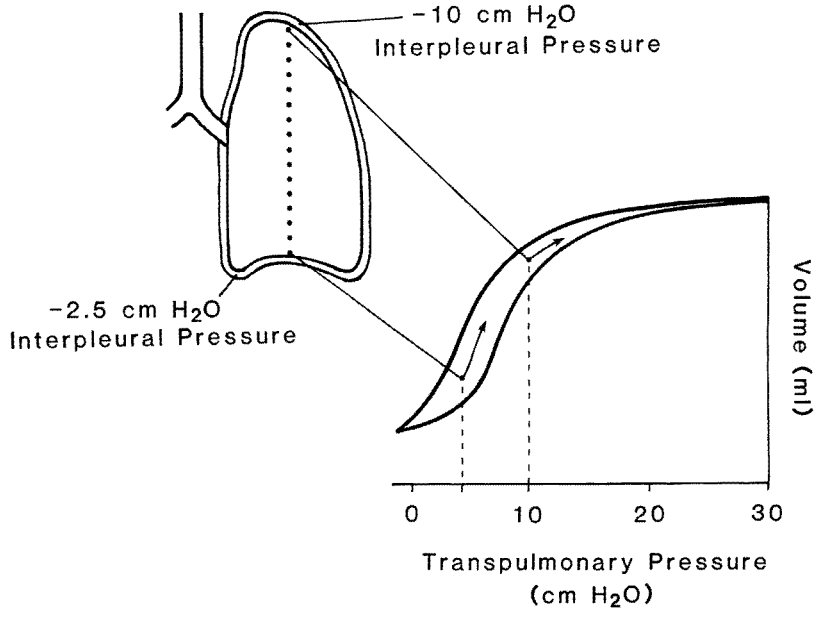

Figure 2-18 Effect of the interpleural pressure gradient up the lung upon the distribution of ventilation. The great est negative pressure is at the top owing to the gravitational tug (weight) of the lung through its visceral pleura on the parietal pleura. Because the upper and lower areas are on different parts of the pressure-volume curve, different amounts of volume (ventilation) are achieved by the two areas given the same pressure change. The steeper compli ance line for the lower area means a greater increase in volume per unit pressure change. (Modified from West JB: Respiratory Physiology: The Essentials, 2nd ed. Baltimore, Williams & Wilkins, 1979, p. 96.)

lung disease such as unilateral PIE. In cases of unilateral PIE, one sees ideal circumstances for the occurrence of airway closure in the "bad" lung when it is placed in the dependent position. In patients with unilateral tension PIE, interpleural pressure on the bad side already is elevated secondary to the presence of high (positive) interstitial pressure because of gas trapping outside of the terminal air spaces. Positioning patients with the PIE side down adds the additional weight of the mediastinal structures, which causes the interpleural pressure to exceed local airway pressure and results in airway collapse. This airway closure in the dependent (bad) lung often facilitates resolution of unilateral PIE, while the infant's gas exchange needs are met by the nondependent lung.[74,75]

The pattern of diaphragmatic motion plays a role in the distribution of ventilation in the newborn infant. When the diaphragm is paralyzed and the patient is supine, mechanical ventilation tends to produce greater motion of the superior than of the inferior portion of the diaphragm because the superior portion is less constrained by the abdominal contents and mediastinal structures. Therefore, ventilation of the upper (anterior) segments of the lung is preferential.[76] Because perfusion still is likely to be better in the dependent regions secondary to gravitational effects, paralysis may result in V/Q mismatch with hypoxemia. The improvement in oxygenation achieved after adults with acute respiratory failure[77] or premature infants with respiratory insufficiency[78] are switched from the supine to the prone position is attributable to the enhancement of V/Q matching (or an increase in ventilation to a level that better matches the existing degree of perfusion). In premature infants the prone position affords better distribution of ventilation throughout the lung, especially to the dependent regions that are better perfused.[78]

The most common causes of uneven distribution of ventilation are conditions characterized by local differences in lung compliance, airway resistance, or both. If the patient is receiving assisted ventilation and is faced with local differences in either lung tissue elasticity or airway resistance, the distribution of gas delivered during the inspiratory phase is influenced by the mode of ventilation chosen. Local or regional (lobar) variations in compliance are determined by (1) local tissue water content; (2) presence or absence of surfactant; (3) presence of volume loss; or (4) presence of gas trapping or overexpansion. For example, pneumonia in one lung area makes that lung less compliant than the normal lung; thus the affected lung receives less volume per unit pressure than do the unaffected areas.

Differences in distal airway resistance may be caused by local narrowing secondary to either obstruction or compression. For example, partial obstruction of a bronchus with meconium increases airway resistance and reduces alveolar ventilation in the area distal to the partial obstruction (see). Many disease processes common in premature infants involve nonuniform regional compliance and resistance. During conventional mechanical ventilation, distribution of the inspired gas is largely controlled by regional variations in compliance and resistance (i.e., time constants). During HFV, the distribution of inspired gas is more dependent on the mechanical properties of the central airways and chest wall (resistance, inertance) and less so on the compliance of lung tissue. If inspiratory pressure is increased slowly (low inspiratory flow rate), the volume of gas delivered depends mainly on the compliance of the lung. If inspiratory pressure is increased quickly (high inspiratory flow rate), the distribution of gas depends mainly on local airway resistance.

Consequently, the largest volumes are delivered to areas with the least resistance. This information is useful to the clinician trying to decide how best to ventilate a patient with meconium aspiration syndrome or BPD. One would like to be able to ventilate the patient's unobstructed lung regions while minimizing air trapping and overdistention in areas behind partially obstructed airways (see). One approach is to use rapid rates (high inspiratory flows) and short inspiration times (T_Is). In this fashion, only regions of the lung with short (or normal) time constants are given sufficient time for pressure equalization (volume delivery); thus these areas are being ventilated while overdistention of lung regions with long time constants is avoided (however, beware of the risk of air trapping if expiratory time is not sufficient for complete exhalation). In cases of pulmonary air leak (pneumothorax or bronchopleural fistula), a strategy incorporating short T_I and a high rate often is effective in decreasing the magnitude of the leak. Several reports have described the successful application of HFV in adults with airway disruption or bronchopleural fistulae[79,80] and in newborns with persistent air leaks through pneumothoraces[81] or tracheoesophageal fistula.

In cases of PIE, the use of low rates and long T_Is might worsen the clinical situation. Because the lung regions with PIE have long time constants (due to elevated resistance), they could become further overdistended with this mode of ventilation. If ventilated with a conventional ventilator using high rates and short Tis or if ventilated with an HFV, lung areas with long time constants would be less likely to become overdistended. However, high rates on conventional ventilation increase the likelihood of delivering inadvertent PEEP. High-frequency jet ventilation has been shown to be safer and more effective than rapid-rate conventional ventilation in the treatment of newborn infants with pulmonary interstitial emphysema.[83] As the PIE resolves and the compression effects on the surrounding lung tissue are alleviated, the distribution of ventilation would become more homogeneous. The clinician's choice of strategy and mode of ventilation can be important determinants of the distribution of ventilation, particularly in situations of nonhomogeneous lung disease.

During assisted ventilation, to minimize risk to the infant, the most minimal amount of pressure required to achieve adequate gas flow and alveolar ventilation should be used. Enough distending pressure should be applied to optimize lung volume and homogeneity of lung expansion and prevent airway collapse. Enough driving pressure should be applied so as to achieve an appropriate V .

Effects of Altering Ventilator Settings on Ventilation

During conventional ventilation, increasing V or increasing the ventilator rate are the two primary methods for increasing ventilation (enhancing CO_2 removal). The ventilator rate is controlled either directly or by altering the

inspiratory and/or expiratory time. V is controlled in different ways depending on the type of ventilator. With volume-controlled ventilators, V can be manipulated directly. However, the volume that is controlled is the volume injected into the ventilator circuit, not directly into the patient's lungs. A significant but variable portion of that volume is lost to compression of gas in the circuit or to leaks around uncuffed endotracheal tubes.[84] Consequently, the ability to directly control effective V is greatly limited. With time-cycled pressure-limited devices, adjustments that increase ΔP (pressure amplitude or difference between PIP and PEEP) will increase V , provided the compliance remains the same. To control ventilation or CO_2 elimination during HFJV, the operator manipulates basically the same parameters in the same direction as during conventional ventilation.[64] Ventilation during HFOV is generally controlled by altering the power setting, which controls the stroke length of the piston and therefore pressure amplitude. The larger the amplitude, the greater the V and thus the greater the CO_2 removal. With both HFJV and HFOV, minute ventilation is more closely related to frequency × V ^{2} and thus even small changes in amplitude result in substantial changes in P_{CO_2}.[65] V delivered during HFOV is frequency-dependent and decreases as the operating frequency increases.[85] This means that in the unusual clinical setting in which amplitude settings are maximized, frequency may need to be reduced if an improvement in ventilation is desired. It is important for the clinician to remember the passive change in amplitude that occurs with changes in frequency. At the other extreme, on the rare occasions when V or power settings are at minimum levels and the infant is not yet ready for extubation, operating frequency may have to be increased to decrease CO_2 removal.[86]

Perfusion

Before delivery, only 8% to 10% of cardiac output flows to the lungs. In the fetus, pulmonary vascular resistance is high and systemic vascular resistance is low.[87] Most of the blood coming from the fetal inferior vena cava flows from right to left through the foramen ovale and much of the right ventricular output shunts through the ductus arteriosus, thus bypassing the lungs. Under normal circumstances after delivery, a relatively rapid transition to the adult pattern of circulation occurs, after which virtually all right heart output goes through the lungs, then the left side of the heart, and out the aorta.

Key to this transition is a decrease in pulmonary vascular resistance and an increase in pulmonary blood flow preceding closure of the fetal shunts. Experiments carried out on fetal lambs and investigations into the actions of certain mediators, including nitric oxide (NO) ( ), have demonstrated a number of factors that contribute to the decrease in pulmonary vascular resistance that occurs at birth. These include (1) expansion of the lung with a gas,[88] (2) increase in P_{AO_2},[89] (3) increase in Pa_{O_2},[90] (4) increase in pH,[91] and (5) elaboration of vasoactive substances such as bradykinin, the prostaglandins [PGE_1, PGA_1, PGI_2 (prostacyclin),[93,94] and PGD_2[95]], and endothelium-derived relaxing factor,[96] which subsequently was shown to be the gas NO.[97] Blood flow through the pulmonary circuit is directly proportional to the pressure gradient across the pulmonary vessels and the total cross-sectional area of the vessels that make up the pulmonary vascular bed. Blood flow is inversely proportional to the blood's viscosity. Increased blood viscosity interferes with gas exchange by reducing pulmonary perfusion.

TABLE 2-1 Factors Affecting Pulmonary Blood Flow

Increasing Flow	Decreasing Flow
Optimization of lung volume	Lung atelectasis
Increase in P_{AO_2}	Decrease in P_{AO_2}
Increase in Pa_{O_2}	Hypoxemia (reduction in Pa_{O_2})
Alkalosis (respiratory or metabolic)	Acidosis (respiratory or metabolic)
Release of mediator substances (e.g., bradykinin, prostaglandins)	Mast cell degranulation with release of histamine
Left-to-right shunting (intracardiac or ductal)	Right-to-left shunting (intracardiac or ductal)
Endogenous production of NO	Systemic hypotension (when right-to-left shunting is already present)
Inhalation of exogenous NO	Lung overexpansion

NO, Nitric oxide; *Pa*O ; partial pressure of oxygen in arterial blood; *P*AO , partial pressure of oxygen in the alveoli.

As the lung expands after birth, pulmonary vascular resistance decreases and pulmonary blood flow increases.[88] With inflation of the lungs, some "straightening out" of pulmonary vessels occurs. The larger vessels are pulled open by traction of the lung parenchyma that surrounds them. The perialveolar capillary lumens enlarge because of the action of surface tension produced by the newly established air-fluid interfaces. There are two types of pulmonary blood vessels: alveolar vessels, which are composed of capillaries and the slightly larger vessels in the alveolar walls (these vessels are exposed to alveolar pressure); and extra-alveolar vessels, which include the arteries and veins that run through the lung parenchyma but are surrounded by interstitial tissue rather than alveoli ( ).[98]

The diameter of alveolar vessels is determined by the balance between the alveolar pressure and the hydrostatic pressure within the vessel. The vessel walls contain little elastic tissue and virtually no muscle fibers. Alveolar vessels collapse if alveolar pressure exceeds pulmonary venous pressure. Extra-alveolar vessels have structural support in their walls and are not significantly influenced by alveolar pressure. The vessel diameter of extra-alveolar vessels is affected by lung volume, because expanding the lung tends to pull these vessels open. If an airless lung is inflated to total lung capacity, pulmonary vascular resistance shows a U-shaped response, with high resistance at the low and high ends of inflation and low resistance in the middle (see). Resistance is high at low lung volumes because the extra-alveolar vessels are narrowed (they are not being pulled open). Resistance is high at high inflation volumes because the alveolar vessels are narrowed due to compression (they may even collapse). The lowest pulmonary vascular resistance, as well as best lung compliance, is found when the lung is neither underinflated nor overinflated.

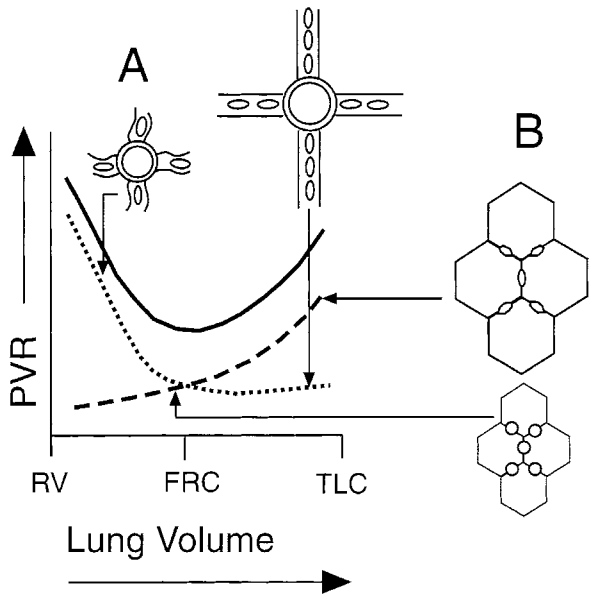

Figure 2-19 Effects of lung volume on pulmonary vascular resistance (*PVR*, solid curved line). **A,** "Extra-alveolar" vessels pose high resistance (*dotted curved line*) at low and high lung volumes, at the former because they become narrow and at the latter because they become stretched. **B,** "Alveolar" vessels pose the least resistance (*dashed curved line*) when they are open widest at the functional residual capacity (FRC) lung volume level, but they become compressed under conditions of lung overinflation. *RV,* Residual volume; *TLC,* total lung capacity. (Modified from West JB: Respiratory Physiology: The Essentials, 2nd ed. Baltimore, Williams & Wilkins, 1979, p. 39.)

The rapid rise in oxygen tension in the alveoli (P_{AO_2}) and in the arterial blood (P_{aO_2}) perfusing the pulmonary vessels plays a major role in the circulatory adaptation that occurs during transition of extrauterine life. It is the influence of P_{AO_2} on adjacent arteries that exerts the greatest effect on decreasing pulmonary vascular resistance with the initiation of breathing air.[90] With the initiation of breathing air, the lung is exposed to a P_{O_2} of approximately 100 mm Hg. P_{aO_2} in the central circulation of the newborn infant rises from the fetal range between 25 and 30 mm Hg to greater than 60 mm Hg within the first hours after birth.

Many mediator substances have been implicated in the pulmonary vasodilation seen in the newborn infant. Bradykinin is a vasoactive peptide that produces pulmonary vasodilation in fetal lambs. Bradykinin concentration increases transiently in blood that has passed through the lungs of fetal lambs ventilated with oxygen, but it does not increase if the lungs are ventilated with nitrogen. Bradykinin stimulates the local production of prostacyclin, which is also a potent pulmonary vasodilator.[93] PGA_1, PGE_1, and prostacyclin decrease pulmonary vascular resistance by dilating both pulmonary veins and arteries. Prostacyclin production is stimulated by lung expansion with air and by mechanical ventilation.

The decrease in pulmonary vascular resistance associated with mechanical ventilation can be attenuated by prior administration of a prostaglandin synthesis inhibitor (indomethacin).[94] PGD_2, another prostaglandin, is a semiselective pulmonary vasodilator. It promotes pulmonary vasodilation without causing the systemic vasodilatory effect produced by other prostaglandins.[95] The pulmonary vasodilatory effect of PGD_2 is present only during the first few days after birth; thereafter, it becomes a pulmonary vasoconstrictor. This observation suggests that PGD_2 plays a role in the transition from fetal to adult-type circulation after birth. PGD_2, like histamine, is released through mast cell degranulation. The number of mast cells in the lungs increases just before birth and then declines after delivery.[100] Mast cells play an important role in the pulmonary vasoconstrictive response to hypoxia.[101] Mast cells are abundant in the lung and are ideally located for modulation of vascular tone. Mast cell degranulation has been demonstrated to occur after acute alveolar hypoxia. Pretreatment with cromolyn sodium (a mast cell degranulation blocking agent) prevents the pulmonary vasoconstriction normally induced by alveolar hypoxia.[103]

NO, previously known as *endothelium-derived relaxing factor*, plays an important role in regulating pulmonary vascular resistance. Its action reduces pulmonary vasoconstriction, thereby increasing pulmonary blood flow. Endogenous NO is generated in vascular endothelial cells by enzymatic cleavage of the terminal nitrogen from L-arginine; production is accelerated at birth due to the increase in P_{O_2}. NO diffuses into the vascular smooth muscle cells and stimulates the production of cyclic guanosine monophosphate (cGMP), which causes smooth muscle relaxation.

The primary factor keeping pulmonary vascular resistance high in the fetus is relative hypoxemia. Because of the preferential perfusion of the pulmonary circuit with the most desaturated blood (venous blood returning from the fetus's head), the P_{aO_2} of blood perfusing the lungs of a fetal lamb is around 18 to 21 mm Hg. Profound fetal hypoxemia causes further pulmonary vasoconstriction. A decrease in pulmonary arterial P_{O_2} to about 14 mm Hg diminishes pulmonary blood flow in the fetus to approximately 50%, its base level.[107] Hypoxemic stress produces progressively greater increases in pulmonary vascular resistance as the gestational age of a fetus advances.[108] Chronic hypoxemia in the fetus produces an increase in the medial smooth muscle of the pulmonary arterioles, which may lead to pulmonary hypertension and increased pulmonary vasoreactivity.[109] This may contribute to the development of persistent pulmonary hypertension of the newborn (PPHN) in some newborn infants and may explain why infants born through meconium stained fluid are at high risk for PPHN. Passage of meconium is thought to be a sign of fetal intolerance of labor, which is more likely to occur in infants whose placental function is compromised and who may have had prolonged fetal hypoxemia.

For these same reasons, infants living at high altitudes have an increase in pulmonary vascular resistance that persists into childhood. They have relative pulmonary hypertension and are at increased risk for developing cor pulmonale.[110] Infants with cyanotic congenital heart disease and chronic hypoxemia are also at risk for developing pulmonary hypertension and cor pulmonale, as are oxygen-dependent infants with BPD. The vasoconstriction

response to alveolar and arterial hypoxemia is potentiated by acidosis.[91]

PPHN is a clinical syndrome, peculiar to the early neonatal period, characterized by severe arterial hypoxemia caused by increased pulmonary vascular resistance with resultant right-to-left shunting through fetal channels (at the atrial and ductal levels). PPHN is associated with a variety of conditions, including RDS, pneumonia, meconium aspiration syndrome, and congenital heart disease (CHD) and is also seen in infants with chronic fetal distress or peripartum stress.[111,]

Infants with PPHN exhibit hypoxemia secondary to extrapulmonary right-to-left shunting; near-systemic or suprasystemic pulmonary artery pressures; and lability in pulmonary artery pressure secondary to pulmonary vasoreactivity ( ). Hyperventilation of infants with PPHN has been shown to decrease pulmonary artery pressure.[113] However, hyperventilation with resultant hypocarbia has been shown also to be associated with poor pulmonary and neurologic outcomes. As such, hyperventilation is no longer advocated as a treatment modality in infants with PPHN.

Inhaled NO causes a decrease in pulmonary vascular resistance and an increase in pulmonary blood flow, without affecting systemic arterial pressure. It is a selective pulmonary vasodilator, because it is inactivated by being bound to hemoglobin upon entering the systemic circulation. When used at low concentrations, inhaled NO also improves ventilation-perfusion matching by selectively vasodilating the well ventilated areas of the lung (see Chapter 14).

The pulmonary arteries, like the airways, form a treelike structure. The pulmonary circulation is perfused by the entire cardiac output. Blood flow is determined by the pressure difference between pulmonary arteries and veins and by the vascular resistance. The pulmonary circulation is a low-pressure low-resistance system. The distribution of blood flow to the gas exchange units depends on the distribution of resistances, which are affected by contraction of the smooth muscle walls of the arteries. In hypoxia, resistance increases, due to hypoxic pulmonary vasoconstriction.

There are regional differences in ventilation and perfusion. The dependent portions of the lung are better ventilated and better perfused than the upper portions. Hypoxic vasoconstriction shunts blood away from poorly ventilated acini, which helps preserve V/Q matching. Ideally, ventilation and perfusion are evenly matched, with a V/Q ratio of 1. When a lung or lung unit is relatively underventilated but normally perfused or is normally ventilated but overperfused, it is said to have a low V/Q (less than 1). When a lung unit is overventilated and normally perfused or is normally ventilated and underperfused, the resultant V/Q is high (greater than 1).

The more dependent the lung region, the greater its perfusion. The vessels in dependent regions of the lung are more distended and thus present less resistance to flow because their transmural pressure is greater. Transmural pressure is the difference between the pressures inside and the pressure outside the vessel wall. Inside "hydrostatic" pressure increases the more dependent a vessel's position is in the lung. Outside interstitial pressure reflects interpleural pressure (see). Interpleural pressure decreases the more dependent the lung region is. Because the hydrostatic pressure increase (inside the vessel) is greater than the interpleural pressure decrease (outside the vessel), the transmural pressure increase is greater the more dependent the lung region.

In the upright adult, the lung is divided into four perfusion zones ( ) based on up-and-down distance and specific pressure differences. Zone I is the least dependent (uppermost) region and has almost no blood flow because alveolar pressure exceeds pulmonary capillary pressure. This causes collapse of the capillaries around the alveoli. Zone II is the upper middle region and has some flow because pulmonary artery pressure exceeds alveolar pressure. Zone III is the lower middle region, where flow is determined by the difference in pressure between the pulmonary arteries and pulmonary veins. Zone IV is the most dependent region, where interstitial pressure is great enough to cause narrowing of extra-alveolar vessels and thus reduce blood flow as a result of increased pulmonary vascular resistance.

In infants, under normal circumstances the entire lung is considered to have zone III characteristics from a physiologic standpoint. In some situations, as in the presence of air trapping or alveolar overdistention, a portion of the lung may behave as zone I or II, with a decrease in pulmonary blood flow. In other conditions such as interstitial edema (fluid overload; left-sided heart failure, as in congenital heart disease or significant patent ductus arteriosus; capillary leakage following hypoxic insult or asphyxia; BPD), much of the dependent portion of the lung behaves like zone IV, with increased vascular resistance and decreased pulmonary blood flow. In this clinical situation, fluid restriction, administration of a diuretic, or both may result in significant improvements in gas exchange because of an improvement in pulmonary blood flow (as well as an improvement in lung compliance and a decrease in airway resistance). Conditions in which

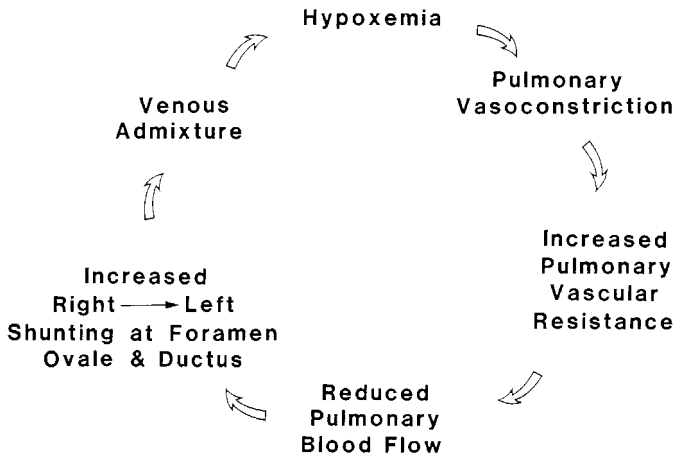

Figure 2-20 Vicious circle touched off by hypoxemia that reverts transitional circulation back to the fetal type, as seen in persistent pulmonary hypertension.

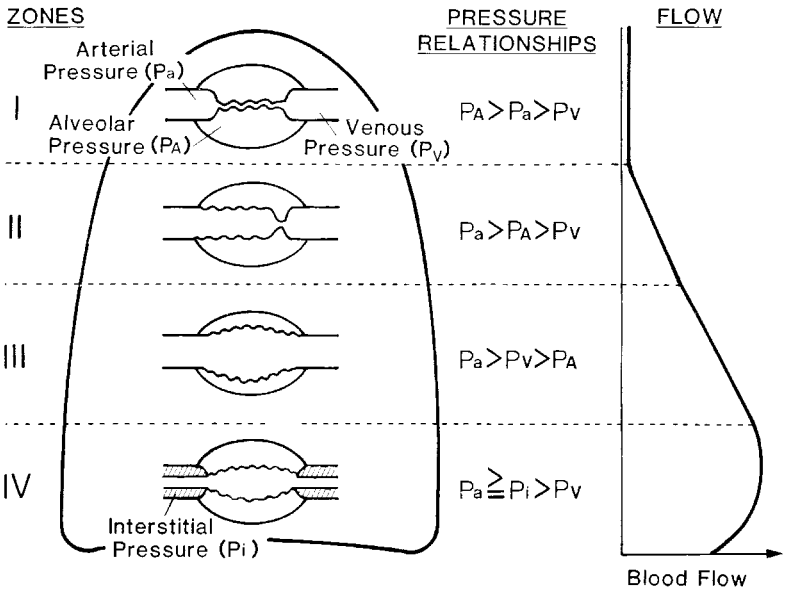

Figure 2-21 Various intraluminal and extraluminal pressure effects on the alveolar vessels of the lung in relation to blood flow in the four perfusion zones. Alveolar vessels represent "Starling resistors," which consist of collapsible tubes in pressure chambers. Note the situation in zone II, where there is a constriction in the "downstream end" of the collapsible vessel. Here, chamber (*alveolar*) pressure exceeds intraluminal downstream (*venous*) pressure and the vessel collapses; pressure inside the tube at the constriction is equal to the chamber (*alveolar*) pressure. Flow is thus determined by the arterial-alveolar pressure difference rather than by the usual arterial-venous pressure difference. (Modified from West JB, Dollery CT, Naimark A: Distribution of blood flow in isolated lung: relation to vascular and alveolar pressures. J Appl Physiol 19:713, 1964.)

significant left-to-right shunting and pulmonary hyperperfusion occur tend to abolish the unevenness of blood flow in the lungs.[68]

Regional hypoventilation produces local pulmonary vasoconstriction that diverts blood flow away from underventilated areas. This is a protective mechanism that decreases the perfusion of nonventilated or poorly ventilated areas of the lung. Term newborn and premature lambs are capable of redirecting blood flow away from hypoxic regions produced by atelectasis or bronchial obstruction. The flow directed away from atelectatic and hypoxic lung segments is directly proportional to the amount of lung volume loss. Lung scans in infants have identified perfusion deficits in areas of atelectasis. Alveolar overdistention secondary to air trapping may reduce area blood flow by collapsing surrounding capillaries.

When CPAP or positive-pressure ventilation is used to recruit atelectatic lung units, improvement in both local ventilation and perfusion may result in those regions. However, those areas of the lung, which already are well expanded, may be further inflated, which can increase rather than decrease pulmonary vascular resistance in those areas. The overall effect on pulmonary blood flow produced by positive-pressure ventilation depends on the initial lung volume status of the various functional lung regions and the net result of the therapy on global pulmonary blood flow.

Control of Ventilation

The respiratory control center in the newborn infant is immature compared to adults and therefore more easily influenced by changes in acid/base status, temperature, sleep state, hypoxia, medications and other variables. Because of this relative immaturity, the central and peripheral chemoreceptors that respond to changes in arterial O_2 and CO_2 tensions act both quantitatively and qualitatively differently from those in adults. Additionally, a set of chest wall stretch proprioceptors is able to reflexively inhibit or drive respiration. REM sleep also has a significant effect on the control of respiration in the newborn infant. During REM sleep, the normal phasic tone changes in the intercostal muscles, which are important for stabilizing the rib cage during inspiration, are inhibited. Because the intercostal muscles fail to tighten with inspiration, the infant's chest wall deforms during inspiration. Contraction of the diaphragm worsens the paradoxical movement, increases its O_2 consumption measured during REM sleep, and may lead to fatigue-induced apnea.

Application of CPAP or PEEP causes the infant's respiratory rate to slow and his or her respiratory efforts to become more regular with a reduction in periodic breathing and apneic episodes.[131] The distending pressure stabilizes the infant's compliant chest wall by providing a "pneumatic splint" that counters the tendency of the chest wall to collapse during inspiration. The application of continuous distending pressure shortens and intensifies inspiratory effort while prolonging expiration. Methylxanthines such as caffeine and aminophylline (or theophylline) increase alveolar ventilation through central stimulation.[133] Methylxanthines cause an increase in diaphragmatic contractility and resistance to fatigue with shift of the CO_2 response curve to the left so that an increase in V occurs in response to an increase in CO_2.[134,135] A more detailed discussion on the control of ventilation can be found in Chapter 3.

Conclusion

Based on an understanding of the physiologic principles of assisted ventilation, we know that ventilation strategies must be individualized for each patient. It is also clear that

the use of the appropriate strategy to provide mechanical ventilatory support and the skill with which this is done is more important than the specific type of device used to deliver that support. Each time we encounter an infant in respiratory distress, we must determine the specific pathophysiology of the infant's condition and then decide what level of support is required, addressing the infant's specific condition. The least invasive level of support that is adequate to accomplish the task should be selected and the infant's response to therapy must be closely monitored.[136] We must be cognizant of how our strategies and techniques of providing assisted ventilation to infants impact their long-term outcomes. Repeated cycling of the terminal airways from below critical opening pressure leads to cellular injury and inflammation (atelectotrauma). This results in alveolar collapse, atelectasis, interstitial edema, and elaboration of inflammatory mediators. The resulting atelectasis leads to a further reduction in lung compliance that necessitates higher inspiratory pressures, which further compromises surfactant production. Atelectotrauma leads to further lung injury, which necessitates increased levels of distending airway pressure and/or increased levels of inspired oxygen . The increase in F_{IO_2} may lead to oxidative injury and further cellular dysfunction. Despite many years of diligent research, there are still more questions than answers. However, we do know that mechanical ventilation causes lung injury that leads to inflammatory response[137]; oxygen exposure is harmful[138,139]; lung overdistention (volutrauma) causes lung injury[140]; lung injury and inflammation exacerbate the deleterious effects of oxygen toxicity and volutrauma[141]; and finally, atelectotrauma is a source of lung injury.

Establishment of an appropriate FRC (optimization of lung volume), administration of surfactant, avoidance of mechanical ventilation (if possible), use of adequate PEEP to avoid the repeated collapse and reopening of small airways, avoidance of lung overinflation caused by using excessive distending airway pressure or supraphysiologic tidal volumes, and avoidance of use of more oxygen than is necessary all are important in achieving the best possible outcomes and long-term health of our patients.[84,143] While caring for your patients, always remember the words of the Hippocratic Oath, "First do no harm."

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3 Control of Ventilation and Apnea

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The transition from fetal to neonatal life requires infants to develop a stable respiratory pattern for successful gas exchange. The complex interaction of maturing anatomy, central nervous system function, neuromuscular integration, sleep state, and the infant's environment make neonates particularly vulnerable to disorders of respiratory control. Intrauterine breathing patterns have been observed in a sheep fetus as early as 5 to 14 weeks of gestation (term is approximately 20 weeks).[1] The irregular breathing movements in the human fetus have been detected as early as 11 weeks of gestation, with a rate ranging from 30 to 70 movements per minute and lasting as long as 55% to 99% of the day.[2] The breathing pattern is altered from a periodic non–air-breathing pattern in the fetus to a continuous air-breathing pattern in infants.

The immaturity of respiratory control among preterm infants almost invariably results in respiratory pauses of variable duration that may require pharmacologic intervention or ventilatory support. Understanding this developmental change in sleep and breathing patterns is important for the neonatologist and pediatrician in the diagnosis and management of apnea and respiratory dysrhythmias in neonates. Adequate establishment of functional residual capacity (FRC) in newborns is essential if their lungs are to meet the metabolic demands placed on them.

Although premature infants maintain their FRC through the tonic activity of the diaphragm and intercostal muscles during expiration, babies born at term use the more efficient method of combine prolonged postinspiratory muscle activity with laryngeal control of the expiratory flow. An infant who is unable to maintain an adequate FRC may progress to respiratory insufficiency and require mechanical ventilatory support, which is associated with an obvious risk of morbidity and mortality.

In this chapter, the development of sleep and respiratory control is reviewed. The pathophysiology, diagnosis, and management of common conditions that cause abnormal control of breathing in neonates and infants are discussed ( ).

Developmental Aspect of Sleep and Respiratory Control

Fetal Development

The fetal respiratory center is active in utero as evidenced by phrenic nerve activity; however, this activity is minimal and has a different pattern than that present after birth.[3,4] In the human fetus, breathing movement can be identified by the 10th to 12th week of gestation.[5,6] By 20 to 28 weeks of gestation, rhythmic breathing activity is observed in utero and is characterized by long silent periods with no respiratory movement alternating with active periods.[7] This cycle varies between 40 and 60 minutes.[8]

Preterm Infant Development

In the preterm infant, active sleep is prominent and accounts for 90% of total sleep time at 31 weeks of gestation. The amount of active sleep decreases to 50% at term. Irregular breathing and apnea are common and occur primarily during active sleep.[9] Premature infants have greater breath-to-breath variability in minute ventilation compared to term infants. In contrast to term infants, preterm infants respond to hypoxia with a sustained decrease in ventilation with no initial hyperpnea, which may reflect an immaturity of the central nervous system involved in breathing control.[10,11]

The reduced hypercapnic response may indicate reduced CO_2 sensitivity of the central chemoreceptors; this response becomes progressively more sensitive with increased gestational age until it reaches the adult level at term.[12] In addition, stimulation of irritant receptors in the carina in preterm infants leads to apnea; term infants respond to the same stimuli with increased respiratory efforts. This paradoxical response to respiratory stimuli may be related to immaturity of vagal myelination. Chest wall instability in preterm infants may contribute to apnea secondary to intermittent airway closure and decreased FRC.[14] Increasing lung volume by continuous positive airway pressure (CPAP) results in resolution of the apnea (see Chapter 8).[15]

Term Infant Development

The amount of quiet sleep increases with age, with a reciprocal decrease in active sleep. Most apneas occur during active sleep. Several studies have shown that most apneas in healthy term infants are central apnea; obstructive and mixed apnea are rare. The number of apneic episodes decreases with increased gestational age.

Most term infants have a normal hypercapnic ventilatory response, with an appropriate increase in minute ventilation.[19] However, the ventilatory response to hypoxia is less effective and is characterized by a biphasic pattern. In response to mild hypoxemia (F_{IO_2} 0.15), term newborns respond by increasing minute ventilation, followed by a decrease in ventilation below baseline.[20]

Box 3-1 ANATOMIC CLASSIFICATION OF RESPIRATORY CONTROL: DISORDERS IN THE NEONATE

Brainstem
- Infection
- Infarction
- Hemorrhage
- Trauma
- Apnea of prematurity
- Congenital central hypoventilation syndrome

Spinal Cord
- Trauma
- Spinal muscular atrophy

Myoneural Junction
- Congenital myasthenia gravis
- Familial infantile myasthenia gravis
- Muscle
- Myotonic dystrophy
- Chest wall, airways, and lung
- Congenital scoliosis
- Skeletal dysplasias
- Craniofacial anomalies
- Airway anomalies
- Bronchopulmonary dysplasia

Miscellaneous
- Gastroesophageal reflux
- Inborn error of metabolism

Periodic Breathing

The development of respiratory patterns parallels the ontogeny of sleep stages in the human neonate.[21] In very young infants, respiratory pauses can be used as a criterion of differentiation between sleep stages as they become more numerous during active (rapid eye movement [REM]) sleep.[22] The respiratory pattern of preterm newborns during sleep is often unstable and characterized by frequent brief apneic episodes and periodic breathing.

Periodic breathing (PB) is generally defined as groups of respiratory movements interrupted regularly by intervals of apnea. The minimal frequency and duration of apneas found necessary to characterize PB varies according to different authors. ,[24] It is characterized by alternation between respiratory pauses of 3 to 10 seconds and breathing periods of 10 to 15 seconds.[25,26] PB is frequent in premature newborns; it accounts for 2% to 6% of breathing time in healthy term infants and as much as 19% to 25% in preterm infants.[27] The cycle duration progressively shortens over the first 3 months of life, suggesting maturation of peripheral chemoreceptors over this time period.[1,28] In full-term newborns, PB is more common in active sleep until 3 weeks of age; then it starts to decrease.

Although there is a general agreement that PB is more common in preterm that in full-term infants, the clinical significance of this respiratory pattern remains uncertain, mainly because previous studies used small samples and did not adjust their results for the compounding effect of clinical complications of prematurity, which might affect the maturation of the respiratory system more than preterm birth itself. The mechanisms involved in the generation of PB include an increased latency for activation of central and peripheral chemoreceptors, leading to short periods of apnea and mild hypoxemia alternated with a strong respiratory drive to restore pulmonary ventilation.[28] Another explanation is that preterm infants have a slower maturation of respiration control because of their precocious exposure to the extrauterine environment. Rigatto and Brady[10] reported an increased incidence of PB when the rate of change in ventilation was maximal.

PB in infants is a situational, episodic, and developmental phenomenon. Acceptable (nonpathologic) values noted in the literature range from 2% to 12% in preterm infants and 2% to 6% in term infants. It should be considered abnormal if it is preceded by significant hypoxemia or if associated with bradycardia or prolonged apnea with alveolar hypoventilation ( ).

Apnea of Prematurity

Definition and Incidence

Apnea of prematurity (AOP) is a common problem that affects premature infants and, to a lesser degree, term infants. The term *AOP* generally applies to apneas that occur in infants of less than 37 weeks of gestation without any other identifiable cause. Pathologic AOP is defined by the American Academy of Pediatrics Task Force on Prolonged Infantile Apnea as cessation of breathing for at least 20 seconds or briefer episodes of apnea accompanied by oxygen desaturation, bradycardia, cyanosis, or changes in muscle tone.

The incidence of AOP is inversely proportional to gestational age and birth weight, occurring in 7% of babies born at 34 to 35 weeks of gestation, 15% at 32 to 33 weeks gestation, 54% at 30 to 31 weeks, and of in nearly all infants born at less than 29 weeks of gestation. Among infants weighing less than 1500 g, the incidence is approximately 25% to 50%, and it reaches 80% for those weighing less than 1000 g. The majority of very-low-birth-weight premature babies will exhibit apnea in the first week unless they receive mechanical ventilatory support. Apnea often starts after the first week of life in babies who manifest uncomplicated respiratory problems, and it may coincide with the time of weaning from ventilatory support. '

Pathophysiology

Apnea is classified traditionally into three categories: (1) central apnea is characterized by a total cessation of inspiratory efforts with absence of airflow; (2) obstructive apnea is characterized by continued respiratory effort with absence of airflow; and (3) mixed apnea is defined as central apnea that is followed by obstructive apnea. The percentage of each type of apnea varies among studies and depends on the definition of the duration of apnea. Upton et al. used an apnea duration of at least 5 seconds and found that 58% were central, 35.5% were mixed, and 6.5% were obstructive. In addition, airway closure was identified in the majority of apneas, including central and

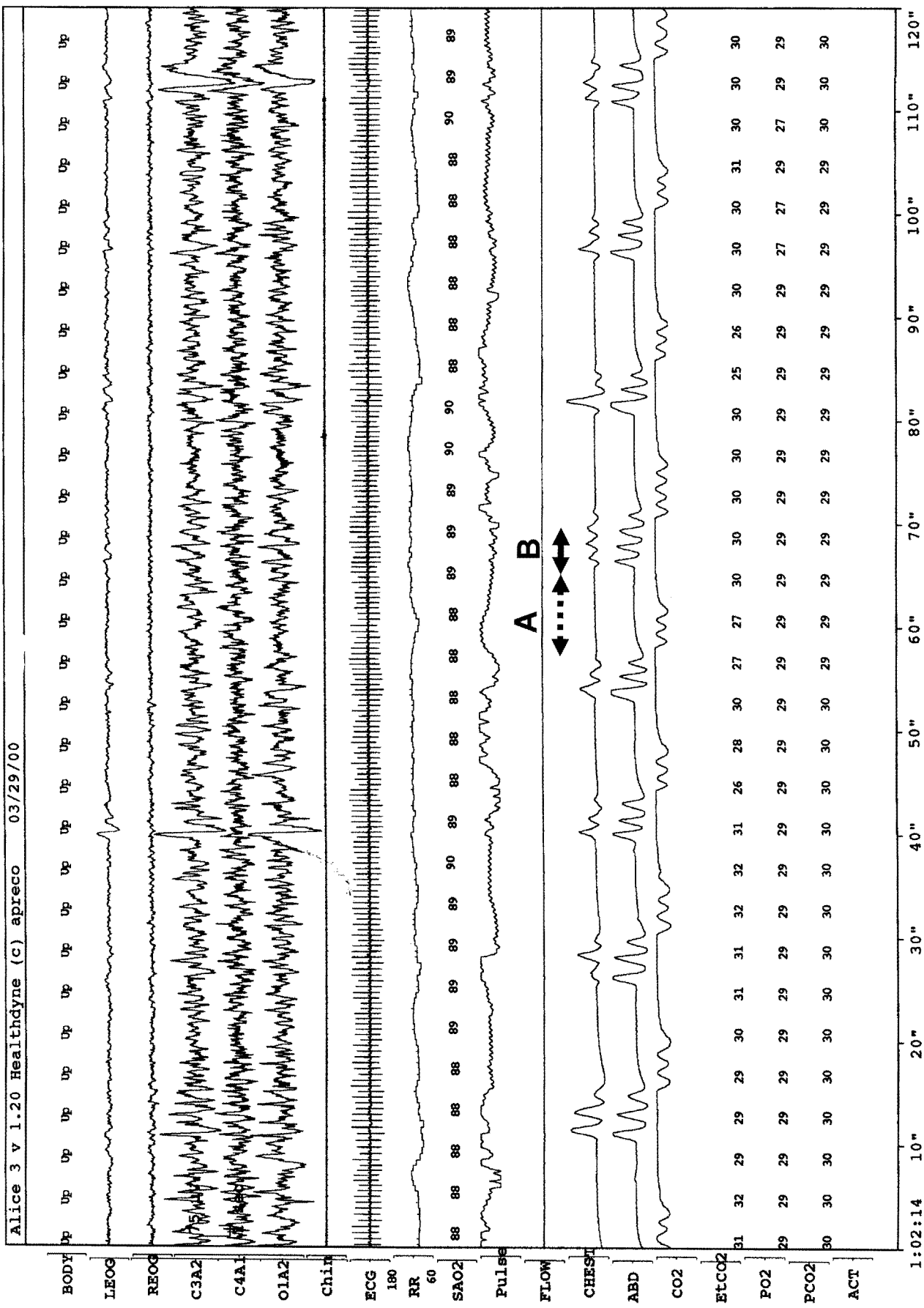

Figure 3-1 Multichannel polysomnography in 2-month-old full-term infant. Recordings from top to bottom are the left and right electrooculogram, three-channel electroencephalogram, chin electromyogram, electrocardiogram, R-R interval, pulse oximetry, pulse waveform, thoracic and abdominal inductance plethysmography, end-tidal co_2, and transcutaneous Po_2 and Pco_2. Recording reveals periodic breathing characterized by alternation between apnea of 3 to 10 seconds (*A*) and breathing periods (*B*) of 10 to 15 seconds during active sleep associated with oxygen desaturation.

mixed apnea, which suggests that that these events are not distinct entities but are part of the continuum of airway closure.

It has been widely assumed that AOP is caused by immaturity of brainstem respiratory rhythm generation thought to be the result of the lack of axodendritic synaptic connections leading to decreased afferent signal from peripheral chemoreceptors to brainstem rhythm generators. Henderson-Smart et al.[40] demonstrated a decrease in the frequency and severity of apnea with maturation, as evidenced by reduced brainstem conduction time using a brainstem auditory evoked response. Immature respiratory drive has also been postulated in the pathogenesis of AOP. Unique features of reflex pathways initiated by hypercapnia, hypoxia, and upper laryngeal afferents are all thought to contribute to the likelihood of apnea in early postnatal life.

During exposure to hypoxia, neonates exhibit a biphasic ventilatory response that consists of an initial increase in ventilation that lasts for 1 to 2 minutes, followed by a decline in breathing, often below baseline ventilation. This late decline has been traditionally termed as *hypoxic ventilatory depression*.[41] The initial increase in ventilation is believed to be secondary to stimulation of peripheral chemoreceptors primarily in the carotid body. Several theories have been postulated to explain hypoxic ventilatory depression, including a decrease in $PaCO_2$ secondary to initial hyperventilation and accompanying decrease in cerebral blood flow and hypoxia-mediated central depression of ventilation. Multiple neurotransmitters have been implicated as mediators for hypoxic depression including adenosine, endorphins, and gamma-aminobutyric acid (GABA). The use of blockers for theses neurotransmitters, such as methylxanthines for adenosine, naloxone for endorphins, and bicuculline for GABA was successful in preventing late hypoxic depression and caused a sustained ventilatory response.[42] The ventilatory response to CO_2 has been clearly shown to increase with advancing postnatal and gestational age in preterm infants. Preterm infants (especially those with demonstrated apnea) have a negligible increase in tidal volume and respiratory frequency in response to increasing hypercapnia, and this ventilatory response is significantly reduced during REM sleep ( ).

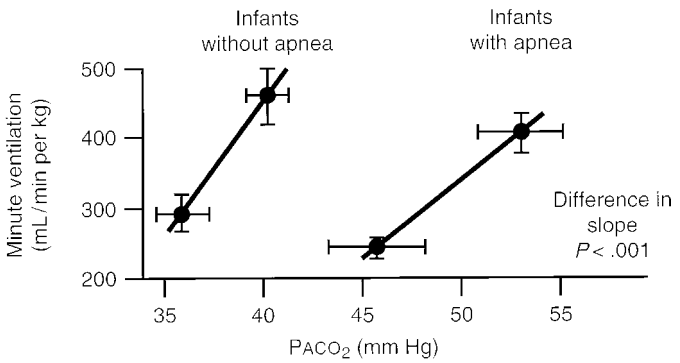

Figure 3-2 Comparison of carbon dioxide sensitivity obtained from ventilatory responses to changing alveolar P_{CO_2} (P_{ACO_2}) in preterm infants with and without apnea. Note the less steep ventilatory response in the apneic group. (From Gerhardt T, Bancalari E: Apnea of prematurity: I. Lung function and regulation of breathing. Pediatrics 74:58, 1984. Reproduced with permission of Pediatrics.)

Box 3-2 CLINICAL SYMPTOMS ASSOCIATED WITH GASTROESOPHAGEAL REFLUX

- Cough
- Stridor
- Hiccups
- Hoarseness
- Bronchospasm
- Failure to thrive
- Aspiration pneumonia

The role of upper airway obstruction in the pathogenesis of apnea has also been described. Cohen and Henderson-Smart[46] have shown the absence of progressive augmentation of inspiratory upper airway muscle activity in response to nasal occlusion. Delayed chemoreceptor activation of the upper airway muscles compared with that of the diaphragm also can reduce the upper airway patency.[47] Posture, especially neck flexion, is another factor that can contribute to airway narrowing.[48] Upper airway reflexes (i.e., laryngeal chemoreceptor reflex) have been demonstrated in preterm infants; water induces a greater apneic response, and a more severe response is noted when water is instilled into the hypopharynx compared to the nose.[49,50] Pickens et al.[51] reported that the majority of spontaneous prolonged apneic episodes in preterm infants have multiple features that are characteristic of an exaggerated protective airway response to a fluid stimulus. Endogenous upper airway secretions can be an important source of stimuli-inducing apneic episodes (e.g., respiratory syncytial virus).[51] Finally, an exaggerated underlying oscillating breathing pattern has been proposed as a mechanism for apnea and periodic breathing. Supplemental oxygen can decrease this oscillation by reducing breath-by-breath variability, leading to a decreased number of apneic episodes.[52]

Gastroesophageal reflux (GER) is a normal physiologic event occurring in neonates at all gestational ages. It occurs in the majority of preterm infants and, in most instances, is related to transient esophageal sphincter relaxation. Symptoms associated with gastroesophageal reflux disease (GERD) are listed in Table 3-2. It is a commonly held concept that GER is not only temporally but also causally related to apnea in preterm infants. Several studies performed in the 1970s and 1980s linked apnea and GER, although subsequent observations have not supported such a relationship.[56,57] Walsh et al.[58] performed polysomnography and intraesophageal pH measurements and were the first of many investigators to find no temporal relationship between GER and apnea. In a further study by Kahn et al.,[59] no temporal association between GER and either central or obstructive apnea was found. In episodes of reflux in which the refluxed material reached the pharyngeal level, there was no increased incidence of apnea. A recent study by Peter et al.[56] using multiple intraluminal impedance found no temporal relationship between acid or nonacid GER and apnea in preterm infants. Di Fiore et al.[60] reaffirmed the lack of association and found no difference in apnea rate or duration before or during GER episodes. Furthermore, there is little proof that

pharmacologic management of reflux has a clinically beneficial effect on apnea of prematurity.

The most apparent effect on cardiovascular function is abrupt bradycardia during apnea. These episodes may be initiated by hypoxemia or may represent a chemoreceptor-mediated vagal reflex. Henderson-Smart et al.[61] reported that the incidence of bradycardia was greater in mixed and obstructive apnea than in central apnea, suggesting an important role of vagal reflex stimulation during obstructed breathing. Other cardiovascular changes during apnea involve an increase in pulse pressure and peripheral vasoconstriction; with minimal change in blood pressure.[62,] The majority of bradycardia in premature infants are related to apnea, and the incidence increases significantly with the prolonged duration of apnea.[61]

Diagnosis

The diagnosis of apnea of prematurity is made by excluding all other causes of neonatal apnea. The etiologies of neonatal apnea include infection, metabolic disorders, thermal instability, gastroesophageal reflux, and neurologic causes ( ). The infant's history should include prenatal, perinatal, and postnatal information to guide the clinician to a specific disease entity. Physical examination should focus on the infant's breathing pattern during awake and sleep periods, including a complete respiratory, cardiac, and neurologic examination. Although clinical observation can give some clue to the diagnosis, studies have shown that a large percentage of apnea episodes were not detected by nursing staff.[64,65] Nursing detection not only identified significantly less true apnea and bradycardia but also misclassified the type of events in a significant number of infants.[66]

An overnight polysomnographic study is the most complete test for evaluation of infant apnea. The standard infant montage includes assessment of the following parameters: body position, left and right electrooculogram, central and occipital electroencephalogram (C3A1, C4A1), chin electromyogram, electrocardiogram, pulse oximetry and pulse waveform, thoracic and abdominal inductance plethysmography, airflow, end-tidal CO_2, and transcutaneous P_{O_2} and P_{CO_2}. The study allows accurate assessment of apnea and its effect on cardiovascular and pulmonary function ( ). It provides not only data on cardiorespiratory events but also information on sleep architecture, sleep organization, and the relationship between sleep states and apnea ( ). Many clinicians, however, elect to perform four or five channel pneumocardiograms, which include heart and respiratory rates, oxygen saturation, nasal airflow, and possibly esophageal pH as the first step in the diagnosis and management of AOP. As a diagnostic tool, pneumocardiogram can objectively quantify rate of respiration, respiratory rhythm, the relative amplitude of respiratory activity, and the incidence of apnea, as well as any resultant bradycardia. This tool, however, does not differentiate among the various types of apnea nor does it detect alveolar hypoventilation as would a polysomnogram.

Management

Treatment of apnea includes supportive care, oxygen, methylxanthine therapy, CPAP, and assisted ventilation.

Box 3-3 APNEA IN NEONATES: DIFFERENTIAL DIAGNOSIS

Infection
- Meningitis
- Sepsis

Metabolic Disorder
- Hypoglycemia
- Hyperbilirubinemia
- Hyponatremia
- Hypocalcemia
- Hypomagnesemia
- Hypochloremia
- Inborn error of metabolism

Intracranial Pathology
- Intracranial bleeding
- Arteriovenous malformation
- Tumors
- Seizures
- Hypoxic-ischemic encephalopathy

Impaired Oxygenation
- Anemia
- Cyanotic heart disease
- Patent ductus arteriosus
- Pulmonary hemorrhage
- Pneumonia/bronchiolitis (respiratory syncytial virus)

Thermal Disturbance
- Hypothermia
- Hyperthermia

Anatomic Narrowing or Obstruction of the Airways
- Choanal atresia
- Micrognathia
- Macroglossia
- Vocal cord paralysis
- Subglottic stenosis
- Laryngomalacia
- Tracheobronchomalacia

Developmental Cause
- Apnea of prematurity

Miscellaneous
- Gastroesophageal reflux
- Hypotension
- Drug depression

General supportive care may include proper positioning of the head and neck to minimize airway obstruction and tactile stimulation, which can be done manually or by placing the infant on an oscillating waterbed. Precipitating factors, which include anemia, hypoxemia, hypothermia, and hyperthermia, should be corrected. If the apnea is prolonged with severe hypoxemia and bradycardia, mechanical ventilatory support should be considered.

Pharmacologic Therapy

For nearly 30 years, methylxanthines (theophylline, caffeine) have been the mainstays of pharmacologic therapy for AOP.[67] Xanthine therapy has been shown to increase

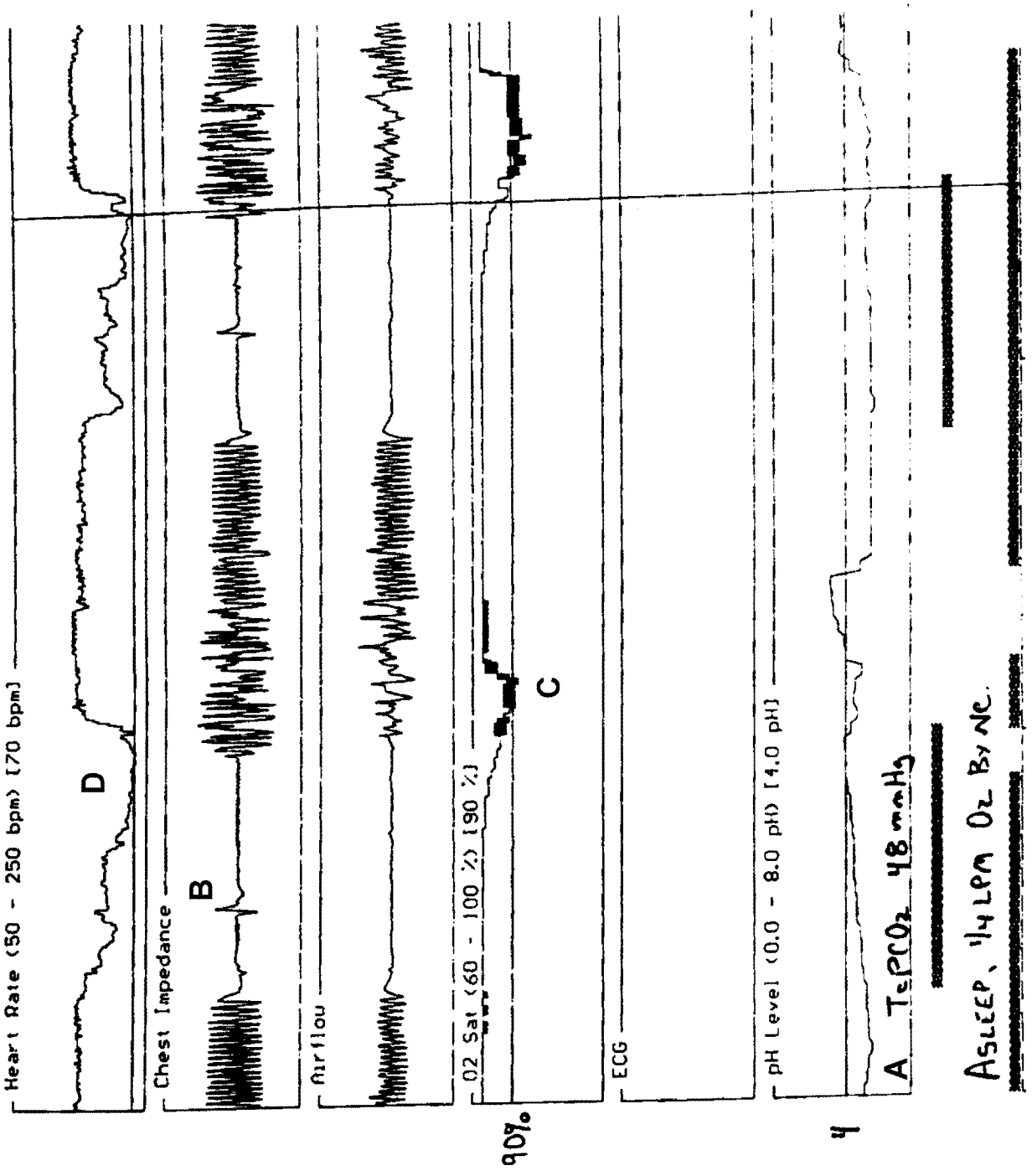

Figure 3-3 Multichannel physiologic recording in a 10-week-old male infant born at 30 weeks of gestational age shows a sequence of gastroesophageal reflux (*A*) (pH <4) to the lower and upper esophagus. These reflux episodes were followed by severe mixed apnea (*B*), hypoxia (*C*), and bradycardia (*D*), which were life threatening and resolved rapidly after a Nissen fundoplication was performed (tracing not shown).

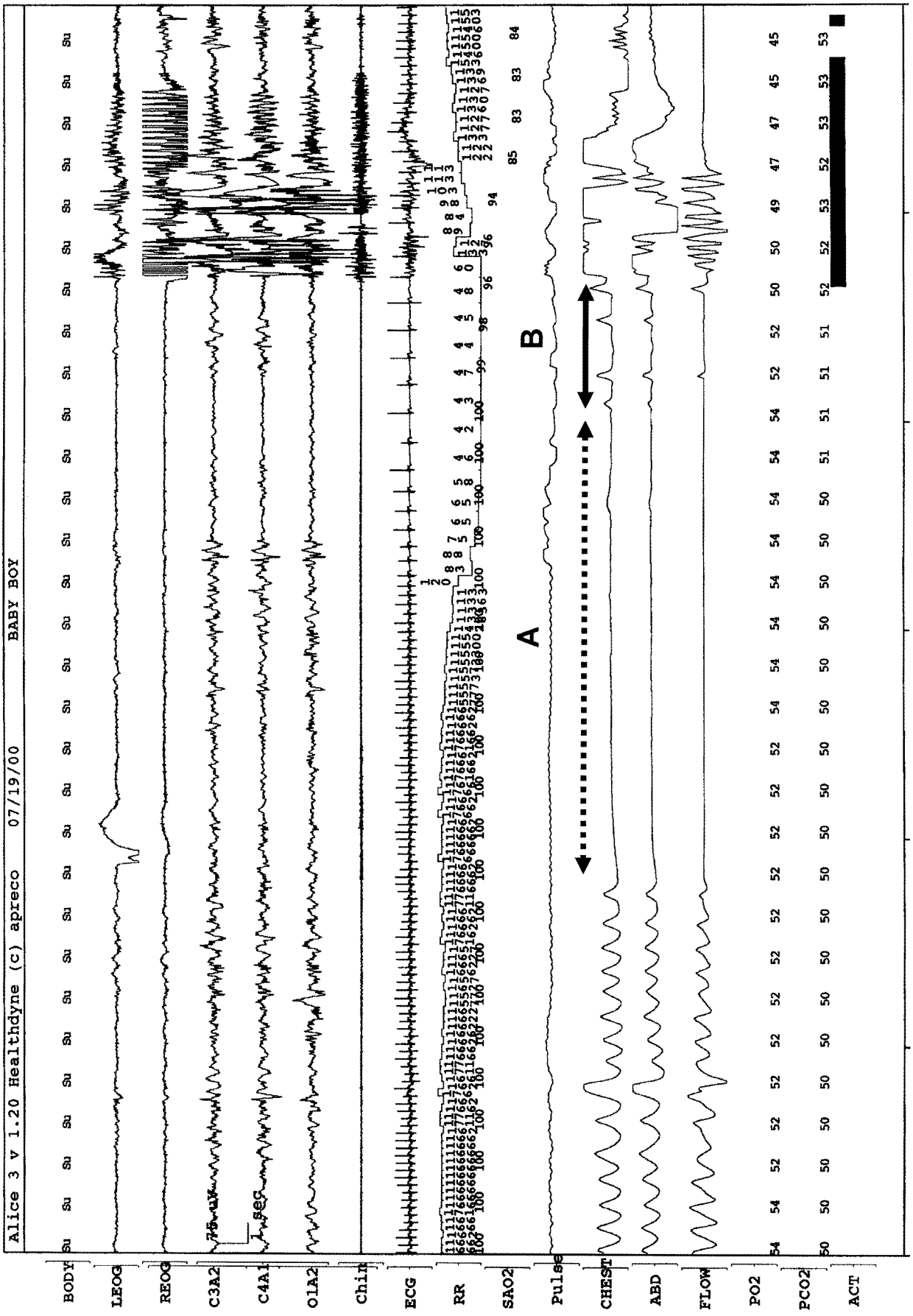

Figure 3-4 Overnight polysomnographic sleep study in a 4-week-old infant, former premature 30-week-gestation infant. Recording demonstrates prolonged mixed apnea with initial central apnea (*A*), followed by an obstructive component (*B*) at the end. This episode of apnea occurred during quiet sleep and was associated with oxygen desaturation, electroencephalographic arousal, and significant bradycardia.

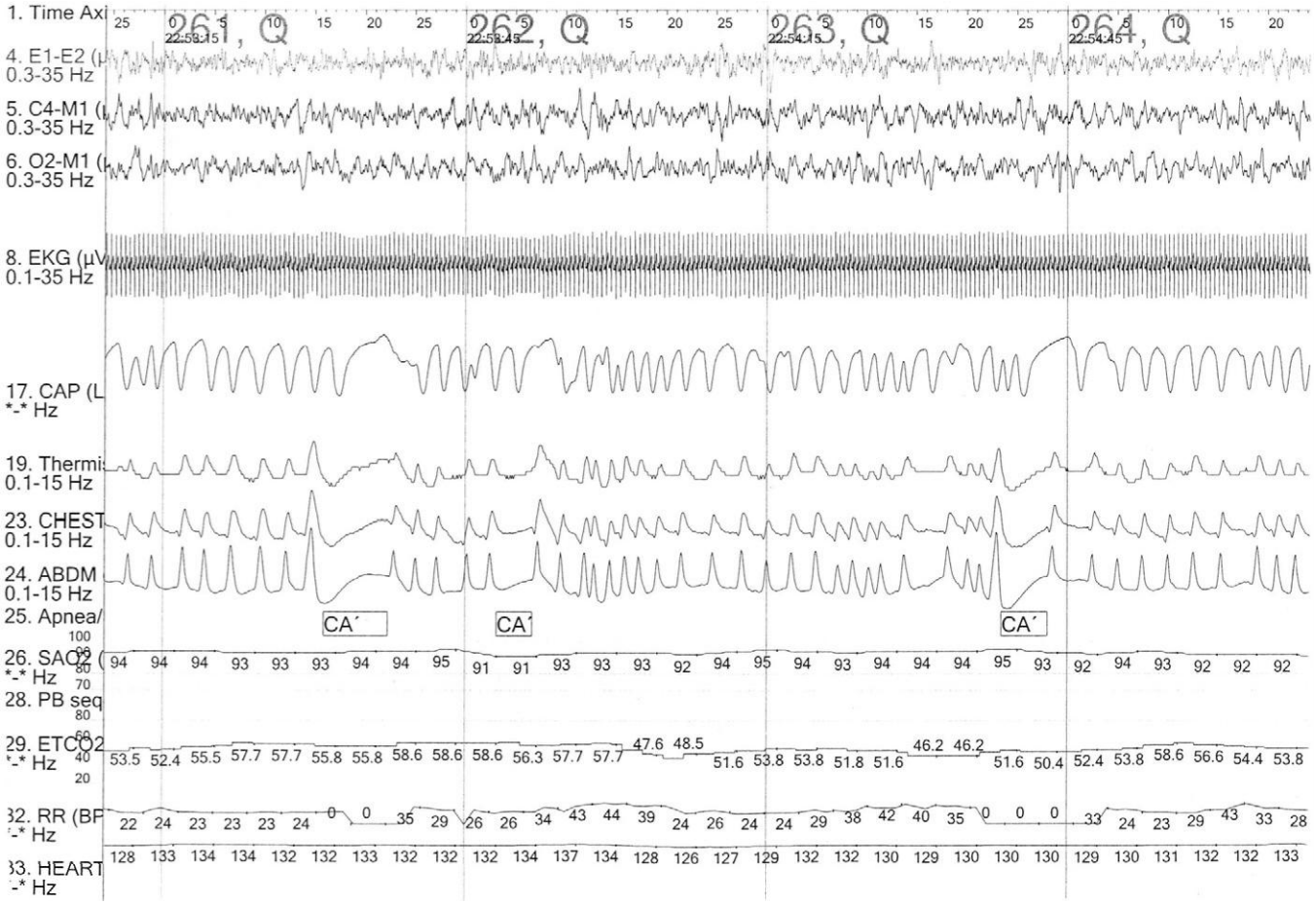

Figure 3-5 Overnight polysomnographic study in a 4-month-old infant with recurrent and persistent apnea. Recording demonstrated severe central apnea with reduced hypoxic and hypercarbic response as exemplified by inappropriate increase in heart rate and respiratory rate.

minute ventilation, improve CO_2 sensitivity, decrease hypoxic depression of breathing, enhance diaphragmatic activity, and decrease periodic breathing. The precise pharmacologic basis for these actions, which are mediated by an increase in respiratory neural output, is still under investigation. A likely major mechanism of action is through competitive antagonism of adenosine receptors, because adenosine acts as an inhibitory neuroregulator in the central nervous system.[68]

A recent Cochrane Database Systematic Review found that both theophylline and caffeine were effective in reducing apnea in the 2 to 7 days after starting treatment.[69] Caffeine is the preferred drug given its lower toxicity. It appears to penetrate cerebrospinal fluid better than does theophylline.[70,71] Caffeine has a much slower elimination time relative to theophylline; its plasma half life is 100 hours compared to 30 hours for theophylline.[72] In the neonate, a substantial amount of theophylline is methylated into caffeine. The majority of the drug is cleared by the kidneys due to inability of the neonate to metabolize caffeine through hepatic pathways. Treatment is usually initiated with a loading dose of 5 to 6 mg/kg (theophylline) or 10 mg/kg (caffeine) followed by a maintenance therapy of 1 to 2 mg/kg every 8 hours (theophylline) or 2.5 mg/kg per day (caffeine). The therapeutic serum level range for theophylline is 5 to 15 mg/mL and 8 to 20 mg/mL for caffeine. Serum concentration, however, may vary considerably from infant to infant and is not entirely predictable based on dosage.

Despite many years of methylxanthine use, relatively little is known about short-term and long-term safety;[67] other concerns center on their possible effects on feeding, growth, and behavior,[74] and increasing the risk for reflux by lowering the lower esophageal sphincter tone. However, a recent large multi-institutional study by Schmidt et al.[75] was reassuring in that caffeine therapy for AOP improved the rate of survival without neurodevelopmental disability at 18 to 21 months in infants with very low birth weight.

Another respiratory stimulant, doxapram, has been used in neonates with refractory apnea. It acts through stimulation of a peripheral chemoreceptor and has been shown to increase minute ventilation, tidal volume, inspiratory flow, and airway pressure.[29] Side effects include irritability, hypoglycemia, gastric irritation, and report of second-degree heart block in a small number of preterm infants.[76,77]

Continuous Positive Airway Pressure

Continuous positive airway pressure (CPAP) at 4 to 6 cm H_2O is relatively safe and effective therapy. Because longer

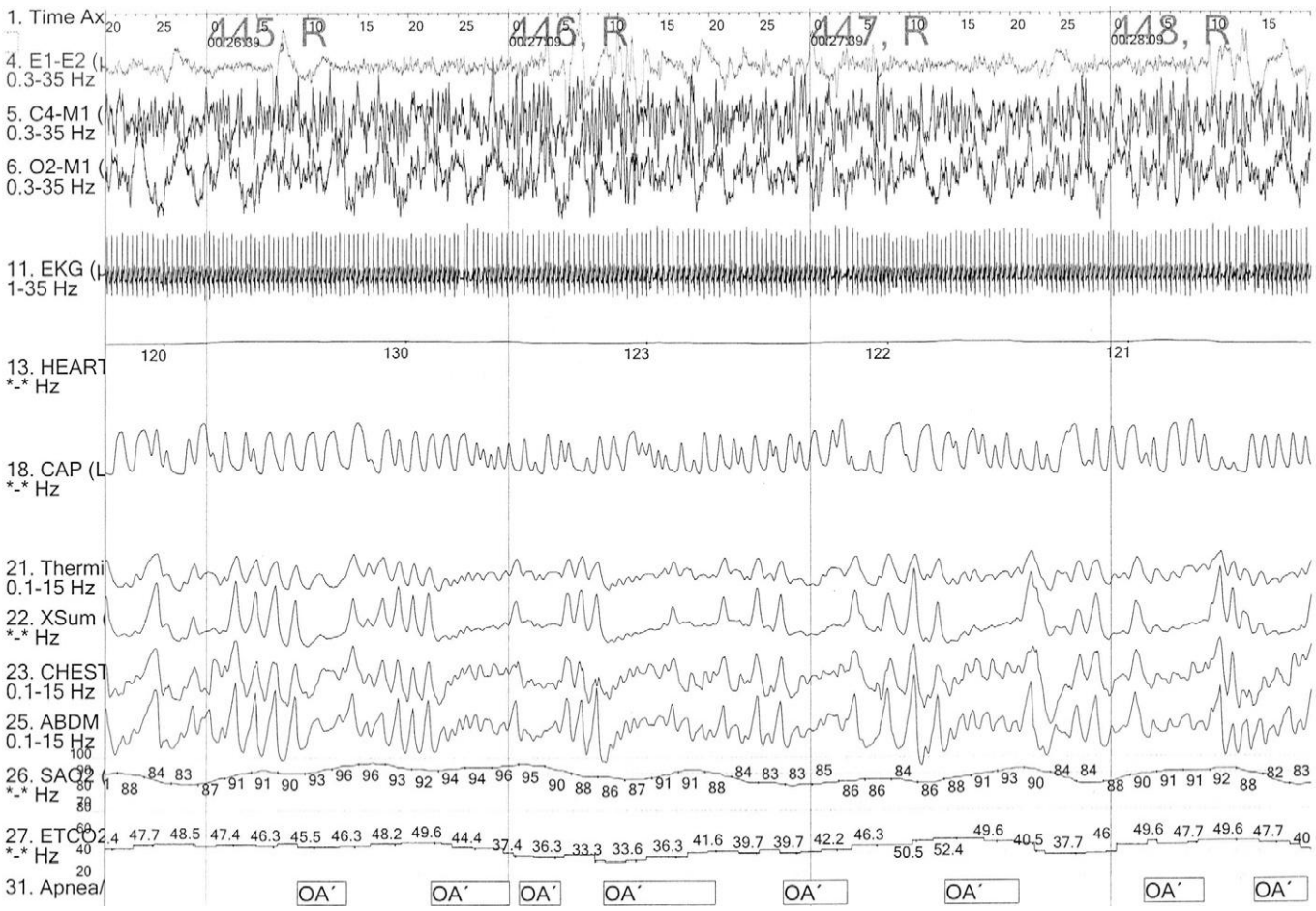

Figure 3-6 Overnight polysomnogram on an 8-month-old male with recurrent apparent life-threatening event (ALTE) and severe developmental delay. Recording showed profound obstructive sleep apnea with severe oxygen desaturation with poor respiratory arousal response.

episodes of apnea often involve an obstructive component, CPAP appears to work by splinting the upper airway with positive pressure and decreasing the risk of pharyngeal or laryngeal obstruction. It also benefits apnea by increasing functional residual capacity, thereby improving oxygenation status.[68] It has no effect on central apnea though. High-flow nasal canula therapy has been suggested as an equivalent treatment modality.[78] Although this approach is widely employed, it has not been well studied. For severe or refractory episodes, endotracheal intubation and artificial ventilation may be needed (see Chapter 8).

Previous studies have shown that AOP and PB resolve when oxygen concentration is increased to the threshold level. Rigatto and Brady[80] reported that inhalation of 100% O_2 is associated with a decrease in PB and an increase in minute ventilation (Ve). Subsequent studies demonstrated that modest increases in oxygen decrease apnea and periodicity in preterm infants, not via an increase in ventilation but through a decrease in breath-to-breath variability in Ve. Simakajornboon[81] reported that low-flow supplemental oxygen significantly reduced the amount of apnea and PB, increased arousabilty after an apneic episode, and altered sleep architecture by increasing the amount of quiet sleep with a reciprocal decrease in the amount of active sleep. No adverse effects on alveolar ventilation were observed with the use of low-flow supplemental oxygen ( ).

Resolution and Outcome

AOP generally resolves by about 36 to 40 weeks of postconceptional age (PCA); however, in more immature infants, apnea frequently persisted beyond this time, and that circumstance may require continued medical therapy and home monitoring. Center for Health Information Management and Evaluation (CHIME) study data showed that cardiorespiratory events in preterm infants return to baseline "normal" level at about 43 to 44 weeks of PCA, which means that the incidence of cardiorespiratory events in preterm infants beyond this age does not significantly exceed that in term babies.[82] The decision to discontinue pharmacologic therapy in these infants is empirical and can be done when infants have been asymptomatic and have reached appropriate PCA. Premature infants with or without a history of apnea are at increased risk for apnea and bradycardia after general anesthesia; hence elective surgery should be deferred until an infant's respiratory control mechanism is more mature (approximately 50 to 60 weeks of PCA). If deferral is not possible, infants should be monitored in the hospital for apnea and bradycardia for at least 12 hours after surgery.

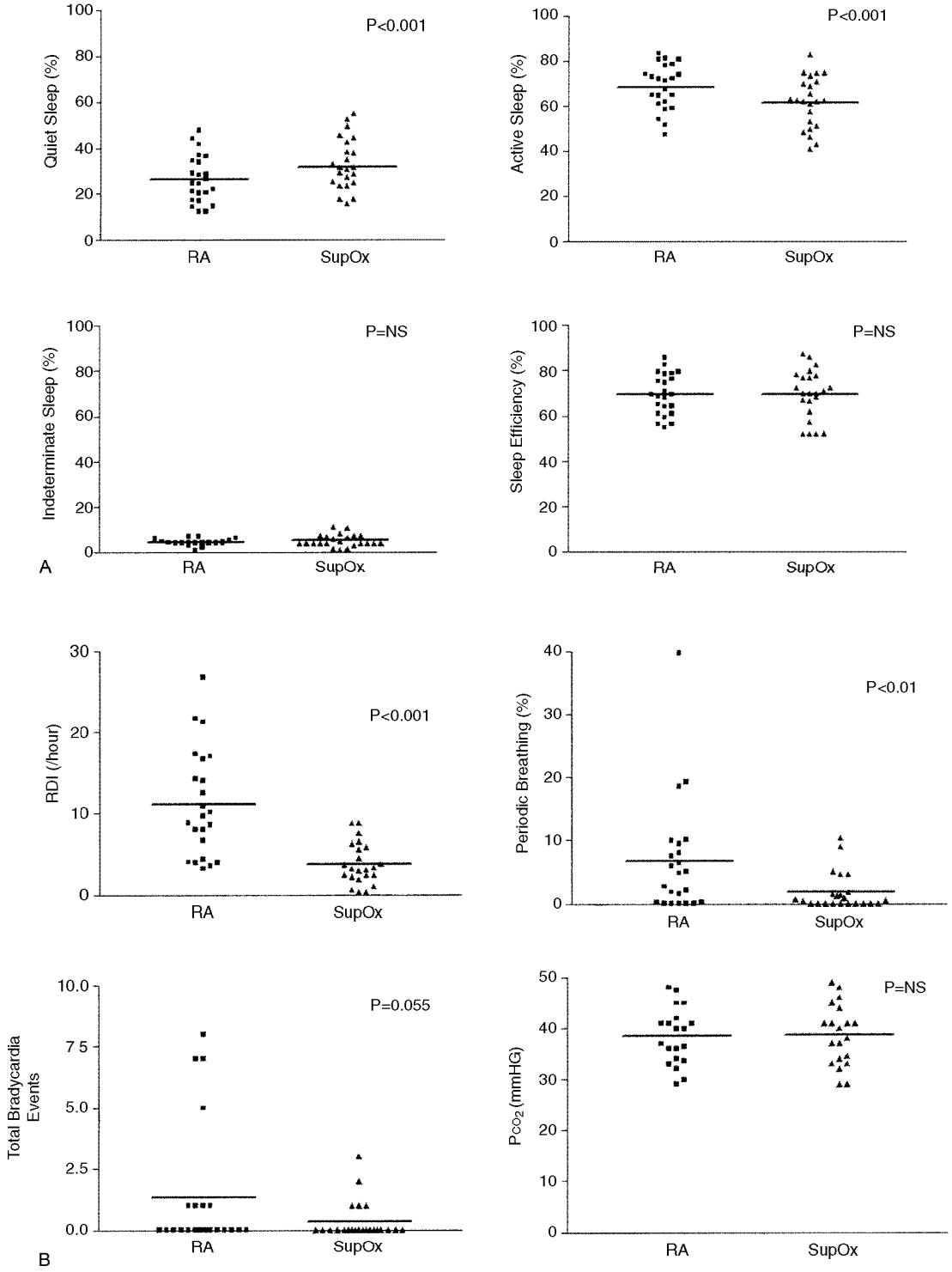

Figure 3-7 Effect of supplemental oxygen on sleep architecture and cardiorespiratory events in preterm infants. **A,** Use of supplemental oxygen is associated with an increase in percentage of quiet sleep with reciprocal decrease in time spent in active sleep. **B,** In terms of cardiorespiratory events, use of supplemental oxygen decreases the frequency of apnea, percentage of periodic breathing time, and number of bradycardias with no adverse effect on alveolar ventilation. *RA*, Room air; *RDI*, respiratory disturbance index; *SupOx*, supplemental oxygen.

Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia (BPD) is a chronic lung disease resulting from mechanical ventilation that commonly occurs in premature infants who remained oxygen dependent at 28 days of postnatal age and/or 36 weeks of PCA (see Chapter 23). First described in 1967 by Northway et al., infants with BPD have abnormal respiratory control, especially during sleep, which predisposes them to episodes of respiratory failure, cor pulmonale, and sudden unexpected death.

Infants with BPD have abnormal pulmonary mechanics, predominantly an increase in airway resistance and a decrease in lung compliance.[84,85] The measurement of this resistance, however, is not a sensitive test for lower airway dysfunction. Plethysmographic measurements of lung volumes in BPD infants demonstrate that although total lung capacity (TLC) is normal, functional residual capacity (FRC), residual volume (RV), and RV/TLC are elevated,[86] which suggests a significant obstructive airway disease with air trapping. Although pulmonary function measurements in BPD survivors reflect abnormalities primarily of the small airways, large airway disease that includes tracheobronchomalacia resulting from a lack of cartilage development and airway injury caused by prolonged mechanical ventilation is also found. Barotrauma and suboptimal nutrition are also common in this population.[87,88] The presence of macroglossia in a small number of these infants with the most severe disease may contribute to airway obstruction and hypercapnia. This finding often portends a poor prognosis, and tracheotomy should be considered.

Abnormalities of sleep architectures and cardiovascular disturbances occur during sleep in infants with BPD. Harris and Sullivan[89] demonstrated that infants with BPD had significant sleep disruption and reduced REM sleep that may be secondary to increased arousal response to minimize oxygen desaturation. Sleep fragmentation was reversed with the use of supplemental oxygen. Garg et al.[90] reported that infants with BPD aroused normally to the hypoxic challenge; however, they required vigorous stimulation after the initial arousal response. These data suggest that such infants may have an abnormal response to hypoxia after arousal that may lead to prolonged apnea and bradycardia.[90] Clinically unexpected hypoxemia during sleep and feeding has been reported despite acceptable awake oxygen saturation. In addition, the total desaturation time in these infants correlated with airway resistance, indicating the important role of airway obstruction.[91] In these infants, a decrease in the inspired fraction of oxygen increased airway restriction that was alleviated with the use of supplemental oxygen.[95,96] Sleep-related hypoxemia also has an adverse effect on cardiac function.

Praud et al.[97] reported a decrease in both right and left ventricular ejection fractions in severe BPD with significant nocturnal desaturations. In addition, abnormal autonomic control of heart rate variability was observed in patients with severe BPD in relation to sleep stages and mild changes in oxygen saturation.[98] A previous study showed an association between BPD and sudden infant death syndrome (SIDS)[99]; however, a subsequent study suggested that infants with BPD were not at increased risk from SIDS if appropriate management that included supplemental oxygen and monitoring was provided.[100]

Management of BPD is aimed at maintaining adequate gas exchange but at the same time avoiding the progression of the disease by reducing factors that predispose to lung damage. Supplemental oxygen is probably the most commonly used therapy. It has been shown to improve central respiratory stability by decreasing central apnea and PB[92] and to promote growth when oxygen saturation is maintained above 90%[101]; supplemental oxygen also may be useful for the treatment of pulmonary hypertension associated with BPD.[102,] Awake oxygenation status, however, does not accurately predict sleep-related hypoxemia; therefore overnight polysomnographic evaluation is necessary to assess the need for oxygen support and to determine when to discontinue oxygen therapy.

The use of positive-pressure ventilation is one of the factors closely associated with the pathogenesis of BPD. For this reason, during mechanical ventilation, it is essential to use the minimal settings necessary to maintain gas exchange. Infants mechanically ventilated for a long time may be at risk for poor ventilatory muscular endurance because of deconditioning. In addition, hypoexcitability of the respiratory center secondary to chronic hypercapnia increases the susceptibility of these infants to respiratory arrest when small doses of sedative drugs are administered.[104] Therefore elective surgery performed on these infants should be planned carefully so that the complications of apnea and alveolar hypoventilation secondary to poor muscular endurance can be prevented. During the process of weaning, a certain degree of hypercapnia must be tolerated as long as the pH is within acceptable limits. In small infants with poor central activity, aminophylline or caffeine can be used as a respiratory stimulant. In smaller infants with soft chest wall and frequent apneic spells, the use of nasal CPAP after extubation can stabilize respiratory function and reduce the need for reinstitution of mechanical ventilation (see Chapter 6).

A tracheostomy may at times be required in preterm infants for prolonged ventilatory support or upper airway obstruction due to craniofacial abnormalities, which precludes safe extubation. Most neonatologists request a tracheostomy when ventilatory support of longer than 8 to 12 weeks is anticipated. Tracheostomy might facilitate weaning from ventilatory support by reducing dead space and decreasing work of breathing by reducing airway resistance. Furthermore, it provides better clearance of secretion and less laryngeal damage and improves patient comfort and mobility.

Multiple adjunctive agents have been used to either reduce the risk of BPD or mitigate its course; however, no specific treatment guidelines have been established. Diuretics using the combination of furosemide or thiazides and spironolactone are commonly used to reduce alveolar and interstitial lung edema and improve pulmonary mechanics. The use of diuretics, however, may impair respiratory control by causing hypochloremic and hypokalemic metabolic alkalosis with secondary retention of bicarbonate that may worsen hypercapnia.[105,106] Because of the side effects and the lack of evidence that prolonged use of diuretics changes the incidence and severity of BPD, this therapy is not recommended for routine use.[107]

Inhaled bronchodilators (e.g., albuterol) have been used because bronchial hyperreactivity and responsiveness may be found in this population. Methylxanthines have been used for more than three decades now to treat apnea of prematurity.[108] These drugs improve the function of ventilatory muscles and central ventilatory drive and relax bronchial smooth muscle, causing mild diuresis and stimulating ciliary motility. However, the frequent side effects of vomiting, irritability, tachycardia, and diarrhea require the monitoring of drug levels and make their use

difficult.[84,104] A multicenter double-blind study known as the CAP (caffeine for apnea of prematurity) trial showed that caffeine reduced the duration of supplemental oxygen, CPAP, and mechanical ventilation.[109] Further discussion of these pharmacologic therapies can be found in Chapter 21.

Congenital Central Hypoventilation Syndrome

Definition and Incidence

Ondine's curse, or more preferably, congenital central hypoventilation syndrome (CCHS) is a rare disorder characterized by failure of autonomic respiratory control. It was first described in 1962 in three patients who became apneic after cervical spinal cord and brainstem injury. The first case of an infant with CCHS was reported in 1970 by Mellins et al.[110] Affected infants develop absent or negligible respiratory response to hypoxia or hypercapnia in the absence of primary cardiac, pulmonary, neuromuscular, or metabolic disease or an identifiable brainstem lesion.[111] The incidence of CCHS is unknown, but the current registry has reported 200 to 300 cases worldwide.[112]

Etiology

The cause of CCHS is unknown but is thought to be a generalized disorder of the autonomic nervous system (ANS). Approximately 15% to 20% of patients with CCHS also have Hirschsprung's disease (the combination of CCHS and Hirschsprung's disease is now called *Haddad syndrome*).[112,] This involves aganglionosis of the bowel, which is thought to be caused by neural crest migration abnormalities.[114] Other associated manifestations of ANS dysfunction are decreased heart rate variability, decreased breath-to-breath variability, attenuated heart rate response to exercise, esophageal dysmotility/dysphagia, ocular muscle and pupillary abnormalities, sporadic profuse sweating, and decreased blood pressure and basal body temperature.[115] Tumors of neural crest origin (neuroblastoma, ganglioneuroma) have also been described.[112]

Recently, a paired-like homeobox 2b (PHOX2B), located on chromosome *4p12*, has been identified as the disease-defining gene in CCHS.[116,117] Individuals with the CCHS phenotype are heterozygous for polyalanine (PA) repeat expansion in the PHOX2B gene in 92% of cases and non-PA repeat mutations in PHOX2B in 8% of cases.
Gronli et al.[120] reported that the PHOX2B gene is related to the severity of cardiac autonomic dysregulation in CCHS.

Pathophysiology

Because breathing during quiet sleep is controlled almost entirely by the autonomic system, ventilation is most severely affected during quiet sleep. Hypoventilation is produced by a pattern of decreased tidal volume, with variation in minute ventilation mostly due to variation in respiratory rate. While asleep, these patients experience progressive hypercapnia and hypoxemia. The severity of hypoventilation is state dependent and is most severely affected during non-REM sleep, for which metabolic respiratory control is predominant. Respiratory control abnormalities are also present to a lesser degree during awake and REM sleep because of the breathing drive from behavioral inputs.

Paton et al.[121] found that children with CCHS have absent chemoreceptor responses to both hypercapnia (central chemoreceptors) and hypoxia (peripheral chemoreceptors), using rebreathing ventilatory response testing, even while awake. Marcus et al.[122] performed hypoxic and hypercapnic arousal responses in CCHS children and showed that most children with CCHS arouse to hypercapnia under very well controlled circumstances, indicating intact central chemoreceptor input. Gozal et al., on the other hand, found that peripheral chemoreceptor function, when assessed by acute hypoxia, hyperoxia, or hypercapnia, was present and intact in CCHS children who were able to sustain adequate ventilation during wakefulness. Thus CCHS appears to represent a primary physiologic abnormality of integration of chemoceptor input to central ventilatory controllers, rather than abnormalities in the chemoreceptors themselves.[124]

Most children with CCHS have no pathologic lesions in the brainstem on autopsy and magnetic resonance imaging (MRI) that are thought to be causal.[125] However, functional MRIs of CCHS patients have shown decreased neuronal signaling in areas of cerebellar vermis when challenged with hypercapnia, hypoxia, and cold pressors.[126,127] Although dysfunction in the deep cerebellar nuclei that integrate sympathetic and parasympathetic responses may explain both the dysregulation of respiratory responses and other dysautonomias in patients with CCHS, much more research is needed to prove a cerebellar etiology.

Presentation

Clinical presentation of infants with CCHS is variable and depends on the severity of the disorder. In the newborn period, many affected infants will not have the classically described sleep-wakefulness differences[128]; thus they may appear to have intermittent duskiness, and measurable hypercapnia. As their oxygen saturations fall and their carbon dioxide saturations rise, affected infants demonstrate no increase in respiratory rate or effort and, usually, do not appear distressed. In severe cases, infants present with severe hypoventilation that requires ventilatory support at birth. This group of infants does not breathe spontaneously and will need 24-hour assisted ventilation during the first few months of life, but they may improve to a pattern of adequate ventilation during wakefulness over time. In less severe cases, infants may present at a later age with cyanosis, signs of right heart failure, and pulmonary hypertension from prolonged periods of hypoxia and hypercapnia.[129] Some may present with unexplained apnea and an apparent life-threatening event (ALTE). The proposed diagnostic criteria include the following: (1) shallow breathing or cyanosis and apnea that is worse during sleep than in wakefulness and has a perinatal onset; (2) hypoventilation that is worse during sleep than wakefulness; and (3) no other disease processes aside from primary hypoventilation syndrome.

Diagnosis

The diagnosis of CCHS depends on the documentation of hypoventilation during sleep in the absence of primary

neuromuscular, lung, cardiac, or metabolic disease, or an identifiable brainstem lesion.[112] The initial evaluation may include a detailed neurologic evaluation that may require muscle biopsy, chest x-ray, fluoroscopy of the diaphragm, electrocardiogram, echocardiogram, and MRI imaging of the brain and brainstem. Serum and urinary organic acids, amino acids, and carnitine levels should be obtained to rule out inborn error of metabolism. Ultimately, a careful evaluation of the infant's respiratory pattern and gas exchange abnormalities by polysomnographic study should be done. Careful observation of the infant's tidal volume and respiratory frequency response to endogenous hypoxemia and hypercapnia, both in awake and sleep states, should be recorded. Although a diagnostic value has not been established, in general, those with CCHS have end tidal pCO_2 readings persistently above 60 torr while asleep. Sending blood work for confirmation of CCHS genetic profile should be routinely done.

Management

No pharmacologic respiratory stimulants have been shown to be effective, and they certainly do not prevent the need for ventilatory support. Doxapram, a central and peripheral respiratory stimulant, has been used primarily to counteract postanesthetic respiratory depression. Clinical trials of doxapram and almitrine bismesylate have not shown consistent improvement in spontaneous ventilatory or gas exchange parameters.

Supplemental oxygen alone is not sufficient treatment for hypoventilation and will not prevent pulmonary hypertension. The most important aspect of management of patients with CCHS is mechanical ventilatory support. Positive-pressure ventilation (PPV) via tracheostomy is the most common method used among infants and children. Bilevel ventilation delivered via nasal or face mask has been used successfully in treating children with CCHS as young as 3 months of age. However, it is not as powerful as PPV via tracheostomy and generally delivers lower pressures. Negative-pressure ventilation has been used with some success in patients with CCHS ; however, it is cumbersome and may lead to upper airway obstruction.

Bilateral diaphragmatic pacing with the use of a high-frequency radio transmitter has been an effective mode of ventilation after the neonatal period, especially for infants who require daytime ventilation support. The patient who benefits most from diaphragmatic pacing is the child who is ventilator dependent 24 hours a day, has no intrinsic lung disease, does not require supplemental oxygen, and has preservation of the cervical nerve roots of the phrenic nerve (C3-C5), the phrenic nerve itself, and the diaphragm. Bilateral rather than unilateral pacing usually is necessary for adequate alveolar ventilation because of the infant's highly compliant rib cage and increased metabolic rate corrected for body weight.

Tracheostomy is necessary for prevention of upper airway obstruction because of the absence of laryngeal and pharyngeal dilator muscle activation. All patients who undergo diaphragm pacing should have pulse oximetric monitoring during sleep as an alarm for pacer malfunction. The arguments against diaphragmatic pacing include its high cost, development of nerve injury or diaphragm fatigue, and discomfort associated with surgical revisions caused by pacer malfunction.

Prognosis

There is currently no known cure for CCHS patients, and the disorder appears to be lifelong. All patients with CCHS will need supported ventilation while asleep, but about 65% of CCHS patients are able to come off assisted ventilation while awake.[140] Early diagnosis and appropriate ventilatory support of infants with these conditions will limit the morbidity from hypoxia and improve long-term outcome.[111]

Apnea of Infancy

During the first 6 months of life, normal full-term infants may have isolated apnea that lasts from 5 to 15 seconds with or without PB.[141] Apnea of infancy is defined as apnea of more than 20 seconds or less if it is associated with color change or bradycardia. The term is used for infants born after 38 weeks of gestation to differentiate it from apnea of prematurity, which occurs in infants of less than 37 weeks of gestation.[142]

Apparent life-threatening events (ALTEs) refer to episodes that are frightening to the observer and usually consist of some combination of apnea, color change, decreased tone, choking, or gagging. This term replaces the term *near-miss SIDS*, which imprecisely indicated an association of these events with SIDS.[142,] The etiologic factors of ALTE include infection, gastroesophageal reflux, seizure disorder, cardiac disease, and metabolic disease. Approximately 50% of ALTEs are idiopathic and sometimes are classified as apnea of infancy. Most studies report high survival rates in infants with ALTE; however, a small percentage of infants with ALTE progress to sudden and unexpected death. Studies of cardiorespiratory function in infants with ALTE have revealed inconclusive results. Several studies showed an increased number of mixed apnea, obstructive apnea, and PB in patients with ALTE. Other studies revealed a blunted hypoxic and arousal response in these infants.[146,147] Some investigations failed to note a difference in hypoxic and hypercapnic response between control and ALTE infants.[148,149] An abnormal cardiac rhythm (prolonged QT) interval was reported initially in these infants but was not confirmed by subsequent studies.

Management of ALTE requires identification of the specific etiology. When a specific cause of an ALTE is identified, an appropriate treatment may then be initiated. The benefit of home apnea monitoring is controversial. There is no evidence that home apnea monitoring prevents any deaths, but it may be cost effective compared with continued hospitalization and may alleviate anxiety in some families.

Craniofacial Syndromes

Neonates with craniofacial anomalies (CFAs) may have airway obstruction secondary to anatomic abnormalities

that narrow the opening of the nasal or pharyngeal airway or displace the tongue posteriorly into the pharyngeal airway. Structural and functional airway narrowing in infants who have a variety of CFAs may lead to sleep-disordered breathing (SDB) and is a major predisposing factor to infant morbidity and mortality. The inability to maintain upper airway patency during sleep in patients with CFA is a result of complex interactions between abnormal airway anatomy and alteration of the normal neuromuscular control of breathing. These structural abnormalities can predispose the infant to obstructive and mixed apnea, episodes that tend to occur more often while the infant is sleeping in the supine position and in the REM stage.

The most common structural anatomic abnormalities in infants and children with CFAs are nasal obstruction, malformation of the cranial base and facial skeleton, macroglossia, and hypoplasia of the lower jaw (see Chapter 25). Patients with these abnormalities often present with SDB or sleep-related disturbance. Patients with choanal atresia often present with nasal obstruction in the newborn period. These malformations can present as an isolated entity or may be associated with branchial cleft sequence, as seen in Pierre Robin syndrome and Treacher Collins syndrome. Nasopharyngeal hypoplasia can occur secondary to malformations of the cranial base or midface, as seen in Apert, Crouzon, Saethre-Chotzen, and Down syndromes. Hypoplasia of the lower jaw can compromise the upper airways, either because of retroglossia or by intrusion of retromandibular structures. In addition to the obstructive lesion, a central respiratory defect may likewise play an important role in the morbidity of these patients.

Craniofacial dysostosis involves the premature and progressive fusion of the skull sutures, which causes increased intracranial pressure that can lead to abnormalities of respiratory control (e.g., Arnold-Chiari malformation). The primary form of this condition occurs in approximately one in 1000 children.[150] The nature and extent of the consequent cranial deformities are determined by the number of sutures involved, the order in which they fuse, and the time at which fusion occurs. In infants and young children, the obstructive mechanism can lead to central apnea; in obese children, central apnea can be a result of low lung volume. Upper airway obstruction can lead to chronic alveolar hypoventilation, which results in hypoxemia or hypercapnia with respiratory acidosis. These gas exchange abnormalities may cause a constrictive response of the pulmonary vascular bed, resulting in increased right ventricular work and eventual cor pulmonale and heart failure. In achondroplasia, severe obstructive sleep apnea is associated with absence of slow-wave sleep and deficiency of overnight growth hormone secretion. Correction of apnea by tracheostomy can improve growth rates postoperatively.[151] SDB abnormalities in infants with craniofacial syndromes are summarized in .

Infants with CFA usually present with upper airway obstruction during wakefulness and sleep that may lead to chronic respiratory failure. The symptoms of SDB are similar in infants who have obstructive sleep apnea syndrome, which is characterized by loud snoring, difficulty breathing during sleep, breathing pauses, nocturnal enuresis, nocturnal sweats, restless sleep, and frequent awakening. The frequency and severity of such symptoms varies. In addition, morning headaches, failure to thrive, respiratory failure, and cor pulmonale frequently accompany SDB in children with CFA. The increased energy required for breathing against resistance created by the upper airway obstruction is associated with sweating, poor growth, and other signs of high metabolic rate. Alveolar hypoventilation results in chronic hypercapnia that can reduce the respiratory center sensitivity to CO_2, and further hypoventilation during sleep. The hypoexcitability of the respiratory center in patients with CFAs makes them, like infants with BPD, susceptible to respiratory arrest when small doses of a sedative are administered.

TABLE 3-1 Prototypical Craniofacial Syndromes and Associated Sleep-Disordered Breathing

Craniofacial Abnormalities	Disorders	Sleep Abnormalities
Craniosynostosis	Crouzon syndrome	OA
	Apert syndrome	
Mandibular hypoplasia	Pierre Robin syndrome	OA
	Treacher Collins syndrome	
Skeletal disorders	Achondroplasia	Hypoventilation, CA, OA
Miscellaneous	Down syndrome	Hypoventilation, OA
	Arnold-Chiari malformation	Hypoventilation, OA, CA

CA, Central apnea; *OA*, obstructive apnea.

Overnight polysomnography is considered the most objective physiologic study for baseline evaluation of cardiorespiratory functions in infants with CFA. Daytime nap studies in patients with Down syndrome have been shown to underestimate the presence and severity of SDB[152] and are considered unreliable. Polysomnograms can quantify the severity of the problem and determine the need for further intervention. Chest and abdominal wall movement are recorded simultaneously so that paradoxical inward movement of the chest can be documented during periods of partial airway obstruction. The study can document the type of apnea present, that is, central, obstructive, or mixed, and its relationship to sleep stage and body position during sleep ( ). It will also reveal the presence of hypopnea, significant hypoxemia, or hypoventilation. A repeat sleep study will provide valuable information on the efficacy of treatment in these children.

Treatment recommendation is based on the underlying cause of SDB. Acetazolamide has been shown to improve SDB in some infants with Arnold-Chiari malformation. Protriptyline has been reported to benefit some patients who have Down syndrome and SDB.[154] Weight loss among obese children is vital in the management of SDB.

Infants with CFA are most appropriately managed by a multidisciplinary team. Any indication for surgical intervention involving the airway such as mandibular reconstruction for Pierre Robin syndrome should be based upon careful evaluation of anatomic and physiologic abnormalities. Affected infants with failure to thrive, chronic

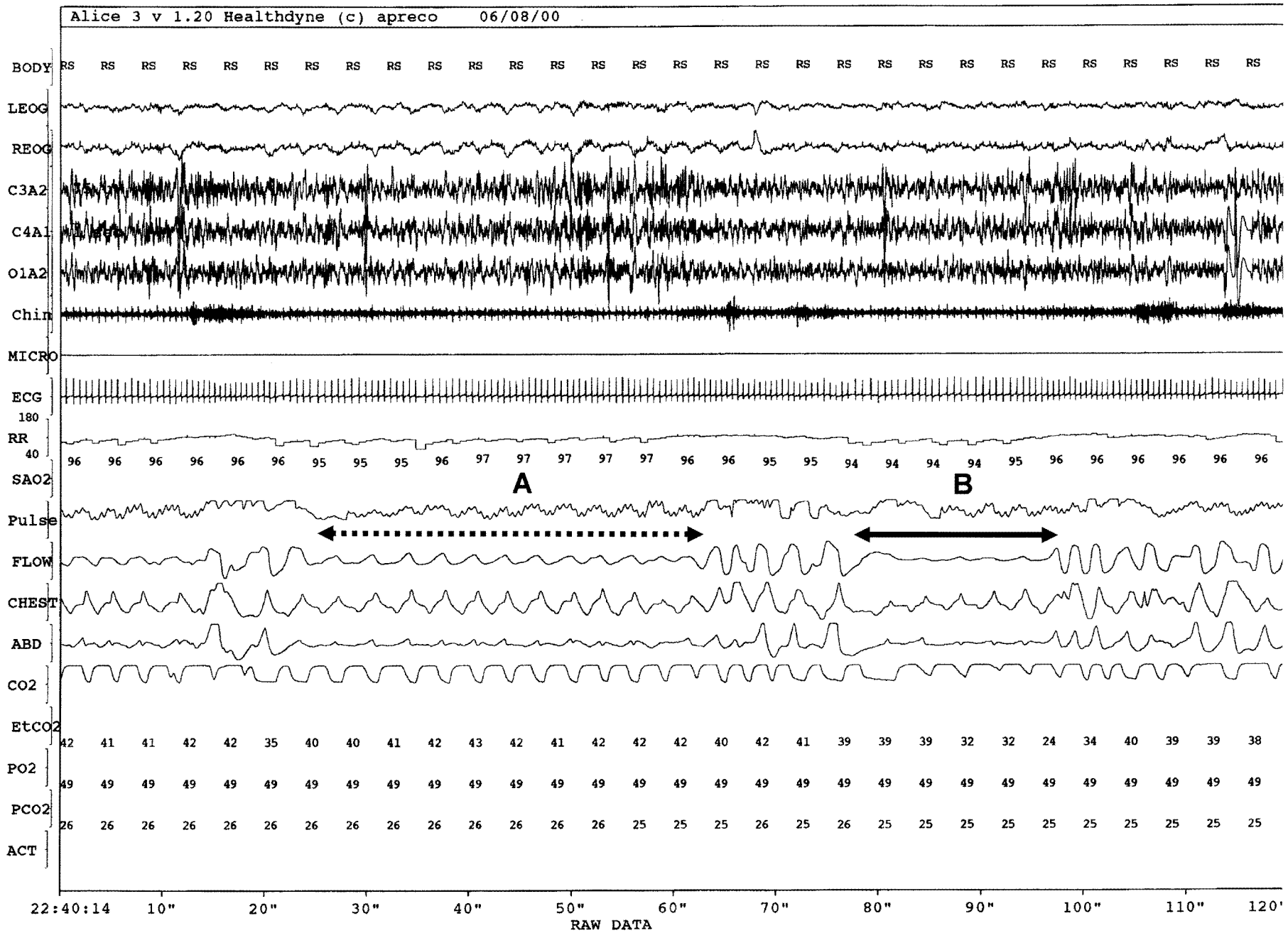

Figure 3-8 Example of polysomnographic study in an infant with Pierre Robin syndrome. Repetitive episodes of obstructive hypopnea and apnea (*A*) occur during rapid eye movement sleep and are associated with mild oxygen desaturation and arousal (*B*).

respiratory failure, and cor pulmonale are at significant risk for prolonged stay in the intensive care unit and repeated endotracheal intubations postoperatively.

Alternative management includes topical nasal decongestants, nasopharyngeal or oral airways, and nasal CPAP. If these approaches fail or if prolonged endotracheal intubation is required, permanent tracheotomy may be necessary. Tracheotomy will immediately reduce airway resistance and anatomic dead space, ameliorate respiratory failure, and ultimately reverse cor pulmonale and promote growth. Reconstructive surgical approaches in children with CFA involve skeletal expansion in combination with soft tissue reduction, which can result in improvement in the naso-oropharyngeal volumes.[155] Definitive reconstructive airway surgery in the absence of a tracheotomy is less likely to be successful and is associated with a greater incidence of complications.[156] Reconstructive surgical airway management has been shown to allow successful decannulation of the airway among infants with CFA.[157] Tonsillectomy and adenoidectomy (T&A) may be indicated later in life.[157]

Successful use of noninvasive positive-pressure ventilation through nasal mask has been reported in infants and children with CFA. Jarund et al.[158] reported that the use of nasal CPAP among children with CFA is a safe and effective treatment option that may reduce the number of airway operations. This, however, is poorly accepted by most children with significant psychomotor retardation. A follow-up polysomnography is needed to evaluate the effectiveness of this treatment.

Neuromuscular Diseases

Respiratory muscle weakness is the inevitable consequence of many childhood neuromuscular disorders (NMD) that results in significant abnormalities in chest wall and lung mechanics. The reduction in chest wall compliance is explained by inability to fully expand and empty the chest, which leads to stiffening of the joints and tissues of the rib cage. The reduction in lung compliance is explained by atelectasis resulting from breathing at low lung volume and from the inability to clear airways of secretion by an effective cough.

Sleep-related respiratory dysfunction in infants with NMD is primarily caused by abnormalities in the respiratory muscle "pump" (chest wall and diaphragm). The physiologic alteration in respiratory mechanics during sleep results in decrease in tidal volume, minute ventilation, and functional residual capacity (FRC). This can be worsened by baseline awake deficiency in respiratory muscle strength and lung function. Hypotonia of the upper airway and intercostal muscles in infants with NMD is also associated with decreased chest wall compliance, rib cage deformability, and reduced FRC.[159] Infants with selective bulbar involvement, resulting in upper airway muscle hypotonia can have reduced protective reflexes that can lead to aspiration of secretions during sleep. Certain NMDs (e.g., spinal muscular atrophy [SMA] and Duchenne muscular dystrophy [DMD]) that affect the diaphragm can also lead to significant hypoxemia or hypoventilation during REM sleep.[160] In addition, patients with progressive NMD and chronic hypercapnia may develop a secondary reduction in hypoxic and hypercapnic response.[161] It is difficult, however, to differentiate between a primary reduction in respiratory drive versus a decline in chest wall and lung mechanical properties caused by muscle weakness. Several published studies have failed to demonstrate true primary abnormalities in respiratory control.[161,162] On the contrary, some studies suggest that central respiratory drive is intact and may increase, to overcome abnormal respiratory mechanics. Finally, most infants and children with NMD, especially those who are wheelchair bound, eventually develop progressive thoracolumbar scoliosis that further compromises lung volumes, respiratory mechanics, and pulmonary clearance.

Certain NMDs can present early in the neonatal period. Myasthenia gravis in infancy may either be transient or congenital. Transient myasthenia occurs in 12% of neonates born to mothers with the disease. The most common presenting symptom is feeding-related problems. Congenital myasthenia, on the other hand, is associated with significant involvement of extraocular muscles, but severe generalized muscle weakness is uncommon. Neither of these types of myasthenia in neonates is likely to be associated with recurrent apnea or respiratory failure. Familial infantile myasthenia, however, has been associated with recurrent apnea and respiratory depression and may cause sudden infant death. This type of neonatal myasthenia is characterized by (1) absence of myasthenia in the mother, (2) occurrence of a similar disorder among siblings, (3) respiratory depression at birth, (4) episodic weakness and apnea during the first 2 years of life, and (5) improvement with age.[164] The condition responds to anticholinesterase medication but requires early diagnosis and intervention to prevent morbidity and mortality.[164]

Congenital myotonic dystrophy is one of the most frequent muscular diseases that manifest during the neonatal period. The incidence is approximately 1 per 3500 live births.[165] It is an autosomal dominant disorder. The affected parent is the mother, who may have a history of miscarriages, stillbirths, and neonatal deaths. The respiratory complications of this disorder start in utero with poor fetal breathing, resulting in pulmonary and diaphragmatic hypoplasia.[165] A short umbilical cord (less than 40 cm) secondary to fetal akinesia may be an early clue to diagnosis. Neonates with mild expression of the disease are hypotonic, have a poor sucking reflex, difficulty swallowing, facial diplegia, and limb contractures. Severely affected infants may present with perinatal asphyxia resulting from respiratory muscle weakness and respiratory failure and will require positive-pressure ventilatory support if they are to survive. Difficulty in swallowing may lead to recurrent aspiration that can lead to morbidity and mortality in the first 2 years of life.

Spinal muscular atrophy (Werdnig-Hoffmann disease) is an autosomal recessive disorder. The primary pathologic change is atrophy of anterior horn cells in the spinal cord and motor nuclei in the brainstem. The disease can be detected at birth in about 30% of cases. Affected infants show weakness and hypotonia of the axial and proximal muscles.[166] Although the diaphragm is relatively normal, weakness of intercostal muscles may cause paradoxical breathing and progressive respiratory paralysis. Recurrent

atelectasis and aspiration pneumonia often occur, which can lead to respiratory failure and death.[167,168] Distal infantile spinal muscular atrophy differs from classic Werdnig-Hoffman disease in that it is characterized by involvement of distal limb muscles and the diaphragm. Pulmonary hypoplasia can occur in utero; diaphragmatic paralysis can be present at birth or occur soon thereafter.[166]

Prader Willi syndrome (PWS) is a congenital disorder characterized by neonatal hypotonia, hypogonadism, psychomotor delay, childhood onset obesity, short stature, and behavioral abnormalities. Sleeping disorders and respiratory disorders such as hypoventilation, obstructive and central apnea, and abnormal ventilatory response and arousal response during hypercapnia may occur.[169,170] The underlying cause of PWS is a paternal deletion or uniparental disomy of *15q11-13*. In 1% to 5% of patients, PWS is the result of an imprinting-center mutation, which causes genes in the paternally inherited chromosome *15q11-13* to be silenced.[171]

Congenital muscular dystrophy such as mitochondrial myopathy; Niemann Pick (types A, B and C); glycogen storage disease such Pompe's; and arthrogryposis may present with muscle weakness in the neonatal period that may likewise interfere with adequate ventilation.

Skeletal dysplasias secondary to a generalized disorder of connective tissue can cause respiratory difficulties because of abnormalities of thoracic anatomy or airway mechanics. Infants with skeletal dysplasia have one or more of the following abnormalities: a barrel-shaped thorax, which accounts for decreased tidal volume; laryngomalacia, tracheomalacia, or bronchomalacia; and cervical spine instability with resultant compression of the upper cervical spinal cord or of the arterial supply to the base of the medulla, which may lead to abnormalities of respiratory control.[172] Thanatophoric dysplasia, Jeune syndrome, and spondyloepiphyseal dysplasia congenita are examples of serious congenital thoracic dystrophy that cause severe respiratory problems during the neonatal period that can lead to respiratory failure and death.

Polysomnography is an essential tool in the evaluation of cardiorespiratory function in infants with NMD and skeletal dysplasia. It also aids in the planning and implementation of elective nocturnal assisted ventilation, assessment of the adequacy of respiratory support, and evaluation of preoperative and postoperative status of patients with NMD. Measurement of noninvasive ventilation such as end-tidal or transcutaneous CO_2 is essential in evaluation of sleep-related disordered breathing in children with NMD. In addition to apnea of any type, it is important to evaluate sleep disruption, paradoxical movement of the chest wall and diaphragm, and nocturnal alveolar hypoventilation. Nocturnal hypoventilation ($\uparrow CO_2$) can occur in the absence of significant oxygen desaturation. REM-related oxygen desaturation correlates with diaphragm weakness and the need to initiate assisted ventilatory support ( ).[174] In the later stages of the disease, hypoventilation and hypoxia occur in all sleep stages. If polysomnography is initially normal, repeat studies should be performed on a yearly basis.

Treatment of NMD involves general supportive care that includes adequate hydration, nutritional support, and airway clearance techniques. Obesity can develop insidiously in patients with significant disability caused by muscle weakness, and therefore assessment of caloric needs of each patient is vital. Correction and spinal stabilization procedures for paralytic scoliosis should be performed before significant loss of lung function occurs.

Various treatments have been tried to improve sleep-related respiratory disturbances in these disorders. Respiratory stimulants, such as theophylline, have been shown to be effective in infants with congenital myotonic dystrophy, although the exact mechanism is unclear. Methylxanthines may work by stimulating the infant's central respiratory drive or by directly increasing the strength of muscle contractions.[165] Nocturnal use of supplemental oxygen has been shown to alleviate REM-related oxygen desaturation in patients with DMD. However, the total sleep time, sleep stage distribution, and frequency and duration of arousals are not different between control and oxygen-treated groups, and supplemental oxygen may prolong the duration of apnea and hypopnea.[175] Simple elevation of the upper body from a supine position can increase FRC and may prevent dependent airway closure and atelectasis. A rocking bed may have the same effect as body positioning, but it also facilitates drainage of secretions from the lower airways. Furthermore, this form of therapy may ameliorate daytime hypercapnia and subjective sleepiness with resultant improvement in sleep fragmentation by inhibiting the arousal associated with phasic accessory muscle activation.[176] Measures to improve airway clearance can minimize or prevent life-threatening conditions among patients with NMD. There are, however, few reports[177] of the use of mechanical devices in pediatric patents.

Long-term ventilation has an established track record in the management of patients with SDB related to NMD. The use of negative-pressure ventilation that involves devices such as Plexiglas lung, cuirass shell, and pulmowrap have been linked with increased frequency of SDB caused by collapse of upper airway muscles.[178,179] Although positive-pressure ventilation via tracheotomy is the most effective mode of long-term assisted ventilation, it is not easily accepted by patients and parents as first-line therapy. It was not until the early 1980s that noninvasive ventilation (NIV) with a mask was pioneered by Rideau et al.[180] in France and subsequently by Bach et al.[181] in the United States. Hill[182] has suggested that NIV may work by (1) improving ventilatory mechanics, (2) resting fatigued respiratory muscles, thereby improving strength and endurance, or (3) enhancing ventilatory sensitivity to CO_2. In addition, improvement in sleep stage distribution may increase chemosensitivity and enhance sleep quality. Nasal mask ventilation has become the preferred and effective method of nocturnal ventilation because it may obviate the need for a tracheotomy tube. It can be provided by CPAP or by nocturnal intermittent positive-pressure ventilation through either bilevel positive airway pressure or a conventional ventilator. Long-term nasal ventilation by any of these methods has been shown to normalize gas exchange and alleviate symptoms of hypercapnia. [183,184] It also has been shown to stabilize declining lung function and prolong life expectancy of patients with DMD.[185]

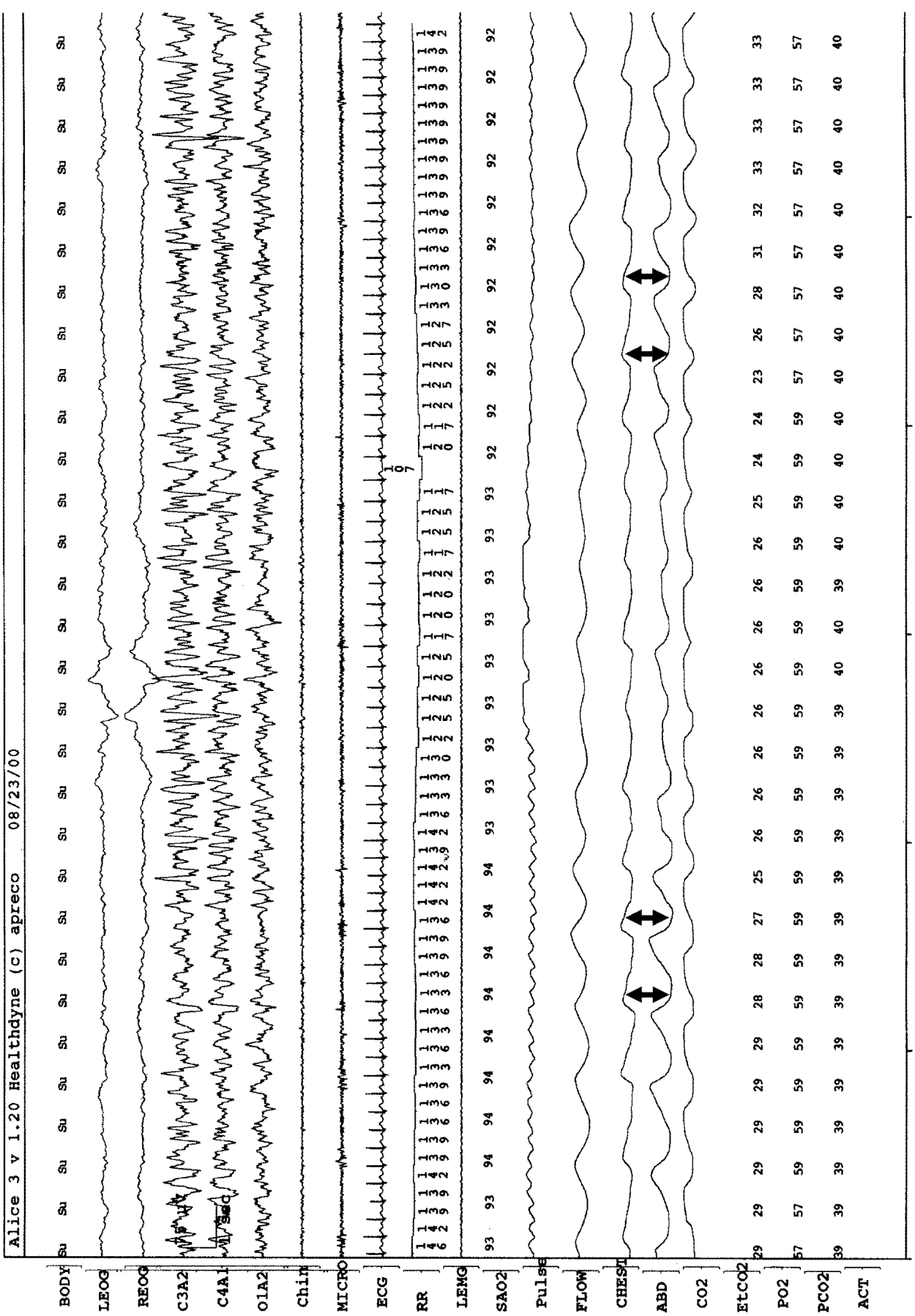

Figure 3-9 Polysomnographic segment recorded from an infant with spinal muscular dystrophy. Episodes of nonapneic oxygen desaturation and paradoxical breathing between chest and abdomen (*arrows*) that occurred during rapid eye movement sleep indicated the need for nocturnal ventilatory support.

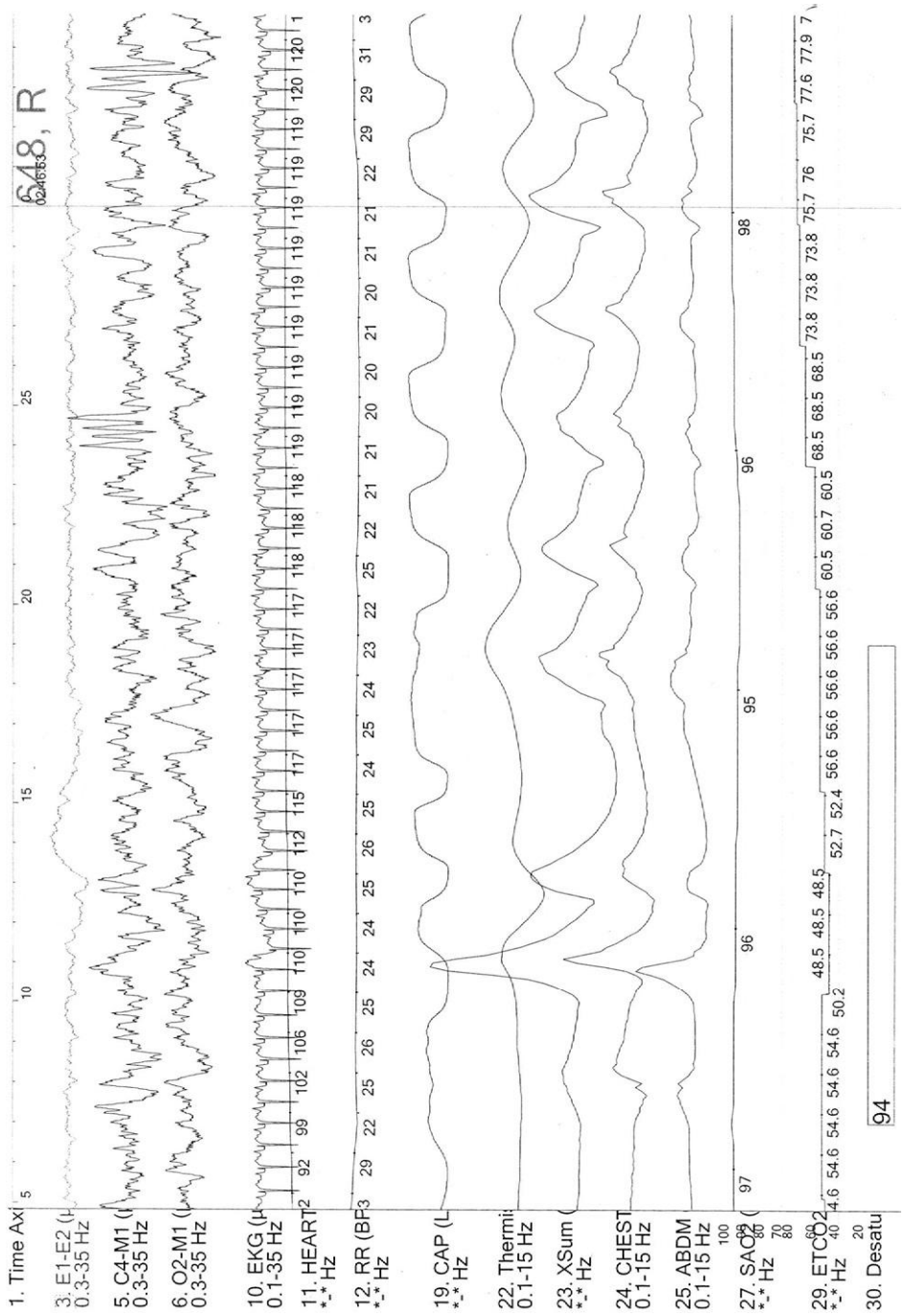

Figure 3-10 Polysomnographic segment in the same patient as in . Note that there was an improvement noted in oxygenation with 1 L supplemental O_2; however, suppression of the hypoxic drive made hypercapnia worse.

Inborn Errors of Metabolism

Inborn errors of metabolism have been associated with apparent life-threatening events (ALTEs) and sudden infant death syndrome (SIDS). However, this association may remain undetected unless postmortem specimen is examined with individual metabolic disorders in mind. Although the incidence is unknown, Arens et al.[187] found inborn errors of metabolism in 4.2% of infants referred for apnea evaluation and in about 8% of infants initially referred for ALTE. Establishing the relationship between ALTE and these metabolic errors is difficult because of the infant's age at the time of presentation.

Disorders that affect energy metabolism and glucose homeostasis, including glycogen storage disorders, gluconeogenic enzyme defects, and defects of fatty acid oxidation, can present as ALTE or SIDS.[189] When the child has been fed, the principal substrate for energy metabolism is glucose. With increased duration of fasting, however, fat replaces glucose. In the neonatal period, this can occur even after only 12 hours of fasting. Most reported cases of ALTE or SIDS involved abnormalities in fatty acid oxidation. The metabolic pathway through which fatty acids provide energy is through mitochondrial beta oxidation, and the main tissues involved are the liver, heart, and skeletal muscles.

Medium-chain acyl coenzyme A dehydrogenase deficiency is the most common inherited disorder of fatty acid oxidation associated with unexpected death. This condition, however, is not a frequent cause of SIDS as shown in a study where a G985 mutation was found in only three heterozygotes of 1224 tissue samples from SIDS victims.[188] Infants with this deficiency commonly present with episodes of encephalopathy and hepatomegaly that are triggered by fasting and viral illnesses. Its clinical presentation resembles that of Reye syndrome.[190,191] Deficiency of long-chain acyl coenzyme A appears to be less common but more severe. It occurs in the neonatal period and is characterized by hypoglycemia, cardiorespiratory arrest, cardiomegaly, and hepatomegaly.[190] Other inherited disorders of fatty acid oxidation associated with SIDS are primary carnitine deficiency, ornithine transcarbamylase deficiency, glutaric aciduria types II and IIB, multiple acyl coenzyme A deficiency, 3-hydroxyl-3-methylglutaryl coenzyme A lipase deficiency, carnitine palmitoyl transferase deficiency, and deficiencies of short-chain acyl coenzyme A dehydrogenase and long-chain 3-hydroxy acyl coenzyme A dehydrogenase.[192]

Asphyxia, Trauma, and Hemorrhage

Various types of perinatal injuries may affect ventilatory control on either a temporary or a permanent basis ( ).[,194] The level of ventilatory support depends on the level of the lesion; for example, brainstem and upper cervical spinal injury may be permanent and require full support. Central alveolar hypoventilation and apnea associated with hypoxic ischemic encephalopathy, intracranial hemorrhage, brainstem hemorrhage, or hydrocephalus are usually self-limiting and reversible.

Box 3-4 VENTILATORY CONTROL ABNORMALITIES SECONDARY TO ASPHYXIA, TRAUMA, OR HEMORRHAGE

- Intracranial hemorrhage or infection involving brainstem structures
- Brainstem infarction secondary to perinatal asphyxia
- Brainstem injury from precipitous delivery, breech presentation, or both
- High cervical cord injury (C1-C3) from breech presentation causing respiratory failure
- Midcervical cord injury (C3-C5) causing unilateral or bilateral phrenic nerve injury with or without respiratory failure

Summary

Sleep and respiratory control in neonates and infants undergo significant maturational changes in an orderly developmental sequence. Several factors can interfere with the normal progression of developmental changes, including immaturity, stress, neonatal insults and injuries, alterations of normal anatomic structure, and neuromuscular control. These changes can lead to disorders of sleep and respiratory control. In this chapter, the normal development of sleep and ventilatory control was discussed, with emphasis on the pathophysiology and clinical aspects of a diverse group of disorders of respiratory control in neonates and infants.

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4 Resuscitation

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Resuscitation is a word derived from the Latin *resuscitare*, meaning "to arouse again." In neonatology, this term is employed in two separate clinical settings. The first is the emergency situation, in which unexpected respiratory or cardiac arrest occurs in the nursery or neonatal intensive care unit (NICU) and measures are begun to restore life. Often a new complication that is not predictable or preventable (e.g., tension pneumothorax) requires immediate intervention (e.g., thoracentesis and tube thoracostomy) as well as resuscitation. Sometimes, resuscitation is necessary because a patient has deteriorated through measurable stages of respiratory or cardiac failure, because of inadequate therapy, poor judgment, or less-than-optimal observation on the part of the health care team.

In the second setting, usually occurring in the delivery room, resuscitation is used to assist the newly born infant in making the transition from dependent fetal to independent neonatal life. Complex changes occur in the fetus during the transition from intrauterine to extrauterine life, yet the birth process is usually accomplished with relative ease. Approximately 10% of newly born infants require some assistance to initiate spontaneous respirations at birth.[1] More intensive resuscitation, including positive-pressure ventilation, is required by 1% of newly born infants,[2] and extensive resuscitation requiring chest compressions (CPR) and/or drug therapy is only required in 1 to 2 per 1000 live births.[3]

Often one can predict which newborn infants will require assistance in the delivery room. Information regarding antepartum or intrapartum risk factors collected during gestation, labor, or delivery can be used by the clinician to prepare for resuscitation ( ). Although the mature fetus may make the crucial adjustments at birth without significant intervention, the preterm or asphyxiated infant may need immediate and skillfully performed life-preserving measures to make this transition. Of critical importance are the expansion of the lungs, the establishment of respirations, and the conversion from fetal to adult circulation so that blood returning to the heart is directed through the lungs. Asphyxia is the major pathologic event that requires correction in both types of resuscitation.

Asphyxia usually implies a complex combination of hypoxemia, hypercapnia, and circulatory insufficiency that may be induced by a variety of perinatal events (e.g., placental insufficiency, abruption placenta, meconium aspiration respiratory failure, pneumothorax, blood loss, etc.). The aim of a resuscitation protocol should be the immediate reversal of hypoxemia, hypercapnia, and circulatory insufficiency to prevent permanent central nervous system damage or damage to other organs. If optimal outcome is to be achieved, a resuscitation protocol should be directed immediately toward achieving the following: (1) clearing the upper airway of secretions, meconium, or other materials so that alveolar expansion can occur; (2) providing adequate oxygenation and elimination of excessive carbon dioxide; (3) ensuring adequate cardiac output; and (4) keeping oxygen consumption to a minimum.

In this chapter, we briefly discuss the pathophysiology of neonatal asphyxia and the steps needed to successfully resuscitate newborn infants, either in the delivery room or in the nursery.

Physiologic Changes During Asphyxia and Resuscitation

When antepartum or intrapartum factors impair fetal-placental gas exchange, asphyxia may result. Dawes and Adamsons et al.[5] described the classic changes of perinatal asphyxia in a rhesus monkey experimental model, which probably approximates events in human neonates.

illustrates the changes in physiologic factors during 10 minutes of total asphyxia and subsequent resuscitation. Immediately after delivery by cesarean section, the head of the monkey was covered with a saline-filled bag to prevent air entry during breathing, and the umbilical cord was ligated. Approximately 30 seconds later, the experimental animal began gasping. The gasping ceased after about 1 minute and was followed by primary apnea, which also lasted about 1 minute. During the period of primary apnea, spontaneous respirations could be induced by tactile stimulation; also, a heart rate decreased from the normal range of 180 to 220 beats per minute to about 100 beats per minute and was accompanied by a transient increase in blood pressure. After primary apnea, the monkey made deep gasping efforts for a period of 4 to 5 minutes; the gasping efforts weakened gradually until they ceased completely, with the last gasp occurring after about 8 minutes of total asphyxia. Secondary apnea began after the last gasp. The heart rate and blood pressure steadily declined. Striking changes in pH, carbon dioxide tension (P_{CO_2}), and oxygen tension (P_{O_2}) occurred during 10 minutes of total asphyxia in the rhesus monkey: pH decreased from 7.3 to

Box 4-1 RISK FACTORS ASSOCIATED WITH THE NEED FOR NEONATAL RESUSCITATION

Antepartum Factors
- Maternal diabetes
- Pregnancy-induced hypertension
- Chronic hypertension
- Rhesus factor sensitization
- Previous stillbirth
- Bleeding in second or third trimester
- Maternal infection
- Polyhydramnios
- Oligohydramnios
- Post-term gestation
- Multiple gestation
- Size-date discrepancy
- Drug therapy
  - Reserpine
  - Lithium
  - Magnesium
  - Adrenergic blocking agents
- Maternal drug abuse

Intrapartum Factors
- Cesarean section (other than uncomplicated repeat section)
- Abnormal presentation
- Premature labor
- Rupture of membranes earlier than 24 hours before delivery
- Foul-smelling amniotic fluid
- Precipitous labor
- Prolonged labor
- Prolonged second stage of labor
- Ominous fetal heart rate patterns
- General anesthesia
- Uterine tetany
- Narcotics given to mother within 4 hours of delivery
- Meconium-stained amniotic fluid
- Prolapsed cord
- Abruptio placentae
- Placenta previa

Modified from Kattwinkel J (ed.) Textbook of Neonatal Resuscitation. Dallas, TX, American Heart Association, Elk Grove Village, IL, American Academy of Pediatrics, 2006. p. 1-15.

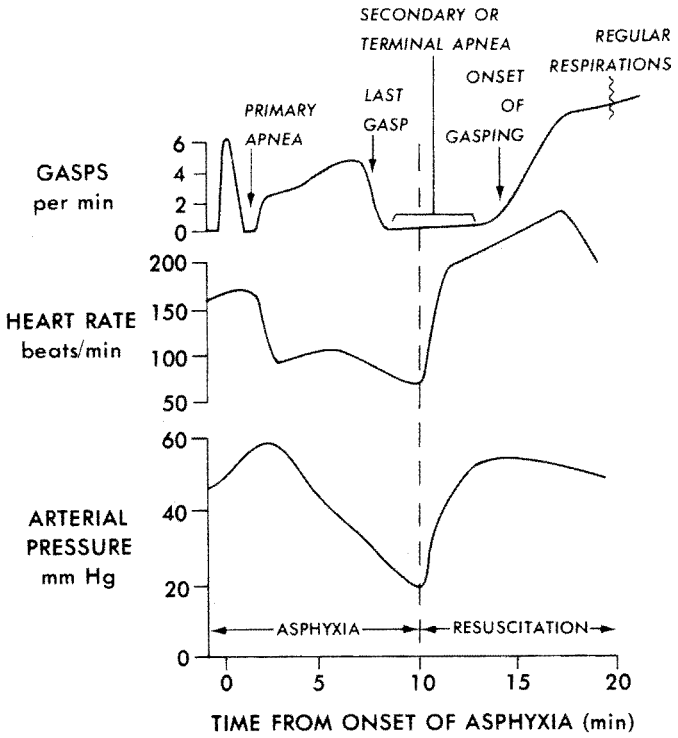


Figure 4-1 Changes in physiologic factors during asphyxia and resuscitation in newborn rhesus monkeys. (Adapted from Adamsons K Jr, Behrman R, Dawes G, et al: The treatment of acidosis with alkali and glucose during asphyxia in foetal rhesus monkeys. J Physiol 169:679, 1963, and Dawes GS: Foetal and Neonatal Physiology. Chicago, Year Book Medical Publishers, 1968. By permission of Elsevier, Inc.)

6.8, P_{CO_2} increased from 45 to 150 mm Hg, and P_{O_2} decreased from 25 mm Hg to nearly zero. Serum lactate concentration also rapidly increased. Death occurred after several minutes of secondary apnea, unless the animal was resuscitated. Tactile stimulation did not induce spontaneous respirations during secondary apnea. The longer the delay in initiating adequate resuscitation after the last gasp, the longer the time to the first gasp after resuscitation was begun. For every 1-minute delay, the time to first gasp was prolonged by approximately 2 minutes and time to onset of spontaneous respirations was delayed by 4 minutes.

During the period of total anoxia, a variety of changes involving the cardiovascular system, pulmonary circulation, and other organ systems and tissues occurred in the fetus in response to asphyxia. These changes reflect the response of the fetus to asphyxia ( ). In view of these experimental observations in the rhesus monkey, one could speculate that several phenomena characterize asphyxia in the human infant. First, the entire sequence of

TABLE 4-1 Fetal Changes in Response to Asphyxia

Parameter	Change
pH	↓
P_{CO_2}	↑
P_{O_2}	↓
Lactate level	↑
Plasma potassium level	↑
Free fatty acid level	↑
Glycerol level	↑
Catecholamine level	↑
Blood pressure	Transient ↑, then ↓ with prolonged asphyxia
Heart rate	Modest ↑, then ↓ with prolonged asphyxia
Umbilical blood flow	↓
Cardiac output	↓
Skin perfusion	↓
Pulmonary vascular resistance	↑
Oxygen consumption	↓
Shunting of blood through foramen ovale	↑
Glucose metabolism	Shifts from aerobic to anaerobic

*↓, Decrease; ↑, increase.

TABLE 4-2 Major Causes of Neonatal Depression in the Delivery Room

Cause	Major Effect	Examples
Drugs	Respiratory depression	Anesthetics, narcotics, alcohol, magnesium sulfate, tranquilizers
Physical/mechanical	Interruption of blood supply	Prolapsed cord, head entrapment
Hemorrhage	Hypovolemia/shock	Abruptio placentae, ruptured umbilical cord, fetomaternal transfusion
Developmental anomalies	Cardiac, pulmonary insufficiency	Congenital heart disease, diaphragmatic hernia, choanal atresia, Potter syndrome
Environmental	Hypothermia	Delivery in cool environment, lack of external heat source
Postmaturity	Pneumonia, pulmonary hypertension	Meconium aspiration syndrome, persistent pulmonary hypertension of the newborn
Iatrogenic		
Excessive airway pressure generated at resuscitation	Pulmonary and cardiac embarrassment	Pulmonary air leak syndrome
Excessive suctioning	Vagal stimulation	Bradycardia, apnea
Misplacement of endotracheal tube	Hypoxia, bradycardia	Intubation of esophagus/right mainstem bronchus
Placental insufficiency	Hypoxia, acidosis	Abnormal fetal heart rate pattern, tetanic contraction
Severe immaturity (weight <1000 g)	Pulmonary insufficiency	Respiratory distress syndrome, inadequate respiratory effort
Extrinsic or intrinsic pulmonary compression or hypoplasia	Pulmonary insufficiency	Diaphragmatic hernia, pleural effusion, pulmonary hypoplasia

events may start in utero and continue after delivery. Second, the irregular and weak gasps of the asphyxiated infant may not generate sufficient intrathoracic pressure to expand the lungs. Third, if the effects of asphyxia are to be reversed, both ventilation and pulmonary perfusion are needed; either alone is not sufficient.

In most animal models of asphyxia, acute total asphyxia occurs; in contrast, in human fetuses, asphyxia is often intermittent, subacute, and/or chronic. This makes it difficult to apply the knowledge gained from animal models of acute asphyxia to the different types of asphyxia seen in human fetuses and newborns. For example, the duration of secondary apnea is probably longer in subacute asphyxia in humans than in the acute total asphyxia in the rhesus monkey model, and the human fetus may tolerate more prolonged intermittent asphyxia before developing permanent brain or other organ damage.

True intrapartum asphyxia cannot easily be differentiated clinically from neonatal depression from a variety of causes. Initial resuscitation responses are similar in both situations, but the diagnosis of "asphyxia" should only be made when certain clinical criteria are met. The major causes of neonatal depression at birth are listed in

.

Moreover, in the clinical setting, primary and secondary apnea cannot be readily distinguished. Therefore, when an infant is born with apnea, it is assumed to be secondary apnea. Neonatal resuscitation, such as the protocol taught in the American Heart Association and American Academy of Pediatrics Neonatal Resuscitation Program (AHA-AAP NRP),[6] should be initiated immediately.

Method

The four principal elements necessary for successful neonatal resuscitation are (1) the anticipation of clinical situations that require the application of resuscitation efforts; (2) the preparation of a treatment area, equipment, and drugs; (3) the availability of qualified personnel; and (4) an organized response to emergencies when they occur.

Anticipation

Although most cardiorespiratory arrests in the nursery are not anticipated, the delivery of a baby requiring resuscitation can often be predicted. In the past, an additional physician or health professional skilled in neonatal resuscitation attended "high-risk" deliveries (cesarean sections, placenta previa, placental abruption, premature deliveries, etc.) in anticipation of circumstances in which neonatal resuscitation might be needed. However, in modern surgical obstetrics, a repeat cesarean birth of a term infant is usually a benign event, and in many hospitals it is routine for either a physician or other NRP-qualified individual to attend these deliveries.

Many other conditions should alert the obstetric team for the need of a skilled resuscitator to attend the delivery. The term "high-risk pregnancy" is not necessarily indicative or predictive of the need for resuscitation of an infant at birth. This classification is quite broad, and only a small percentage of high-risk pregnancies result in perinatal asphyxia or require significant assistance in making the transition from intrauterine to extrauterine life. The AAP and the American College of Obstetricians and Gynecologists have published guidelines urging each institution to develop a list of maternal and fetal indications for the presence of an individual qualified in newborn resuscitation in the delivery room.[7] According to these guidelines, elective repeat cesarean delivery is not necessarily a high-risk situation. A review by Press et al.[8] on the cesarean delivery of full-term infants showed that interventions in the delivery room for *repeat* cesarean delivery are quite rare (tracheal intubation was required in 1 of 111 deliveries), whereas resuscitations after cesarean deliveries performed

because of fetal distress were quite common (intubation was required in 24 of 66 deliveries). Moreover, these investigators noted that in their hospital, the rate of tracheal intubation in the repeat cesarean group infants was lower than that for infants delivered vaginally. Levine et al.[9] reported no increased incidence of low Apgar scores in cesarean deliveries using regional anesthesia for nonfetal reasons compared to vaginal deliveries and concluded that there was no need for pediatrician attendance at such deliveries. Thus a graded response to the so-called "high-risk" delivery seems appropriate, and traditional hospital policies for mandatory pediatric attendance at certain types of deliveries (e.g., cesarean deliveries using regional anesthesia for nonfetal indications) should be reviewed.

The truly high-risk pregnancy resulting in a high-risk delivery can be anticipated in most cases. Under certain circumstances, and if time allows, the mother may be transferred to a level III center (see Chapter 1), where the infant can be delivered under optimal conditions. However, advanced labor and imminent delivery preclude transfer of the mother. Often telephone consultation with a neonatologist or request for the neonatal transport team *before* delivery is worthwhile.

Those pregnancies identified as high-risk require special management and intensive monitoring during gestation, labor, and delivery. Fisher and Paton[10] divide monitoring into the following four phases: (1) evaluation of the fetal placental unit during gestation; (2) estimation of fetal growth; (3) evaluation of fetal maturity, especially pulmonary maturity; and (4) acute monitoring of the fetus during labor and delivery. Problems detected during any phase of monitoring allow for prenatal identification of most infants who have difficulty in making the transition from intrauterine to extrauterine life.

Preparation

Preparation for a neonatal resuscitation is a two-stage procedure. The first stage occurs days, weeks, or months before the emergency. During this time, an area in or near the delivery room is designated as the "resuscitation area." Provision is made for adequate space, ample heat (e.g., the presence of a radiant warmer), blended O_2, and suction. Supplies and drugs are identified, obtained, and placed in a code cart or bag, or they are pegged to a wall board for easy access.[11] A resuscitation protocol should be written out, identifying procedures to be followed and personnel responsibilities during the emergency. A standardized neonatal cardiac arrest record should be developed and copies of it placed in the resuscitation area to simplify record-keeping during the procedure (see Appendix 27). In hospitals in which actual resuscitations are infrequent, periodic mock resuscitations should be performed to practice neonatal resuscitation.

Effective resuscitation is a team effort, and preparation of the team requires an effective training program within the hospital. Skills that are necessary to a well prepared team include cognitive knowledge, technical competence, and behavioral abilities to work together effectively. The attendance at a resuscitation course and the successful completion of a cognitive test does not assure competence in this complex and intense procedure. Very recently, an interactive neonatal simulator, SimNewB™ was developed by Laerdal collaboratively with the American Academy of Pediatrics to meet the training requirements of the AHA-AAP NRP. SimNewB™ has multiple features including an anatomically accurate realistic airway for endotracheal tube insertion and laryngeal mask airway insertion; CO_2 exhalation, so CO_2 detectors can be used to document endotracheal intubation; an umbilicus with a life-like pulse; a cuttable umbilicus with venous access that can be catheterized with simulated blood flashback; and six preset patient states ranging from vigorous to severely compromised newborn, which can be changed with the push of a button on a remote handheld control. It is hoped that periodic simulations with different resuscitation scenarios using SimNewB™ will not only reinforce retention of basic NRP skills but also enhance the effectiveness of the entire neonatal resuscitation team in both NICUs and referring hospitals.[12]

The second stage of preparation occurs only when need for resuscitation can be predicted in a high-risk patient. With adequate time, the resuscitation team can be alerted and arrangements can be made to have appropriate personnel present in the delivery room to assume care of a potentially depressed infant. The person in charge of the resuscitation should review the mother's chart, looking for clues in the perinatal history that may signal the possibility of asphyxia in the baby. Of particular importance is the mother's medication record, especially if analgesics, which are known to depress infants in the perinatal period, have been used. This is also an excellent time for the pediatric team to talk with the parents, explaining the procedures that are to be carried out and the difficulties that can be expected. Meanwhile, everything needed for resuscitation after delivery can be prepared so that confusion is minimized: equipment can be organized; medications can be drawn up and made ready for administration; the proper operation of the laryngoscope's light is checked; and O_2 is turned on.

Personnel

The most important aspect of resuscitation is the availability of competent personnel who are able to respond immediately to any emergency. If a high-risk delivery is anticipated, the necessary personnel can be summoned to the hospital. If ventilation of neonates is underway in the hospital NICU, competent personnel should be available "in house" at all times.

Smith[13] describes an individual properly prepared to lead a resuscitation effort as having "the diagnostic competence of a pediatrician and an internist, the technical skills of an anesthesiologist and a surgeon, and the organizational ability of a gang boss." As Smith notes, these talents are rarely found in one person, but recent simulation training has been focused on developing the cognitive, technical, and behavioral skills necessary to be a competent member of a resuscitation team. Fortunately, not every high-risk delivery requires all of these skills. The person attending a high-risk delivery should be able to intubate, to perform ventilation and cardiopulmonary resuscitation, and to place an umbilical catheter. It is our belief that this person does not have to be a physician. A properly qualified neonatal nurse-clinician skilled in resuscitation may be the appropriate person to attend a

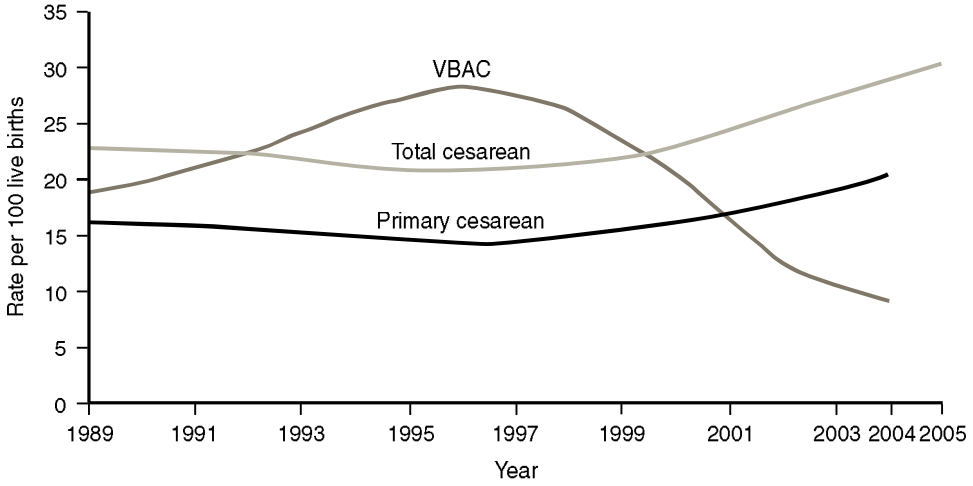


Figure 4-2 Rate of total cesarean deliveries, primary cesarean deliveries, and vaginal births after previous cesarean deliveries (VBAC) in the United States, 1989-2005. (From Ecker JL, Frigoletto FD: Cesarean delivery and the risk-benefit calculus. N Engl J Med 356:885, 2007.)

moderate-risk delivery. This deviation from traditional practice has economic advantages as well, especially since the cesarean delivery rate in the United States increased to 30% of all deliveries in 2005 ( ).[15] The true high-risk delivery does require a full team approach. Various tasks are assigned to team members and everyone on the team knows his or her role in the resuscitation process.

Response

The three steps in an appropriate resuscitation response are evaluation, diagnosis, and treatment.

Evaluation

The evaluation of an infant before treatment is begun is essential in an emergency situation if mistakes are to be avoided. For newborn infants, the Apgar scoring system[16] may be helpful in assessing the infant's condition ( ); however, in most cases of neonatal asphyxia, resuscitation commences before the first Apgar score is assigned.

TABLE 4-3 The Apgar Score

	SCORE		
Sign	**0**	**1**	**2**
Heart rate	Absent	Slow (<100 bpm)	≥100 beats/min
Respirations	Absent	Slow, irregular	Good, crying
Muscle tone	Limp	Some flexion	Active motion
Reflex irritability (catheter in nares, tactile stimulation)	No response	Grimace	Cough, sneeze, cry
Color	Blue or pale	Pink body with blue extremities	Completely pink

The Apgar scoring system was devised as a means for documenting a newborn's condition at specific intervals after birth.[16] The five signs are usually assessed at 1 and 5 minutes of age. If the score at 5 minutes is less than 7, additional scores are obtained every 5 minutes until the score is greater than 6 or until the infant is 20 minutes old. In the past, the Apgar scoring system was used to guide resuscitative efforts. It is not used in the AHA-AAP NRP[6] for decision-making regarding resuscitation, because delays of even 1 minute could be critically important in the severely asphyxiated infant. Instead, frequent and repeated assessment (every 30 seconds) of breathing, heart rate, and color are performed for evaluation of successful resuscitation.

Intrapartum asphyxia is not the only factor that affects the Apgar score. Tone, color, and reflex irritability depend on the physiologic maturity of the infant. A preterm infant with no evidence of perinatal hypoxia normally has a reduced Apgar score because of immaturity.[17] Other factors depress the Apgar score, including maternal sedation and analgesia, neonatal neuromuscular disease and cerebral malformations, and congenital cardiac malformations.

Apgar scores do not correlate with the results of umbilical cord arterial blood gas analysis (e.g., low Apgar scores are not associated with severely acidotic pH values, and vice versa).[18] This may be due in part to problems in obtaining accurate umbilical cord blood gas values (e.g., analyzing a venous rather than arterial sample), or the clinical situation of umbilical cord occlusion in which there is "no flow" through the cord during the asphyxial episode.[19] It is noteworthy that a large, retrospective cohort analysis showed that the 5-minute Apgar score predicted neonatal death more accurately than the umbilical-artery pH value.[20] In fact, the risk of neonatal death in term infants with a 5-minute Apgar score of 3 or less was eight times that in term infants with umbilical-artery pH values of 7.0 or less. In an accompanying editorial, Papile[21]

concluded that until a more useful tool for assessing newborns is developed, the 5-minute Apgar score is still valid as a rapid method for evaluating the effectiveness of resuscitative efforts and risk of neonatal mortality in the 21st century.

Nelson and Ellenberg[22] have shown that the Apgar scores obtained at 1 and 5 minutes are poor predictors of neurodevelopmental disability. Therefore, low Apgar scores, by themselves, should not be considered evidence of severe asphyxia. Nevertheless, Apgar scores are useful for prognostication when combined with other clinical indicators of asphyxia. The American College of Obstetricians and Gynecologists Task Force on Neonatal Encephalopathy and Cerebral Palsy (including AAP liaison members) defined criteria for identifying perinatal asphyxia that is sufficiently severe to cause neurologic damage. All of the following must be present: profound metabolic or mixed acidemia (pH less than 7.00) in an umbilical cord arterial blood sample; early onset of severe or moderate neonatal encephalopathy; the later development of cerebral palsy of the spastic quadriplegic or dyskinetic type; and exclusion of other identifiable etiologies. Other criteria that suggest intrapartum timing for the asphyxial event include a sentinel event during labor; sudden or sustained fetal bradycardia or other significant fetal heart rate abnormalities; Apgar score of 0 to 3 beyond 5 minutes; multisystem organ involvement within 72 hours of birth; and early brain imaging showing acute nonfocal abnomalities.[23]

Scoring systems can be used to rapidly identify infants at risk of acute multiorgan dysfunction from asphyxia and to facilitate clinical management. Carter and associates have shown that a scoring system consisting of graded abnormalities in fetal heart rate monitoring, umbilical arterial base deficit, and 5-minute Apgar score was useful in rapidly identifying term and near-term infants at risk for multiple organ system morbidity after acute perinatal asphyxia.

Diagnosis

The most important requirement for a successful resuscitation is accurate diagnosis. Although treatment must be immediate, each step should be undertaken on the basis of knowledge of clinical and historical information, on the findings of evaluation, and on an accurate diagnosis. Procedures that are lifesaving in one situation (needle thoracostomy in tension-generating pneumothorax) may be harmful in another clinically similar situation (diaphragmatic hernia).

Although the causes of asphyxia are numerous, several pieces of clinical and historical information should guide the clinician in his or her response. The differential diagnosis can be narrowed considerably, depending on whether the emergency takes place in the delivery room, nursery, or NICU; whether the infant is preterm or term; and whether the infant has received assisted ventilation before the emergency.

The response to an "arrest" of an intubated, mechanically ventilated infant in the NICU must be directed initially toward the correction of a possible mechanical problem (e.g., dislodgment or displacement of an endotracheal tube, pneumothorax, plugging of a tube, and ventilator malfunction) whenever cardiopulmonary resuscitation is started (see Chapter 9). The most important and effective action in neonatal resuscitation is to effectively ventilate the baby's lungs. Once cardiac compressions are initiated, the true cause of the emergency may be obscured. With adequate anticipation and preparation, the organized response to the expected diagnosis is simplified; however, adequate anticipation and preparation are not always possible. While evaluating the situation, determining the proper diagnosis, and organizing the emergency care, the clinician should bear in mind three important principles: (1) *primum non nocere* (Latin, meaning "first do no harm"); (2) avoid useless diagnostic or therapeutic procedures that waste time; and (3) do not initiate a costly procedure to prolong life when the situation is hopeless or irreversible.

The performance of cord blood gas studies may greatly assist the pediatric team in resuscitating the depressed newborn infant in the delivery room. A section of cord is clamped during the first 30 seconds of life, and a small sample of umbilical artery blood is obtained for determination of pH, P_{CO_2}, and base deficit. The results of this examination may be available within minutes and can be helpful in determining the magnitude of the resuscitation team's response by indicating the acid-base status of the baby immediately after birth. Often, the results obtained on this test do not correlate with the Apgar score at 1 minute[18] for the reasons stated above. Nonetheless, the performance of the test may precede by many minutes the obtaining of neonatal blood gas values by a sample collected from an umbilical artery catheter or a radial artery puncture and guide the subsequent resuscitation.

A review of 30,839 births by Perlman and Risser[3] revealed that only 39 (0.12%) required chest compressions or epinephrine, or both, as part of delivery room resuscitation. Severe fetal acidemia (pH less than 7.00, or a base deficit greater than 14 mEq/L) occurred in approximately one third of infants and portended poor outcome. In the other two thirds of neonates without fetal acidemia, the investigators concluded that malposition of the endotracheal tube and ineffective or improper initial ventilatory support was the presumed mechanism for continued neonatal depression.[3] This insightful study highlights the importance of accurate diagnosis, the usefulness of umbilical artery cord blood gas studies, and the necessity of appropriately administered positive-pressure ventilation for successful resuscitation.

Resuscitation should proceed according to a predetermined protocol; the protocol that has received national acceptance is the American Heart Association (AHA)–American Academy of Pediatrics (AAP) Neonatal Resuscitation Program (NRP).[6] The protocol for neonatal resuscitation is outlined in the algorithm shown in .

American Heart Association–American Academy of Pediatrics Neonatal Resuscitation Program

The following discussion of a neonatal resuscitation protocol is derived mostly from the 2006 AHA-AAP *Textbook of Neonatal Resuscitation*, 5th edition,[6] the *2005 American*

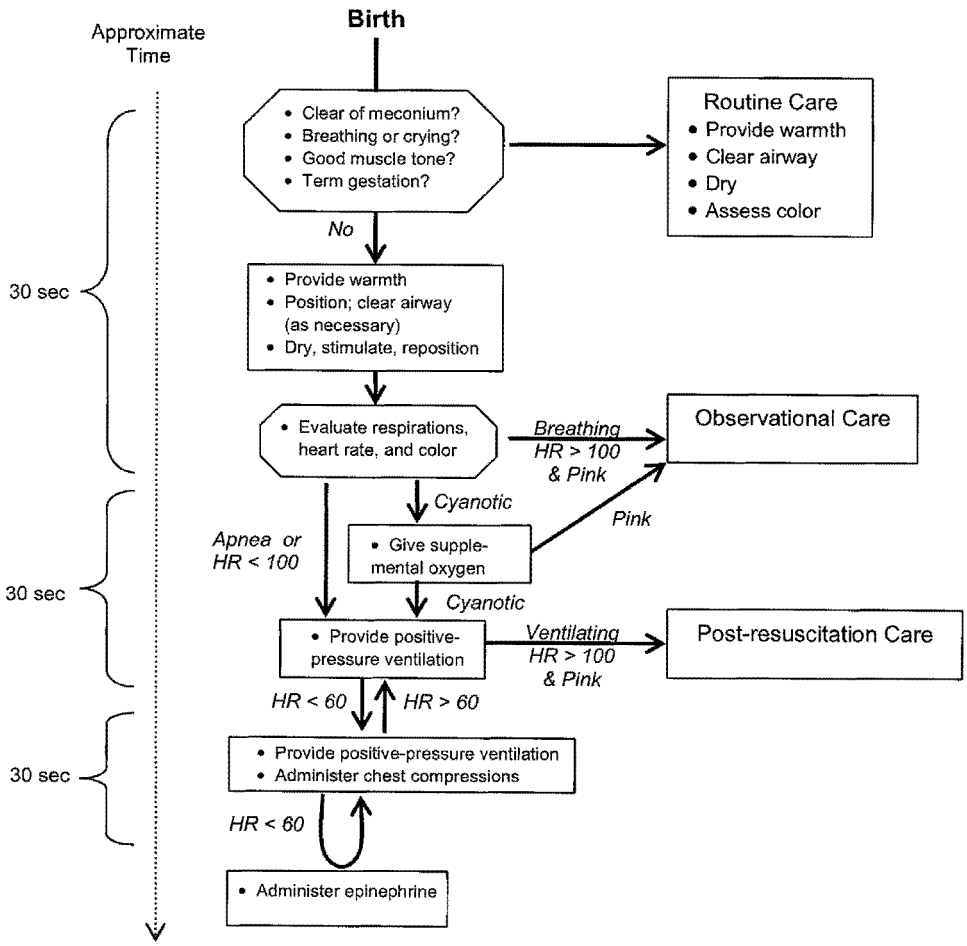


Figure 4-3 Algorithm for resuscitation of the newly born infant. (From Kattwinkel J, ed: Textbook of Neonatal Resuscitation, American Heart Association and American Academy of Pediatrics, 2006, pp. 1-19. Reproduced with permission.)

Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care of the Neonate,[25] and *The International Liaison Committee on Resuscitation (ILCOR) Consensus on Science with Treatment Recommendations for Neonatal Resuscitation.*[26]

Preparation for Delivery

Universal Precautions

Universal precautions should be followed because exposure to blood and other body fluids is likely in the delivery room. Gloves and other protective barriers should be worn when handling newly born infants and potentially contaminated equipment. Any technique that involves mouth suction (e.g., DeLee suction) must be avoided.

Personnel

At least one person skilled in initiating newborn resuscitation should be present at every delivery. This person should be trained in the AHA-AAP NRP or a similar program. Renewal of training is required every 2 years. At least two persons are required for resuscitation of a severely depressed neonate, one to ventilate and intubate, if necessary, and another to monitor heart rate and perform chest compressions, if indicated. When extensive resuscitation (including medication administration) is anticipated, a team of three to five persons with designated roles is recommended, including one person to record events and a designated team leader. With multiple gestation delivery, a separate team should be present for each infant.

Equipment

A complete inventory of resuscitation equipment and medications should be present and in fully operational condition wherever deliveries occur. lists the recommended equipment, supplies, and medications.

Initial Evaluation and Basic Steps of Resuscitation

The initial assessment of the newborn infant should be performed within a few seconds of birth and should determine whether routine care is indicated or whether some form of resuscitation is required. The algorithm (see) shows the initial steps of evaluation, decision, and action. Four signs need to be evaluated rapidly and simultaneously because they are indications for further evaluation and intervention. They include the following: (1) meconium in the amniotic fluid or on the skin, (2) apnea or gasping, (3) absence of flexor tone, or (4) preterm birth. Most full-term newborn infants, who are not meconium-stained, will respond to the stimulation of the extrauterine environment with a vigorous cry and movement of all

Box 4-2 RECOMMENDED EQUIPMENT AND SUPPLIES FOR NEONATAL RESUSCITATION

- Radiant warmer
- Stethoscope
- Cardiotachometer with electrocardiogram (oscilloscope desirable)
- Suction with manometer
- Bulb syringe
- Meconium aspirator
- Wall O_2 with flowmeter and tubing
- Suction catheters (5- or 6-French, 8-French, and 10-French)
- Neonatal resuscitation bag (manometer optional)
- Face masks in newborn and premature infant sizes
- Oral airways in newborn and premature infant sizes
- Endotracheal tubes (2.5-, 3.0-, 3.5-, and 4.0-mm)
- Endotracheal tube stylets
- Laryngoscope(s)
- Laryngoscope blades (straight no. 0 and 1)
- Umbilical catheters (3.5- and 5-French)
- Three-way stopcocks
- Sterile umbilical vessel catheterization tray
- 20-mL syringe and 8-French feeding tube for gastric suction
- Needles, syringes
- Medications
  - Epinephrine (1:10,000 solution)
  - Naloxone hydrochloride (1 mg/mL or 0.4 mg/mL solution)
  - Volume expander
  - Sodium bicarbonate (0.5 mEq/mL solution)

From Neonatal resuscitation. JAMA 268:2277, 1992. © Copyright 1992, American Medical Association.

extremities. Color is no longer included in this initial evaluation because it has been shown that it may take several minutes for a normal baby to become pink after delivery and efforts to accelerate this color change have led to an excessive use of oxygen, which may not be benign.[27] If the baby has good tone and is breathing adequately, color will improve from cyanotic to pink over the first several minutes, and it can be assumed that the heart rate is adequate. The vigorous term infant can remain with the mother to receive routine care (providing warmth, clearing the airway, and drying).

Basic Steps of Resuscitation

Ensure Adequate Warmth

Newborn infants do not tolerate cold stress, and hypothermia delays recovery from acidosis.[28] Cold stress can increase oxygen consumption and hinder effective resuscitation.[29,30] A vigorous newborn may be placed on his mother's chest for further transition and bonding. The compromised infant should be placed under a radiant warmer, the skin rapidly dried, and wet linen removed immediately. The baby should be left uncovered to permit full visualization and to allow effective radiant warming. Hyperthermia should also be avoided, because it is associated with respiratory depression in the neonate.[31,32] A subsequent section on preterm infants in this chapter discusses the special measures needed to avoid hypothermia in premature newborns.

Positioning and Suctioning

The baby should be positioned supine or lying on his side, with the neck slightly extended in the "sniffing" position. This position will facilitate unrestricted air entry by bringing the posterior pharynx, larynx, and trachea in line ( ). Overextension or flexion of the neck should be avoided because these positions obstruct the airway. A rolled blanket or towel under the shoulders may help maintain the correct position, especially if the baby has a large occiput secondary to molding, edema, or prematurity (*B*).

The person assisting delivery of the baby should suction the mouth and nose with a bulb syringe after delivery of the shoulders, but before delivery of the chest. Vigorous newly born infants do not need suctioning after delivery.[33,] When fluid appears to be blocking the airway, secretions should be cleared first from the mouth and then the nose with a bulb syringe or suction catheter (size 8- or 10-French). The mouth is suctioned before the nose ("m"

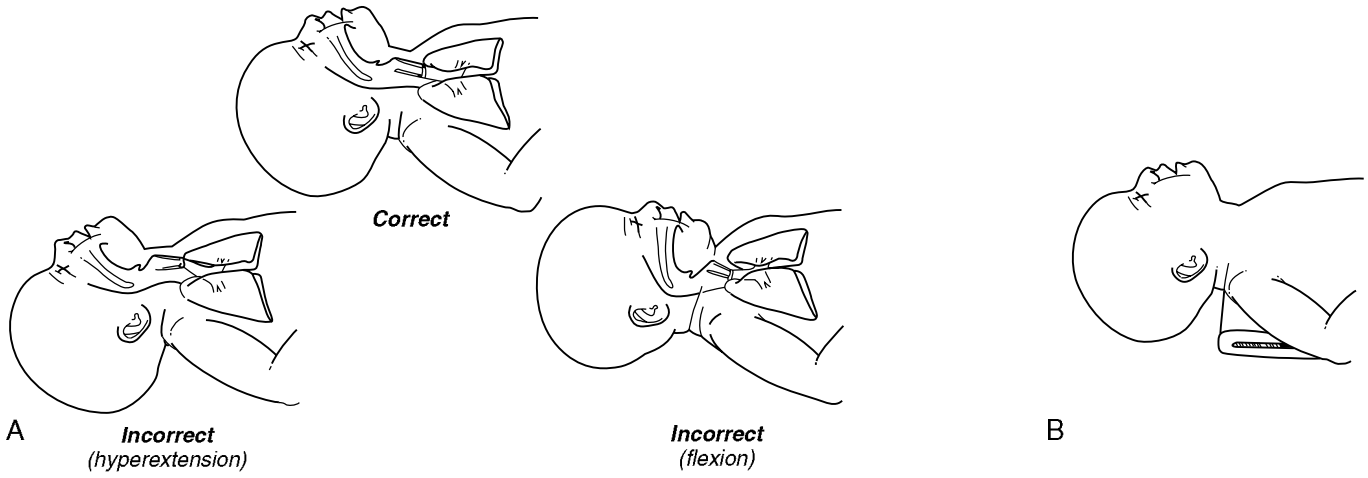


Figure 4-4 **A,** Correct and incorrect head positions for resuscitation. **B,** Optional shoulder roll for maintaining correct head position. (From the AHA-AAP: Textbook of Neonatal Resuscitation. Dallas. American Heart Association, 2000, p. 2-6, 2-7.)

before "n") to ensure that there is nothing to aspirate if the infant should gasp when the nose is suctioned. The negative suction pressure should not exceed 100 mm Hg. If there are copious secretions, the head should be turned to the side, because this allows secretions to collect in the cheek where they can be easily removed. Prolonged or deep suctioning with the catheter should be avoided, because stimulation of the posterior pharynx during the first minutes after birth can produce a vagal response consisting of apnea or severe bradycardia.[35]

Tactile Stimulation

Most newborn infants are stimulated to breathe with drying and suctioning. Gentle rubbing of the back or flicking the soles of the feet are two safe methods of tactile stimulation. Tactile stimulation may stimulate spontaneous respirations in newborns with primary apnea. If there is no response to one or two flicks of the soles of the feet or rubbing the back once or twice, then the resuscitator should assume that the infant is in secondary apnea. Continuing tactile stimulation in an infant with persistent apnea wastes valuable time. Tactile stimulation should be stopped, and positive-pressure ventilation should be initiated.

Oxygen Administration

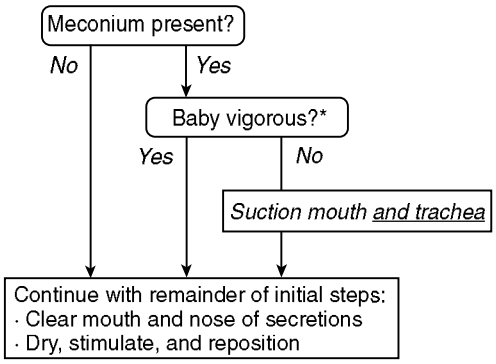
Initially color can range from normal acrocyanosis to pallor to central cyanosis. It may take the normal term vigorous newborn several minutes after birth to become pink. If after several minutes, central cyanosis is present in the spontaneously breathing newborn, 100% free-flow O_2 should be provided. The O_2 can be delivered via a face mask and flow-inflating bag, an oxygen mask, or a hand cupped around oxygen tubing held close to the face (for maximization of O_2 concentration). Self-inflating bags will not passively deliver sufficient oxygen flow through the mask. The O_2 source should deliver at least 5 L/min. Oxygen administration is potentially a hazard even during a brief period of resuscitation.[27]

Clearing the Airway of Meconium

Meconium is present in the amniotic fluid in approximately 12% of deliveries.[36] For many years, it was a widely accepted practice to perform intrapartum oropharyngeal and nasopharyngeal suctioning of babies born through meconium-stained amniotic fluid because it was thought that it reduced the incidence of meconium aspiration syndrome. Routine intrapartum suctioning of the meconium-stained newborn is no longer recommended, because it did not prevent meconium aspiration syndrome or its complications in a large, multicenter, randomized, controlled trial.[37] In addition, Wiswell et al.[38] performed a large, randomized, controlled, multicenter trial of delivery room intubation of the apparently vigorous meconium-stained neonate and found no difference in a 3% rate of meconium aspiration syndrome between infants intubated and nonintubated at birth. They concluded that tracheal suctioning of the vigorous newborn with meconium-stained fluid does not improve outcome and may cause complications. Therefore, as shown in , the AHA-AAP NRP recommends suctioning of the mouth and trachea of the meconium-stained newborn only if it is *not* vigorous. Wiswell et al.[38] also recommended that if apnea or respiratory distress develops in meconium-stained, newly born infants who were initially vigorous, then they should receive tracheal suctioning before positive-pressure ventilation.

A "vigorous" newborn infant is defined as one with good muscle tone, strong respiratory efforts, and heart rate greater than 100 bpm immediately after delivery. Management of the vigorous meconium-stained infant should proceed with the remainder of the initial steps of resuscitation.

The nonvigorous meconium-stained infant should be placed in the bed of the radiant warmer immediately after delivery, and direct laryngoscopy should be performed to suction residual meconium from the hypopharynx (under direct vision) and to intubate and suction the trachea.[6]



*Vigorous is defined as strong respiratory efforts, good muscle tone, and a heart rate greater than 100 bpm. The technique of determining the heart rate is described later in this lesson.

Figure 4-5 Steps in clearing the airway of the newly born infants with meconium-stained amniotic fluid. (From Kattwinkel J, ed: Textbook of Neonatal Resuscitation, American Heart Association and American Academy of Pediatrics, 2006, pp. 2-6. Reproduced with permission.)

Drying and stimulation should be delayed. Tracheal cleansing should be accomplished by suctioning through a meconium aspirator device ( ) attached directly to the endotracheal tube, applying suction as the endotracheal tube is withdrawn from the airway. Suction catheters inserted through endotracheal tubes may be too small to successfully accomplish initial removal of particulate meconium. After suctioning of particulate meconium is accomplished, use of suction catheters through the endotracheal tube may adequately remove residual meconium. Intubation and suctioning should be repeated until there is minimal residual meconium, unless the baby's heart rate becomes depressed, making it necessary to begin positive-pressure ventilation.

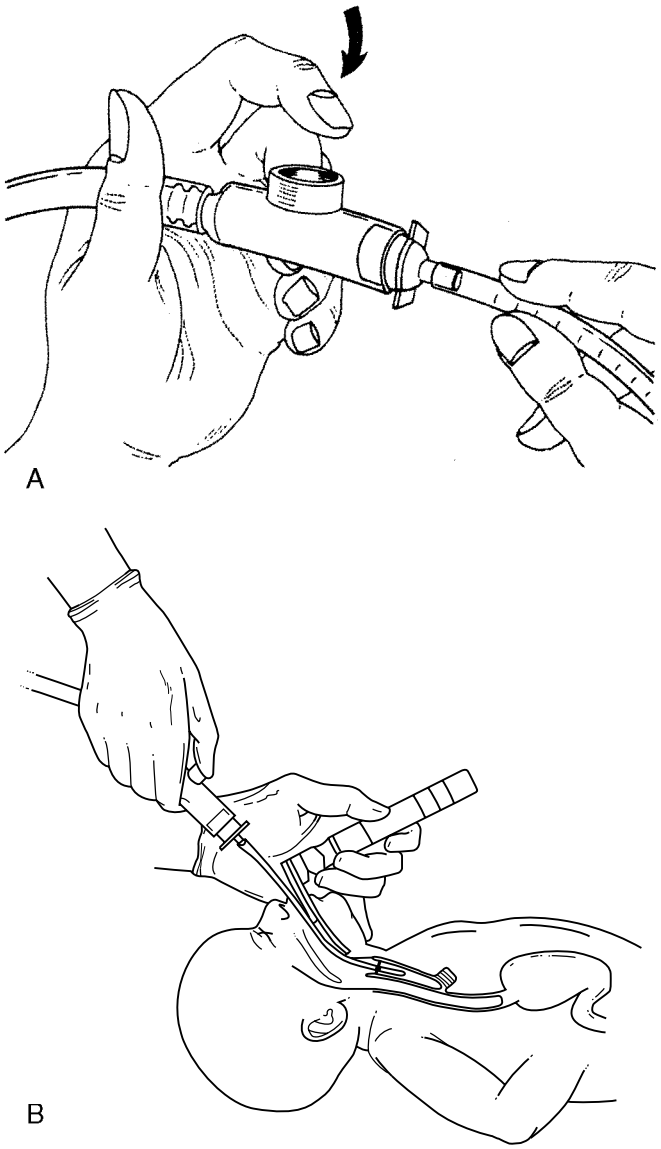


Figure 4-6 **A,** Adapter used to connect an endotracheal tube to mechanical suction. **B,** Visualizing the glottis and suctioning meconium from the trachea using a larynogscope and a meconium aspirator connected to an endotracheal tube. (**A,** from the American Heart Association/American Academy of Pediatrics: Textbook of Neonatal Resuscitation. Dallas, American Heart Association, 2006, p. 2-7 **B,** from the American Heart Association/American Academy of Pediatrics: Textbook of Neonatal Resuscitation. Dallas, American Heart Association, 2006, p. 2-4 Reproduced with permission.)

Subsequent Evaluation and More Advanced Resuscitation

After initial stabilization, subsequent evaluation of the newly born infant uses the triad of respiration, heart rate, and color with periodic reevaluation at 30-second intervals. Apnea or gasping indicate the need for positive pressure ventilation. Heart rate is determined by auscultation of the precordium with a stethoscope or by palpating pulsations at the base of the umbilical cord. The AHA-AAP NRP recommends counting the number of heart beats for 6 seconds and multiplying by 10 to make a quick estimate of beats per minute. If the heart rate is less than 100 bpm, positive pressure ventilation is indicated. Persistent central cyanosis despite 100% oxygen is also an indication for positive-pressure ventilation.

Administration of Oxygen

Traditionally, 100% oxygen has been used for rapid reversal of hypoxia during resuscitation to minimize tissue damage from oxygen deprivation during and after asphyxia. But 100% oxygen generates free radicals that could cause tissue damage, and 100% oxygen could have adverse effects on cerebral circulation and respiratory physiology. Conflicting results have been reported in studies of cerebral perfusion, blood pressure, and biochemical markers of tissue damage in asphyxiated animals resuscitated with 100% oxygen versus air.

Meta-analysis of four human studies show reduced mortality and no evidence of short-term harm in full-term infants resuscitated with air versus 100% oxygen, but there were many methodological concerns, including (1) failure to conceal the randomization process, (2) lack of blinding, and (3) significant loss to follow-up. In addition, closer analysis of the four human trials showed that all studies were actually investigating 100% oxygen resuscitation versus initial use of air resuscitation with 100% oxygen rescue, and up to 25% of air-resuscitated infants were switched to 100% oxygen.

No definitive recommendations can be made about safety of resuscitation with air until a large randomized, controlled trial is performed that includes long-term follow-up with reduction in neurodevelopmental disability as the primary outcome. In the meantime, as noted by Fowlie in his commentary, the only randomized controlled trial with long-term (18-24 months) neurodevelopmental follow-up showed an increased rate of neurodevelopmental disability (15%) in surviving infants initially resuscitated with air, compared with those survivors who were resuscitated with 100% oxygen (10%), albeit the difference was not statistically significant.

Until new evidence resolves the controversy, the AHA-AAP NRP[6] recommends that oxygen be used whenever positive-pressure ventilation is required during resuscitation of term newborns. Pending further evidence, it might be reasonable to initially provide positive-pressure ventilation with less than 100% oxygen, even room air. However, the AHA-AAP NRP[6] recommends that if positive-pressure ventilation is started with room air, that supplemental oxygen up to 100% be available and that

supplemental oxygen be used if there is no improvement in clinical status within 90 seconds of birth. A subsequent section on preterm infants in this chapter discusses the special need for oxygen blenders in managing oxygen in resuscitation of premature newborns.

Ventilation

Most neonates can be effectively ventilated with a bag and mask. Positive-pressure ventilation is indicated for any neonate with (1) apnea or gasping; (2) a heart rate less than 100 bpm; or (3) persistent central cyanosis, for at least 5 to 10 minutes, despite the delivery of free-flow O_2.

A tight seal between the face and mask is necessary for successful bag-and-mask ventilation; therefore, face masks with cushioned rims that fit preterm, term, and large newborns must be available in the delivery room. The recommended ventilation rate is 40 to 60 breaths per minute. Normal, not excessive, chest wall movement is the sign of successful positive-pressure ventilation. When starting ventilation of the newly born infant, visible chest expansion is the most reliable sign of appropriate inflation pressure, not any specific inflation pressure. Chest expansion should be the focus of attention, not the pressure manometer. At first, inflation pressures may need to be 30 to 40 cm H_2O or higher. Satisfactory inflation of fluid-filled lungs with air or oxygen expedites reversal of bradycardia, hypoxia, and acidosis.

Asphyxiated neonates who are born apneic with fluid-filled lungs may need an initial prolonged inflation lasting 3 to 5 seconds for prompt establishment of a functional residual capacity.[,50] Once functional residual capacity is achieved, less pressure and shorter inspiratory times are usually adequate for subsequent ventilation. If chest wall movement is not adequate, then (1) reapply the mask, ensuring that a tight seal has been obtained; (2) reposition the head; (3) repeat suctioning of the mouth and nose if secretions are present; (4) open the mouth slightly, especially in extremely low-birth-weight infants; and (5) increase the inflation pressure.[6] If chest wall movement does not improve, immediately intubate the infant to secure the airway. If bag-and-mask ventilation is prolonged, it may produce gastric distention, which should be relieved with insertion of an 8-French orogastric tube that is aspirated with a syringe and then left open to air.

One controversial aspect of the AHA-AAP NRP protocol is its reliance on bag-and-mask ventilation in the severely depressed infant (i.e., with a 1-minute Apgar score of less than 3). Bag-and-mask ventilation initiates a gasp in approximately 85% of cases and has proved to be an acceptable and efficient way of resuscitating the mildly or moderately asphyxiated or depressed infant. But, when face-mask ventilation was compared with intubation-ventilation in a small group of asphyxiated term newborns, Milner et al.[51] found that the face-mask system was relatively inefficient because tidal volume was less than one-third of that seen after intubation, which may not be sufficient to produce adequate alveolar ventilation. Despite this, all the newborn infants resuscitated with bag-mask ventilation responded satisfactorily and were spontaneously breathing within 4 minutes of birth. Milner and colleagues concluded that successful resuscitation depended on stimulation of a baby to make his or her own respiratory efforts (Head's paradoxical inflation reflex). Therefore, when severe depression is present at birth (e.g., heart rate is zero), and it is unlikely that the infant will initiate and sustain spontaneous ventilation, immediate intubation is suggested. Moreover, when prolonged ventilation is necessary during any resuscitation, the insertion of an endotracheal tube is preferable because it affords greater airway stability than other ventilatory measures.

After positive-pressure ventilation has achieved good chest wall movement for 30 seconds, the heart rate should be evaluated. If the heart rate is greater than 100 bpm and if spontaneous breathing is present, positive-pressure ventilation can be gradually discontinued. Mild tactile stimulation can be provided while the infant is closely monitored to ensure that effective spontaneous respirations continue. Assisted ventilation must continue if spontaneous respirations are absent or ineffective, or if the heart rate is less than 100 bpm. If the heart rate is less than 60 bpm, continue positive-pressure ventilation, begin chest compressions, and intubate.

Ventilation Bags

Newly born babies have small tidal volumes (4 to 8 mL/kg). Resuscitation bags for neonates should be no larger than 750 mL, because it is difficult to deliver small tidal volumes with bigger bags. There are two types of ventilation bags ( ): self-inflating bags and flow-inflating bags.

The self-inflating bag is more commonly found in the delivery room and on the resuscitation cart because it is somewhat easier to use. The recoil of the bag enables the self-inflating bag to refill even with no compressed gas source. Self-inflating bags have an air inlet at one end that permits rapid re-inflation, but which will pull in (entrain) room air and dilute oxygen flowing into the bag and deliver a maximum of 40% oxygen. An oxygen reservoir must be attached to the air inlet ( ) to enable the self-inflating bag to deliver 90% to 100% oxygen to the patient. Most self-inflating bags have a pressure-release valve to prevent excessive pressure build-up and should release at approximately 30 to 35 cm H_2O pressure. The pressure-release valve should have an override feature that permits delivery of higher pressures if necessary to achieve good chest expansion. Most self-inflating bags have a pressure manometer attachment site, which should be attached to an in-line manometer. Self-inflating bags cannot be used to deliver 100% free-flow oxygen through the mask, because the flow of oxygen is unreliable unless the bag is being squeezed.

The flow-inflating (anesthesia) bag will only inflate when compressed gas is flowing into it and the patient outlet is occluded. Proper use of the flow-inflating bag requires successful coordination of three tasks: adjustment of flow of gas into the bag and adjustment of flow of gas out of the bag through the flow-control valve, while maintaining a tight seal between the mask and the face of the infant. More training and practice are required to effectively and safely use a flow-inflating bag in contrast to the self-inflating bag.[52] A manometer must be connected to the flow-inflating bag to monitor peak and end-expiratory pressures, because the flow-inflating bag can deliver very high pressures. Potential advantages of the flow-inflating

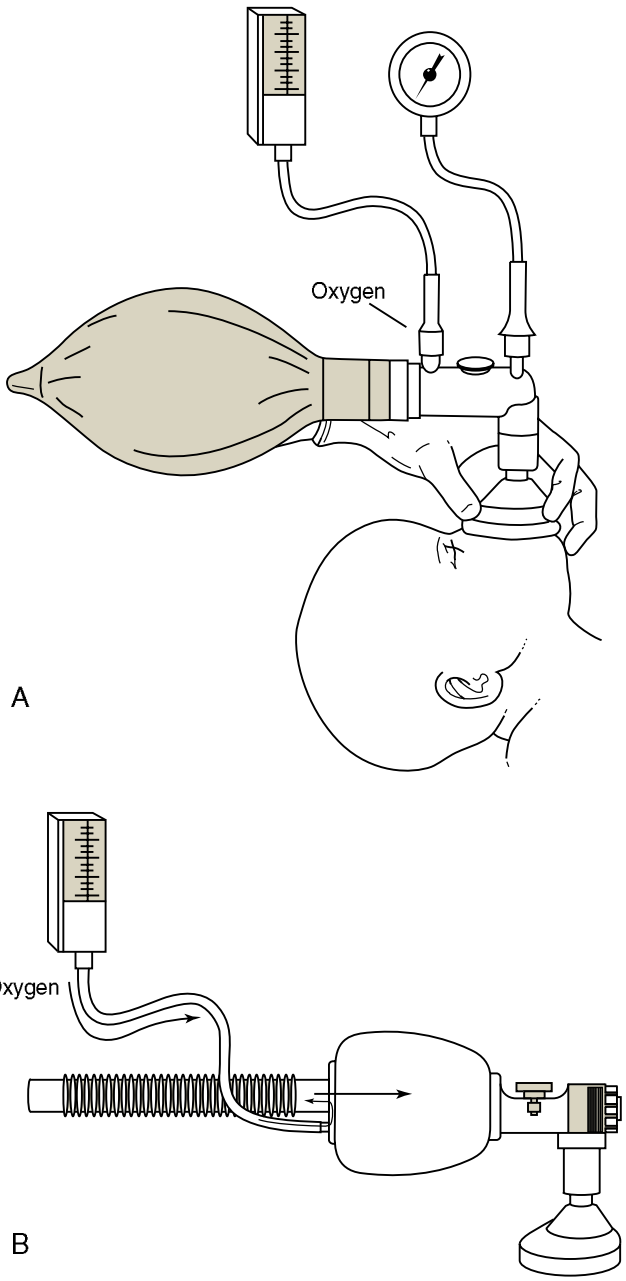


Figure 4-7 Types of ventilation bags. **A,** Flow-inflating bag inflates only with compression gas source and with mask sealed on face; oth erwise, the bag remains deflated. **B,** Self-inflating bag remains inflated without gas flow and without mask sealed on face. However, it is shown with oxygen line attached because oxygen is recommended for resus citation. (From the American Heart Association/American Academy of Pediatrics: Textbook of Neonatal Resuscitation. Dallas, American Heart Association, 2006, p. 3-11. Reproduced with permission.)

bag are that stiffness (or compliance) of the lungs can be "felt" by an experienced resuscitator when squeezing the bag, in contrast to a self-inflating bag, and that 100% free-flow oxygen can be delivered through the mask with a flow-inflating bag.

T-Piece Resuscitator

A third type of neonatal resuscitation device, the T-piece resuscitator can be used to deliver positive-pressure ventilation and up to 100% oxygen. One example of a T-piece resuscitator is the Neopuff,™ which is an FDA-approved mechanical device that is flow-controlled and pressure-limited, and specifically designed to facilitate neonatal resuscitation.[53] Like the flow-inflating bag, the T-piece resuscitator depends upon a compressed gas source and requires a tight face-mask seal or intubation to inflate lungs. It is easier to set and maintain positive end-expiratory pressure (PEEP) with a T-piece resuscitator than with a flow-inflating bag.[53] Positive-pressure ventilation is provided by alternately occluding and releasing the hole in the PEEP cap of the T-piece resuscitator. It is also easier to set and to deliver a consistent peak inspiratory pressure with the T-piece resuscitator than with either the flow-inflating bag or the self-inflating bag.[53] If either a T-piece resuscitator or flow-inflating bag are used, there needs to be a back-up self-inflating bag in case of failure of the compressed gas source, because the self-inflating bag will refill and provide positive-pressure ventilation without compressed gas.

Face Masks

Face masks should be cushioned and should be the correct size so that the rim covers the tip of the chin, the mouth, and the nose, but not the eyes. It is important to have three sizes of masks in order to fit full-term infants, premature infants, and extremely low-birth-weight infants. Masks that are too large may cause damage to eyes and will not provide a good seal. Masks that are too small will not cover the mouth and nose and may occlude the nose. Cushioned masks conform more easily to the shape of the newborn's face creating an effective seal, require less pressure to make a seal, and are less likely to damage eyes if positioned incorrectly. Masks can be round or anatomically shaped. Anatomically shaped masks are designed to fit the contours of the face and should be placed on the face with the pointed part of the mask fitting over the nose.

Endotracheal Intubation

Timing of endotracheal intubation depends upon the experience and skill of the resuscitator. Endotracheal

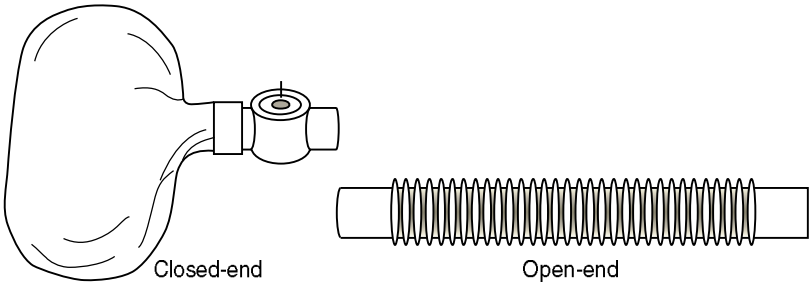


Figure 4-8 Types of oxygen reservoirs. (From the American Heart Association/American Academy of Pediatrics: Textbook of Neonatal Resuscitation. Dallas, American Heart Association, 2006, p. 3-46. Reproduced with permission.)

intubation may be considered at several steps during neonatal resuscitation (see):

1. When tracheal suctioning for meconium is required
2. When bag-mask ventilation is ineffective or prolonged for more than a few minutes
3. When chest compressions are performed, to facilitate coordination of chest compressions and ventilation, and to achieve maximum efficiency with each ventilation
4. To administer endotracheal epinephrine while intravenous access is being established
5. In special resuscitation circumstances, including extremely low-birth-weight infants (less than 1000 g) and newborns with prenatal diagnosis of congenital diaphragmatic hernia

Supplies and equipment for endotracheal intubation need to be readily available. Endotracheal tubes should have uniform diameter, a natural curve, a radiopaque indicator line, and markings to indicate depth of insertion. Use of a stylet is optional, but if used, the stylet must never protrude beyond the tip of the tube. shows recommended tracheal tube size and depth according to weight and gestational age. illustrates proper placement of the laryngoscope and the landmarks that should be seen on intubation. The clinician can avoid inserting the endotracheal tube too deeply by using a length of tubing measuring no more than 6 cm (from tip of the tube to the lip of the infant) plus the infant's weight in kilograms. For example, a 2-kg infant should have a "tip-to-lip" distance of 6 + 2 = 8 cm. This rule may not apply in infants with hypoplastic mandibles, (e.g., Robin sequence) or with short necks (e.g., Turner syndrome). Babies weighing less than 750 g may require only 6 cm of tracheal tube insertion.

TABLE 4-4 Guidelines for Endotracheal Tube Size

Tube Size (mm, Inside Diameter)	Infant Weight (g)
2.5	<1000
3.0	1000 2000
3.5	2000 3000
3.5-4.0	>3000

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In the past, the following clinical signs were used to confirm successful endotracheal intubation:

1. Observing symmetrical chest-wall movement
2. Listening for equal breath sounds, especially in the axilla, and for absent breath sounds over the stomach
3. Confirming absence of gastric inflation
4. Observing condensation in the tube during exhalation

Unfortunately, these signs can be misleading. According to the AHA-AAP NRP,[6] the combination of an increasing heart rate and CO_2 detection is now the primary method for confirming endotracheal tube placement and effective ventilation. If the heart rate does not promptly increase after endotracheal intubation, a CO_2 detector can help differentiate between esophageal intubation and the need for increased ventilatory support.

Use of a CO_2 Detector

CO_2 levels are usually much higher in the trachea than the esophagus because the lungs are the primary organ for removal of CO_2 from the body. Monitoring of exhaled CO_2 is useful in confirmation of tracheal intubation in the newly born infant, including very-low-birth-weight infants.[55] Detection of exhaled CO_2 confirms placement of the endotracheal tube in the trachea, and failure to detect CO_2 strongly suggests esophageal intubation in nearly all patients who are not in complete cardiac arrest.[56-58]

There are two types of CO_2 detectors: portable disposable colorimetric devices, which are readily available and which change color in the presence of CO_2; and capnographs, which continuously display a specific CO_2 level and should read greater than 2% CO_2 if the endotracheal tube is in the trachea.[59,60] Colorimetric CO_2 detectors contain a pH sensitive chemical indicator, metacresol purple, which changes from purple to yellow with expired CO_2. When the endotracheal tube is correctly inserted into

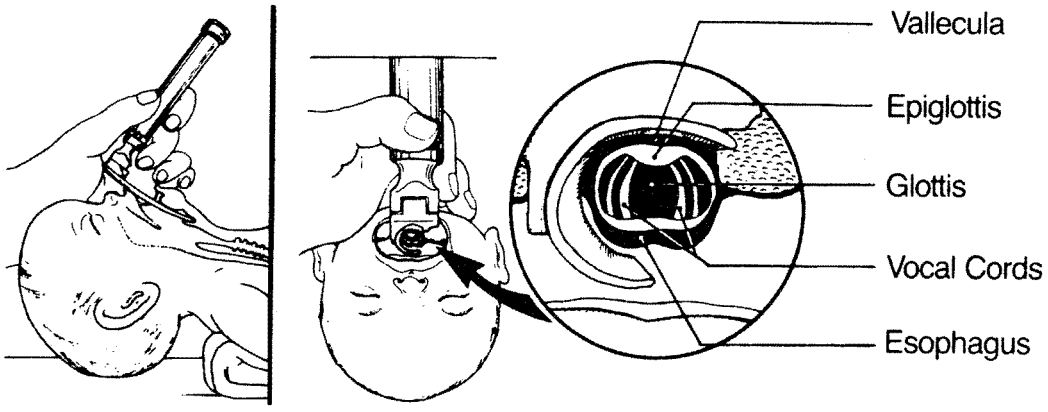

Figure 4-9 Proper placement of laryngoscope and landmarks for intubation. (From the American Heart Association/American Academy of Pediatrics: Textbook of Neonatal Resuscitation. Dallas, American Heart Association, 2006, p. 5-13. Reproduced with permission.)

the trachea, the colorimetric CO_2 detector will show a color change, from purple to yellow after six positive-pressure ventilations have been given ("P" = purple = problem; "Y" = yellow = yes). If the colorimetric CO_2 detector is contaminated with acidic fluids such as epinephrine, the result is a persistent yellow discoloration giving a false positive result.[59]

CO_2 monitoring can also give false negative results, that is, indicate esophageal intubation when the endotracheal tube has been correctly place in the trachea. These false negative cases can occur in infants with very poor or absent cardiac output or severely reduced pulmonary blood flow, because they do not exhale enough CO_2 to be reliably detected, despite proper position of the endotracheal tube. Fortunately, false negative results with CO_2 detectors are rare events in neonates, as reported by Aziz and colleagues,[52] who found only three false negatives in 45 neonates with severe cardiopulmonary arrest.

If there is any doubt that the endotracheal tube has passed through the glottis, repeat visualization of the larynx with a laryngoscope must be performed for verification. An endotracheal tube in the esophagus of a critically ill neonate is worse than having no tube at all. If the infant is to remain intubated, a chest radiograph should be obtained for confirmation of proper position of the tube.

Laryngeal Mask Airway

The laryngeal mask airway (LMA) is an airway device designed to fit over the laryngeal inlet ( ). The LMA is a safe, reliable, and effective alternative for establishing an airway in near-term and full-term infants and for providing effective ventilation.[61,62] The size-1 LMA has been approved for neonates weighing greater than 1500 g. There are case reports of successful use of size-1 LMAs in preterm neonates 0.8 to 1.5 kg.[63,] Case series and case reports have shown that the LMA can provide effective ventilation in neonates in which attempts at endotracheal intubation are not successful or when positive-pressure ventilation is ineffective with bag-mask or T-piece resuscitator and mask.[65] An LMA may be helpful in neonates with congenital anomalies of the mouth, tongue, palate, pharynx, or neck; and especially with micrognathia and glossoptosis, as in Robin sequence; or with a large tongue, as in Down syndrome or Beckwith-Wiedemann syndrome. Trevisanuto and colleagues[62] published an excellent review of the use of LMAs in neonates that is a useful reference for clinicians. Because of all the potential benefits, the AHA-AAP NRP,[6] now includes an appendix (pp. 5-37 to 5-42 in the 2006 *Textbook of Neonatal Resuscitation*) with instructions for proper insertion of the laryngeal mask airway in neonates. Neonatal code carts should be equipped with LMAs and clinicians should be trained in their use.

Chest Compressions

Chest compressions should be started after 30 seconds of effective positive-pressure ventilation with 100% oxygen if heart rate is less than 60 bpm. Ventilation should be the priority in neonatal resuscitation, and chest compressions may compete with provision of effective ventilation. The AHA-AAP NRP[6] clearly states that if any step in resuscitation is not being delivered effectively, resuscitators may need to take longer than 30 seconds to correct the problem

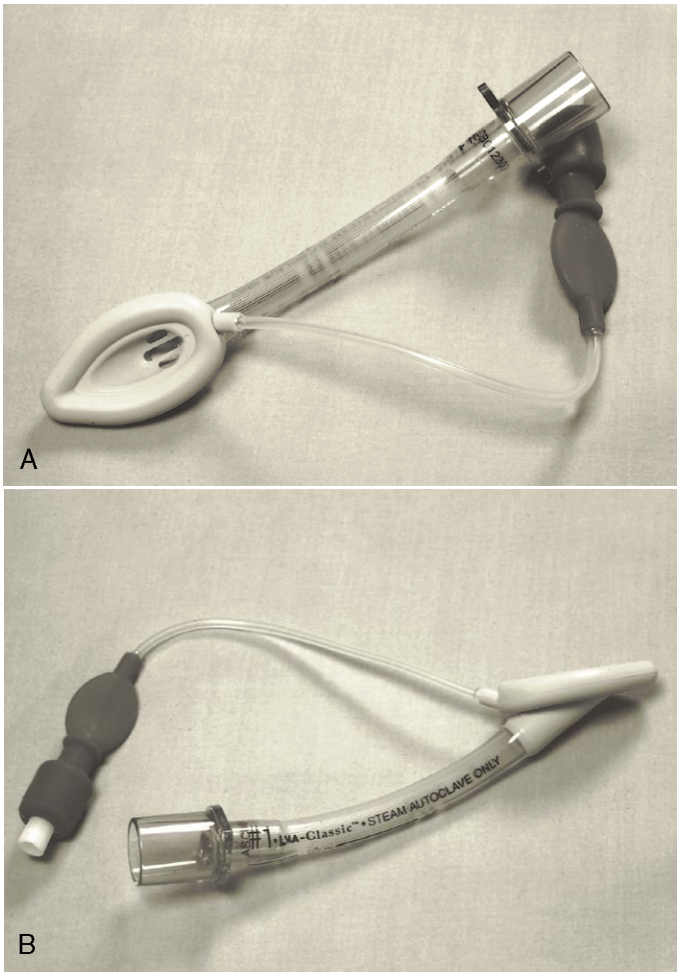

Figure 4-10 Laryngeal mask airway, number 1, for use in neonates weighting less than 5 kg. **A,** Frontal view. **B,** Side view.

before proceeding to the next step; and this is especially true of the need to provide effective positive-pressure ventilation.

The two-thumb technique is the preferred technique for performing chest compressions in neonates and is illustrated in .[66-69] Both thumbs are placed on the lower third of the sternum,[70,71] superimposed or adjacent to each other according to the size of the chest, and the fingers encircle the chest to support the back. The thumbs should be placed on the sternum just below an imaginary line passing between the nipples. Abdominal organs can be damaged with direct compressions of the xiphoid or lower end of the sternum. If the resuscitator's hands are two small to encircle the chest, then two-finger compressions should be performed with the other hand supporting the back (see). The thumbs or fingers must remain in contact with the sternum during all phases of compression. The sternum should be compressed to a depth approximately one third of the anterior-posterior diameter of the chest in a smooth, fluid fashion. A compression phase duration that is slightly shorter than the relaxation phase is recommended, because such timing improves blood flow in neonatal animal experiments.[72]

Simultaneous chest compressions and ventilations must be avoided in neonates,[73] because effective ventilation

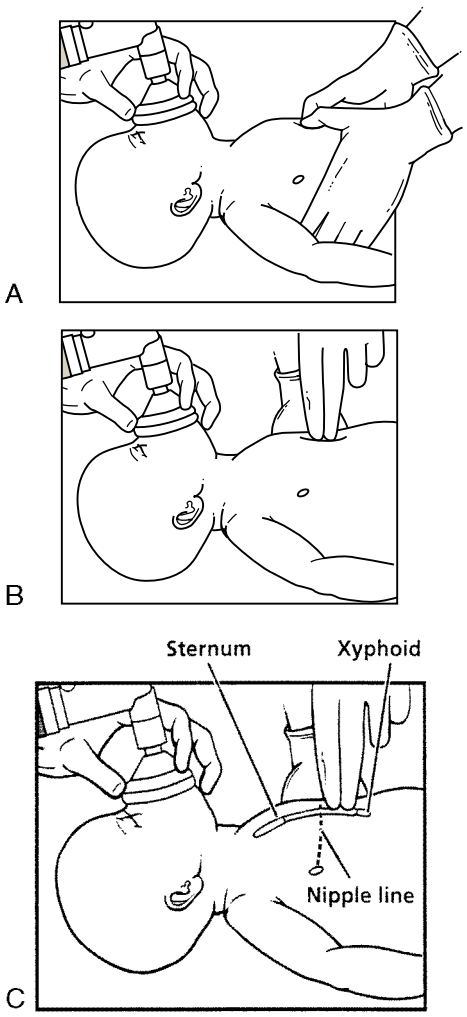

Figure 4-11 Two methods of applying chest compression. **A,** Thumb method. **B,** Two-finger method. **C,** Correct finger position on the sternum. (From the American Heart Association/American Academy of Pediatrics: Textbook of Neonatal Resuscitation. Dallas, American Heart Association, 2006, pp. 4-5 and 4-7 Reproduced with permission.)

should be the priority in neonatal resuscitation. Chest compressions should be interposed with ventilation in a 3:1 ratio. This means that the combined rate of chest compressions and ventilations is approximately 120 events per minute, that is, 90 compressions and 30 breaths. It is recommended that the compressor count aloud so that the ventilator knows when to perform the ventilation. The cadence should be "one-and-two-and-three-and-breathe-and. . . ." Heart rate should be checked every 30 seconds. Chest compressions should be discontinued when heart rate equals 60 or more bpm.[6]

Medications

Medications are rarely indicated in neonatal resuscitation.[3] Bradycardia in the newly born infant usually occurs because of inadequate lung expansion and hypoxia. Effective positive-pressure ventilation is the most important step in correcting bradycardia. Medications should be administered if heart rate is less than 60 bpm after 30 seconds of chest compressions and adequate ventilation.

Epinephrine

Epinephrine is indicated when heart rate is less than 60 bpm, and especially when asystole is present, despite a minimum of 30 seconds of chest compressions and effective ventilation with 100% oxygen. Although epinephrine has both α- and β-adrenergic-stimulating properties, α-adrenergic-mediated vasoconstriction is probably the more important action during cardiac arrest. Vasoconstriction enhances delivery of oxygen to the heart and brain by elevating perfusion pressure during chest compression.[75] Epinephrine also increases the heart rate, stimulates spontaneous heart contractions, and strengthens the contractile state of the heart.

Previous editions of the AHA-AAP NPR recommended that initial doses of epinephrine be given through an endotracheal tube, because they could be given quickly and would not be delayed by the time it would take to establish intravenous access via the umbilical vein. One recent study in newborn piglets showed that the previously recommended dose of endotracheal epinephrine (10 μg/kg) had no benefit when compared with intravenous epinephrine during cardiopulmonary resuscitation.[76] Furthermore, animal and adult human studies show that higher doses are required for endotracheal epinephrine to be effective.[77,78]

The current AHA-AAP NRP[6] recommends that the dose of intravenous epinephrine be 0.1 to 0.3 mL/kg of a 1:10,000 solution (0.01 to 0.03 mg/kg), and repeated every 3 to 5 minutes. The intravenous route is the preferred route for epinephrine administration, but while umbilical venous access is being obtained, epinephrine may be given via the endotracheal tube, but at a higher dose, 0.3 to 1 mL/kg (0.03 to 0.1 mg/kg). The concentration of epinephrine for neonatal resuscitation is the same, 1:10,000 (0.1 mg/mL) for either intravenous or endotracheal administration.

When giving epinephrine by endotracheal tube, be sure to give it directly into the tube and follow the drug by several positive-pressure breaths to distribute it throughout the lungs to maximize absorption. The safety and efficacy of higher dose endotracheal epinephrine has not been studied in newborn infants. Therefore, repeat doses of endotracheal epinephrine are not recommended, and the preferred intravenous route should be established as soon as possible. To shorten the time to the first intravenous dose of epinephrine, it is prudent to open and prepare an umbilical venous catheter tray and the dosing needed prior to delivery for certain clinical situations such as a crash cesarean section being performed for a sentinel event (i.e., persistent fetal bradycardia).

The higher doses of endotracheal epinephrine must not be given intravenously, because higher doses (greater than 0.3 mL/kg of 1:10,000 solution) of intravenous epinephrine have been associated with extreme hypertension, low cardiac output, and worse outcomes in animal experiments[79,80] and pediatric studies.[81]

With the current NRP recommendations for epinephrine in the delivery room, there is a potential safety issue with the two different ranges of doses (0.1-0.3 mL/kg for intravenous and 0.3-1 mL/kg for endotracheal epinephrine) and two different routes of delivery (intravenous and

TABLE 4-5 Emergency Dosing for Epinephrine (1 : 10,000) in Delivery Room When Exact Birth Weight is Not Known*

Birth Weight	Gestational Age	IV Dose	Endotracheal dose
<1.500 g	<32 weeks	0.3 mL	1 mL
1500-2.500 g	32-36 weeks	0.6 mL	2 mL
>2500 g	>36 weeks	1 mL	3 mL

*(Goal: To give 0.3 mL/kg intravenous epinephrine and 1 mL/kg endotracheal epinephrine.)

endotracheal), especially when the actual birth weight is not known and can only be estimated. Dosing errors in the delivery room may be avoided by using two different sizes of syringes for preparing the drug before delivery (1-mL for IV and 3-mL for endotracheal use) and labeling the syringes carefully. Confusion in dosing and delays in giving epinephrine may be lessened by using a table to guide dose selection when the need for epinephrine is anticipated as part of delivery room resuscitation ( ).

Volume Expanders

Volume expanders should be considered whenever an infant appears to be in shock (pale, poor perfusion, weak pulse) or when the infant has not responded to chest compressions, effective ventilation, and intravenous epinephrine administration. Maternal history is important in this circumstance because a report of vaginal bleeding or abruption of the placenta would raise the possibility of fetal hypovolemia. The initial dose of volume expander is 10 mL/kg given over 5 to 10 minutes by slow intravenous push. Although higher bolus volumes of volume expander have been recommended for resuscitation of older infants, intracranial hemorrhage or volume overload may result from inappropriate intravascular volume expansion in asphyxiated newly born infants and especially preterm infants.[82] Normal saline is the fluid of choice for volume expansion because it has been shown to be as effective as albumin in treatment of neonatal hypotension without having its disadvantages.[83] Albumin-containing solutions are not recommended because of added cost, theoretical risk of infectious disease, and no advantage over isotonic saline. Ringer's lactate is an alternative volume expander, but may not be as readily available as normal saline. Administration of O-negative packed red blood cells should be considered for replacement of large volume blood loss.

Bicarbonate

Routine use of sodium bicarbonate is not recommended in neonatal resuscitation, because of insufficient data supporting the practice. In addition, sodium bicarbonate may be harmful to myocardial and cerebral function because of its hyperosmolarity and CO_2–generating properties.[85-87] Use of sodium bicarbonate should be discouraged during brief resuscitation. If bicarbonate is used during prolonged cardiopulmonary arrests unresponsive to other therapy, it should be given only after adequate ventilation and circulation are established.[88] After an infant has been successfully resuscitated, use of bicarbonate for treatment of persistent severe metabolic acidosis or hyperkalemia should be directed by blood gas analysis or serum chemistries. The recommended dose of sodium bicarbonate is 2 mEq/kg of a 0.5 mEq/mL solution given by slow intravenous push over at least 2 minutes after adequate ventilation and perfusion have been established. Bicarbonate should never be given faster than 1 mEq/kg/min.

Concern about the CO_2–generating properties of bicarbonate led to development of 0.3 *N* tromethamine, or THAM, which is a carbon dioxide–consuming alkalinizing agent. Unfortunately, THAM has not been shown to be safer than bicarbonate during resuscitation. In fact, THAM has been reported to cause hepatic necrosis in neonates as well as hyperkalemia, hypoglycemia, and ventilatory depression.[89] Therefore, THAM is not recommended for use in neonatal resuscitation and should not be routinely substituted for bicarbonate.

Naloxone

Use of the narcotic antagonist naloxone hydrochloride is indicated for the neonate with severe respiratory depression attributable to narcotics given to the mother within 4 hours of delivery. Naloxone should be given only if severe respiratory depression persists after positive-pressure ventilation with 100% oxygen has restored a normal heart rate and color.[6] The administration of naloxone should not be the first step in a neonatal resuscitation. The dose is 0.1 mg/kg.[90] Intravenous route of administration is preferred, but the intramuscular route is acceptable with adequate perfusion. The initial dose can be repeated once in 3 to 5 minutes if there are still no spontaneous respirations. The duration of action of narcotics can exceed that of naloxone. Therefore, continuous monitoring is required for at least 6 hours in an infant who required naloxone for the reversal of opiate-induced respiratory depression. The use of naloxone is contraindicated in a neonate whose mother is suspected to be narcotic-dependent because sudden narcotic withdrawal can induce severe seizures.[91] In this setting, the neonate should receive mechanical ventilation until narcotic-induced respiratory depression resolves. Monitoring for signs of fetal abstinence syndrome should be initiated in infants of narcotic-dependent mothers.

Despite the long-standing recommended indication for naloxone administration by AHA-AAP NRP, there appears to be considerable variability in use of naloxone from one hospital to another,[92] which is not explainable by differences in maternal exposure to opiates. Herschel and colleagues[93] evaluated use of naloxone at a university hospital and a community hospital and reported that in neither hospital was naloxone given as recommended by AHA-AAP NRP. They found that naloxone was given even when mothers did not receive opiates within 4 hours of delivery; it was given to infants who did not have severe respiratory depression; and it was given without first supporting ventilation. Naloxone may be given by some practitioners because of a belief that endogenous opiates might play a role in the pathogenesis of perinatal asphyxia. Chernick and colleagues performed a blinded clinical trial of naloxone in newly born infants with low 1-minute Apgar scores who were born to women who had not received opiates within 4 hours of delivery and who had not received general anesthesia. Naloxone had no significant

effect on heart rate or restoration of spontaneous respirations in these infants. They concluded that naloxone showed no benefit in resuscitation of the asphyxiated newborn infant. Therefore, as per AHA-AAP NRP, naloxone should be used only when there is a history of maternal narcotic administration within the past 4 hours and only after positive-pressure ventilation has restored normal heart rate and color. Other drugs given to the mother can depress respirations in the newly born infant, such as magnesium sulfate or general anesthetic, and will not respond to naloxone.

Routes of Medication Administration

The endotracheal route is the most rapidly accessible route for drug administration during resuscitation in the delivery room. Although the tracheal route may be used for administration of epinephrine, it must not be used to administer caustic substances such as sodium bicarbonate, and it is not a recommended route for naloxone.

The intravenous route is the preferred route for epinephrine administration, but while umbilical venous access is being obtained, epinephrine can be given via the endotracheal tube. The umbilical vein is the recommended site for intravenous administration of drugs in the delivery room because it can be identified and catheterized fairly rapidly. A 3.5- or 5-French radiopaque catheter with a single end hole should be inserted only far enough (approximately 2 to 4 cm below the skin, less in preterm infants) to yield a free flow of blood return. If the catheter is inserted too deeply, there is risk of damaging infusion of hypertonic and vasoactive drugs directly into the liver. During cardiac arrest in neonates, it is usually impossible to administer drugs through a peripheral vein, because venous collapse makes cannulation very difficult and drug delivery to the central circulation may be impaired. Resuscitation drugs should not be administered through the umbilical artery because it is not rapidly accessible and there is a high risk of complications if vasoactive or hypertonic drugs are given by this route.

Intraosseous lines are not often placed in newly born infants. It is believed that the umbilical vein is more readily accessible; the intraosseous space is small in the premature infant; and neonatal bones are fragile. Nevertheless, Ellemunter and colleagues[95] reported a series of 27 term and preterm infants who were successfully resuscitated within 5 hours of birth via rapid intravascular access with intraosseous lines. They used an intraosseous infusion needle with an 18-G internal diameter. Nine of the patients had birth weight less than 1000 g, including one 515-g infant. There were no failed attempts and the entire procedure took less than 2 minutes. Previously reported complications with use of intraosseous needles in infants include osteomyelitis, skin infection, skin necrosis, subcutaneous abscess, fractures, and compartment syndrome.[96] In the case series reported by Ellemunter et al.,[95] three patients had dislocation and malfunction of the intraosseous needle requiring placement of a new one. The only other complications included one case each of subcutaneous necrosis and hematoma. There were no adverse effects during follow-up from use of the intraosseous needle on limb growth in the 15 long-term survivors. Intraosseous access is considered an acceptable, safe, and useful alternative route for medications and volume expanders if umbilical venous access is not readily available. Its major use has been in older neonates who return to the emergency room and have limited intravenous access.

Although umbilical venous catheterization has been the recommended route of intravenous access in the delivery room, Abe and colleagues[97] reported that intraosseous line placement is significantly faster and easier than umbilical venous catheterization. In their study, Abe and colleagues[97] taught 42 medical students, without prior experience, how to insert intraosseous needles or umbilical venous catheters, and then timed how well they performed with models of newborn emergency vascular access. Skill with placement of intraosseous lines is easily mastered even with limited opportunity for practice.[96] The recommended method of emergency vascular access in the newly born infant may need to be reconsidered pending further study. In the meantime, intraosseous infusion needles (18 G) should be available on neonatal code carts, and clinicians should be trained in their use ( ).

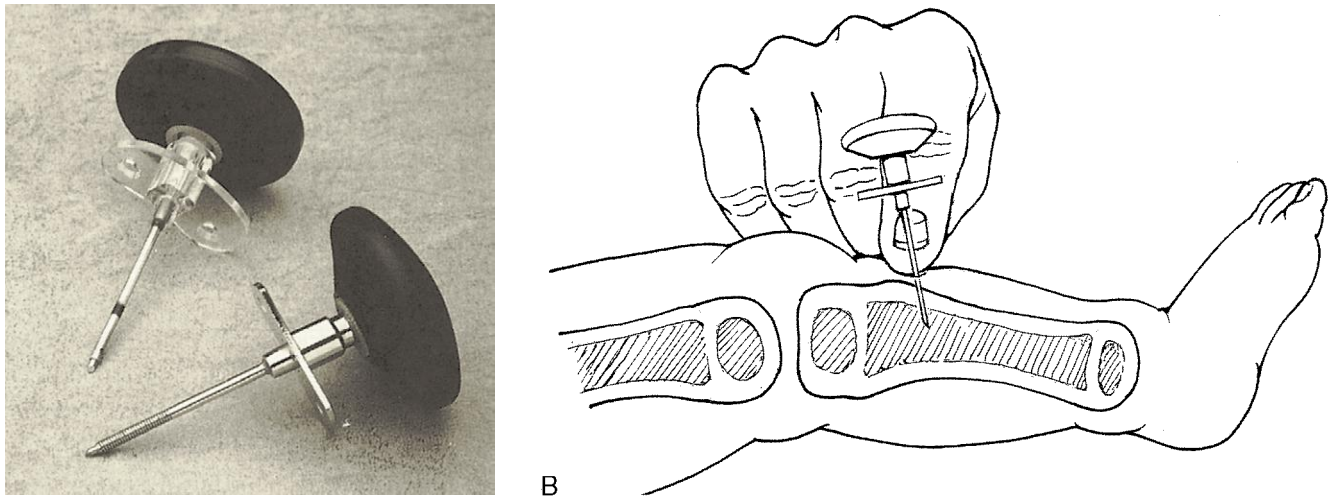

Figure 4-12 **A,** Disposable intraosseous infusion needles. **B,** Diagram of the insertion of an intraosseous needle into the femur of a neonate.

Special Considerations

Preterm Neonates

Whenever a preterm birth is anticipated, there should be sufficient notification so that specially trained personnel can be present and the necessary special equipment is at hand. Asphyxia and the need for resuscitation are much more common in the preterm than the term neonate.[98] Preterm infants have an increased risk of heat loss, intraventricular hemorrhage, and respiratory distress. Susceptibility to heat loss increases with decreasing gestational age because extremely premature infants have a large surface area relative to body mass and decreased thickness of the epidermis. Minimizing heat loss in preterm infants improves survival.[99] The preterm infant's brain has a fragile subependymal germinal matrix that is prone to intraventricular hemorrhage; therefore, the volume and rate of infusion of volume expanders should be monitored closely so that sudden changes in vascular pressure can be avoided.[100]

Premature infants are at risk of hypothermia if provided the same warming measures recommended for full-term newly born infants (drying the infant, removing the wet linens, and placing the infant on a radiant warmer).[101] Two randomized controlled trials have demonstrated the efficacy of food-grade heat resistant plastic bags or plastic wrapping, in addition to customary radiant heat, in significantly improving the admission temperature of premature infants less than 28 weeks' gestation compared to controls.[102,103] Temperature must be monitored continuously because there is a small risk of hyperthermia.[103] A recent systematic review[106] of using plastic bags or plastic wrapping to prevent hypothermia in very-low-birth-weight premature infants noted a very low number needed to treat (NNT) of 2 (range 2-4), and recommended that this intervention be used in the delivery room. The AHA-AAP NRP[6] now recommends that food-grade heat resistant plastic bags or plastic wrapping, in addition to radiant heat, become the standard technique of maintaining temperature in infants less than 28 weeks' gestation in the delivery room.

The AHA-AAP NRP[6] also recommends that any facility electively delivering babies less than 32 weeks' gestation must have available to the premature infant an oxygen blender, a compressed air source, and a pulse oximeter in the delivery room. The compressed air source and oxygen blender are required so that between 21% and 100% oxygen can be delivered to the premature infant. The pulse oximeter is used in conjunction with the oxygen blender to help maintain oxygen saturation in the premature infant between 85% and 95% to avoid hyperoxic injury. Two recent studies have shown the air resuscitation of very-low-birth-weight infants is not advisable because there is an excessive delay in reaching acceptable saturations or persistent bradycardia in premature infants resuscitated with air. [,105] Many centers now start with an intermediate range of oxygen (40%-50%) and then adjust the F_{IO_2} up or down depending on the response of the baby and the pulse oximeter reading.

Preterm infants have an increased need for assisted ventilation because they have decreased lung compliance, respiratory musculature, and respiratory drive. In fact, early elective intubation of extremely low-birth-weight (1000 g or less) neonates at birth has become common practice in many medical centers.[107] Studies have shown that infants less than 30 weeks' gestation benefit from being intubated and given surfactant in the delivery room after resuscitation,[108] and ideally before 10 minutes of age,[109,110] even if they have not yet developed obvious respiratory distress syndrome. Other centers practice early initiation of nasal continuous positive airway pressure (CPAP) instead of intubation to establish an air-fluid interface in extremely preterm infants.[111]

Progressive Distress After Birth

Occasionally, an infant deteriorates rapidly in the delivery room without evidence of perinatal asphyxia. Diagnostic evaluation must be systematic if treatment is to be prompt. An infant with diaphragmatic hernia develops asymmetric breath sounds with a scaphoid abdomen and shift in the cardiac apex. Avoidance of bag-and-mask ventilation with the application of early intubation and nasogastric suctioning can decrease the amount of air in the intrathoracic gastrointestinal tract that is compressing the lungs. Unilateral pneumothorax also manifests as a decrease in breath sounds on the affected side, with a shift in the cardiac apex to the opposite side. Emergency chest radiography definitively demonstrates both diaphragmatic hernia and pneumothorax. Needle aspiration or chest tube insertion may be needed for the treatment of pneumothorax.

Bilateral choanal atresia with obstruction of both posterior nares can cause progressive respiratory distress immediately after birth. Insertion of an oral airway provides an unobstructed pathway for air through the mouth. Severe micrognathia and posterior displacement of the tongue in Robin sequence can also block the airway and cause rapid respiratory deterioration. Prone positioning and insertion of a nasopharyngeal airway displaces the tongue and permits the movement of air through the mouth. A nasopharyngeal airway or laryngeal mask airway can be lifesaving for an infant with Robin sequence because even experienced neonatologists may have difficulty intubating.

Hydrops Fetalis

The survival rate has been reported to be as high as 50% for infants with nonimmune hydrops fetalis without chromosomal abnormalities or major malformations.[112] The cause of the hydrops fetalis has a profound influence upon the outcome. A recent review of 598 neonates with hydrops fetalis reported considerable variation in mortality rate depending upon the associated diagnoses, ranging from 58% mortality in neonates with congenital anomalies to as low as 9% in neonates with congenital chylothorax.[113] Furthermore, Abrams and colleagues[113] found that the risk of death among neonates with hydrops fetalis was independently associated with younger gestational age and critical illness during the first day after birth in addition to the underlying diagnosis.

Close collaboration between perinatologists and neonatologists is essential for successful management of infants with a prenatal diagnosis of hydrops fetalis. The perinatologist may need to remove excess fluid from either the

Box 4-3 SUGGESTED ADDITIONAL EQUIPMENT AND SUPPLIES FOR DELIVERY ROOM RESUSCITATION OF NEWBORNS WITH HYDROPS FETALIS

- Four thoracentesis/paracentesis kits (one for each side of the chest, and one for each side of the abdomen)
- Normal saline for infusion (avoid 5% albumin)
- If severe anemia is suspected, O-negative blood cross-matched with the mother
- Three doses of epinephrine already prepared for estimated fetal weight
- Furosemide recommended dose for severe hydrops fetalis is 2 mg/kg V
- Heparinized blood gas syringe
- Cardiac arrest orders/record

fetal abdomen or thoracic cavity before delivery. The neonatologist and perinatologist need to collectively decide on the appropriate timing and route of delivery. Queenan recommends cesarean section for neonates with hydrops fetalis because vaginal delivery frequently leads to severe asphyxia and postpartum hemorrhage. shows the additional equipment and supplies recommended for the resuscitation of the infant with hydrops fetalis.

Immediate and vigorous resuscitation is usually required, with multiple procedures being necessary for effective ventilation of the infant.[115] Personnel experienced in performing paracentesis and thoracentesis should be present in addition to staff members who can ventilate, perform cardiac compressions, insert umbilical vessel catheters, and administer medications. If any difficulty with effective ventilation occurs after intubation, paracentesis should be performed immediately. If ventilation is still ineffective, thoracentesis should be performed.

Infants with hydrops fetalis often have extremely stiff lungs and may require high ventilatory pressures as well as high end-expiratory pressures for initial stabilization. They are often premature with an increased risk of respiratory distress syndrome, and they may benefit from surfactant therapy. In 1980, Giacoia[116] recommended avoiding the use of salt-poor albumin as a volume expander because the albumin quickly moves into the extravascular space, worsening hydrops fetalis and increasing the risk of pulmonary edema. Albumin is not recommended as a volume expander in critically ill patients. Normal saline should be used if volume expansion is needed in the delivery room.[6] Intravenous furosemide, 2 mg/kg, may be given in the delivery room to help mobilize edema fluid.

Both umbilical vein and artery catheters should be inserted in hydropic infants because peripheral venous access can be very difficult. If severe anemia is present, partial exchange transfusion with O-negative packed red blood cells crossmatched against the mother can be performed immediately upon admission to the NICU. Transferring the infant from the delivery suite to the intensive care unit for the partial exchange transfusion facilitates continuous monitoring of O_2 saturation and vital signs and ensures radiologic confirmation of proper position of the umbilical vein and artery catheters.

Ethics

Noninitiation of Resuscitation

Current evidence indicates that resuscitation of certain types of newly born infants is unlikely to result in survival; if survival is achieved, it most likely will be with severe disability. (See Chapter 5 for further discussion of noninitiation of resuscitation.) Therefore, the 2006 AHA-AAP NRP considers that noninitiation of resuscitation in the delivery room is appropriate for infants with confirmed gestation of less than 23 weeks or birth weight less than 400 g, anencephaly, or confirmed trisomy 13 or 18.[6] Resuscitation is nearly always indicated in conditions associated with a high rate of survival and acceptable morbidity, including babies with gestational age of 25 or more weeks and those with most congenital malformations. On the other hand, in newborns with gestational age of 23 to 24 weeks, in whom survival is borderline, the morbidity rate is high, and there is a high anticipated burden for surviving infants; parental desire concerning initiation or withholding of resuscitation should be supported.[6] Parents should be counseled that decisions about viability and corresponding neonatal management made before birth may need to be altered in the delivery room and afterward depending upon the assessment of gestational age in the delivery room, condition of the neonate, and the infant's response to resuscitation.[117]

In extremely low-birth-weight infants, there is no advantage to delayed or partial resuscitation in the delivery room; moreover, if the infant survives, outcome may be worse because of such an approach. Initiation of resuscitation in the delivery room does not mandate continued aggressive intervention. Delayed withdrawal of support and noninitiation of resuscitation are considered to be ethically equivalent. Later withdrawal of support allows clinicians time to collect more complete clinical information and to provide counseling to the family. There should be ongoing frequent reevaluations of the infant's clinical condition and discussion between the parents and the health care team to guide continuation versus withdrawal of support.[117]

Unsuccessful Resuscitation

It is reasonable to want to avoid prolonged resuscitation that results in only delayed death or in the survival of a severely disabled infant. Jain and colleagues[118] reviewed the outcome of 93 "apparently stillborn" infants who received resuscitation despite their having no detectable heartbeat at birth because signs of life were observed shortly before birth. Developmental assessment of 23 long-term survivors available for follow-up showed normal outcome in 14 (62% of the infants assessed, but only 15% of the total cohort). Similar results have been reported by others.[119,120] Therefore, aggressive resuscitation should be initiated in newly born infants with no detectable heartbeat, if signs of life were observed shortly before birth. However, Jain and colleagues[118] also reported that 58 of the 93 infants had no heartbeat at 10 minutes of life; all but 1 of the 58 died; and the 1 survivor had cerebral palsy. These findings led to the recommendation by Jain and colleagues that resuscitation be stopped if the heartbeat remains undetectable at 10 minutes of life. The 2006

AHA-AAP NRP concluded that discontinuation of resuscitation may be justified after 10 minutes of continuous and adequate resuscitative efforts of an infant in cardiorespiratory arrest if there are no signs of life (no heartbeat and no respiratory effort).[6]

Postresuscitation Care

After an infant has been stabilized, a thorough reevaluation should be made. The infant should undergo a complete physical examination to determine whether any congenital anomalies that might have contributed to the asphyxia are present. Persistent cyanosis with adequate ventilation and normal pH may alert the physician to consider primary structural heart defects or persistent pulmonary hypertension of the newborn (see Chapter 26). An orogastric tube should be passed into the stomach as a diagnostic and therapeutic device. By removing air and gastric secretions, the stomach can be decompressed; this allows better movement of the diaphragm and prevents regurgitation and possible aspiration. Failure to pass the tube may indicate esophageal atresia. Finding less than 20 mL of gastric contents may indicate a high bowel atresia or stenosis. This is also a good time for abdominal palpation for the assessment of kidney size because the accumulations of air in the bowel over time makes this procedure more difficult.

If an infant has required vigorous resuscitation or if extended Apgar scores are low, he or she should be admitted to a special or intensive care unit for close observation and monitoring for at least 24 hours. Seizures may develop, indicating the need for treatment. Initial tests should include determination of serum electrolyte, glucose, and calcium levels; arterial blood gas analysis; and chest radiography.

All tubes and monitoring devices should be securely fastened in place while preparations are made for the transfer of the patient to the NICU. A transport incubator with a portable electrocardiographic monitor facilitates the movement of the infant from the delivery room to the NICU without loss of heat or interruption of intensive care. All specimens collected during the resuscitation (e.g., samples for culture and blood samples) should be delivered promptly to the laboratory. All notes (e.g., those on the cardiac arrest record; see Appendixes 26, 27) made during the procedure should become part of the patient's permanent record. Before the transfer begins, the NICU should be alerted so that preparations for the accommodation of the infant can be made.

Glucose

In neonatal animal models of anoxic or hypoxic-ischemic insult, the animals that were also hypoglycemic had larger areas of cerebral infarction and decreased survival.[121,122] In a neonatal animal model of asphyxia and resuscitation, the animals that were also hypoglycemic had worse neurologic outcome.[123] One recent retrospective clinical study of perinatal asphyxia in 185 term infants with umbilical arterial cord pH less than 7.00, reported that an initial blood glucose of less than 40 mg/dL was independently associated with poor neurodevelopmental outcome. The investigators speculated that early detection and treatment of hypoglycemia in the delivery room in asphyxiated newborns might improve neurodevelopmental outcome. Currently available evidence does not define timing or the range of blood glucose concentration associated with the least brain injury in asphyxiated newborns that have been resuscitated. Nevertheless, newborns who require vigorous resuscitation should have timely monitoring of blood glucose concentration during the resuscitation (if prolonged) and upon admission to the newborn intensive care unit, and there should be prompt treatment of hypoglycemia with 2 mL/kg of D10W (10% aqueous dextrose solution) to maintain blood glucose in the normal range.

Therapeutic Hypothermia for Hypoxic-Ischemia Encephalopathy in Newborn Infants

The 2006 AHA-AAP NRP[6] concluded that at that time there was insufficient data to recommend moderate hypothermia after resuscitation of infants with suspected perinatal asphyxia. Subsequently, two systematic reviews of therapeutic hypothermia for neonatal hypoxic-ischemic encephalopathy were conducted in 2007.[125,126] Both reviews concluded that in neonates with post-intrapartum hypoxic-ischemic encephalopathy, therapeutic hypothermia resulted in a statistically significant and clinically important reduction in the risk of death or of moderate to severe neurodevelopmental disability compared with control infants (RR 0.76 [95% CI: 0.650.88]). The risk reduction was 15% to 16%, and the NNT was 6 to 7. Cardiac arrhythmias and thrombocytopenia were more common with therapeutic hypothermia, but were clinically benign.

It is anticipated that future recommendations from the AHA-AAP NRP will recommend the use of therapeutic hypothermia in those infants meeting treatment criteria. In the United States, with 4 million annual births, Shah and colleagues[125] estimated that therapeutic hypothermia could prevent death or severe disability in 1200 newly born infants per year, or at least 3 per day. Clinicians need to keep in mind that therapeutic hypothermia must be initiated within 6 hours of birth in newly born infants with suspected perinatal asphyxia. It is advisable for clinicians to already have identified a referral center with an established protocol for therapeutic hypothermia, and to contact the center within 1 to 2 hours of birth to see whether their patient meets criteria for treatment. Key clinical information that helps the therapeutic hypothermia center decide whether a newly born infant might benefit from referral for therapeutic hypothermia include the following: gestational age of 35 or more weeks and birth weight of 2000 or more g , required vigorous resuscitation with 10-minute Apgar score of less than 6; early neurologic signs of hypoxic-ischemic encephalopathy (abnormal tone, abnormal reflexes, autonomic dysfunction, lethargy, tonic posturing, or seizures); and cord pH less than 7.00, first hour postnatal pH less than 7.10, or base deficit greater than 13.[126]

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5 Ethical and Legal Issues in Assisted Ventilation

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In the nearly three decades since the now infamous "Baby Doe" regulations[1] attempted to provide federally mandated rules on treatment of neonates, the norms on who is to make treatment decisions for newborns and on what standard to use have been significantly altered and revised. There is now a strong consensus in the medical, legal, and ethical literature that it is the best interests of the infant—not the desires of the parents or the determination of the physician—which must prevail in the care of newborns.[2] That standard, unlike *substituted judgment*, does not rest on autonomy or self-determination but solely on the protection of the patient's welfare. That protection is particularly important with regard to infants and children because with it they are now seen not merely as the property of parents, but as patients in their own right.[3] The implication is that although parents may continue to be involved in decision making for their children, they do not have an absolute right to refuse or require medical treatment for their infant. It is the child's best interests, and those alone, that are to be the focus and goal of medical treatment decisions.

One explanation of those interests is found in the neonatal resuscitation guidelines jointly issued in 2005 by the American Heart Association and the American Academy of Pediatrics.[4] (See Chapter 4). There we read that when gestation, birth weight, or congenital anomalies are associated with almost certain early death and when unacceptably high morbidity is likely among the rare survivors, resuscitation is not indicated. Translated into practice, that standard means that if the burden on the infant is overwhelming or the prospects are extremely bleak—as is true, for example, in the presence of a lethal abnormality or the birth of an extremely premature very-low-birth-weight infant—there is no obligation to subject the child to further procedures.[5] In such cases, the parents' decision to omit further treatment is to be respected. Alternatively, if out of ignorance, fear, misguided pessimism, or simple refusal to accept a compromised infant, parents were to decline relatively low-level, high-benefit interventions that would save the life of a child, even if the child were to evidence some permanent handicap, there is no question today that the physicians should treat.

Before applying these standards to the use of assisted ventilation in newborns, it will be helpful to place them in the context of some nearly 40 years of shifting practice patterns. That is best done by reviewing some of the landmark medical-legal cases of the last four decades, cases that have not only shaped our present posture but also at times have warped or distorted our perspective on how best to care for seriously compromised infants.

From the Johns Hopkins Baby to Baby Miller

The first of these issues to come to public attention is the now infamous 1963 Johns Hopkins[6] case in which a child born with Down syndrome and duodenal atresia was left untreated and allowed to starve to death over a 15-day period. The parents, a nurse and a lawyer, determined to forgo the relatively easy corrective surgery because the child would be "a financial and emotional burden on the rest of the family." The doctors at Hopkins concurred in that decision. In the words of the treating physician, "In a situation in which the child has a known, serious abnormality … I think it unlikely that a court would sustain an order to operate on the child against the parents' wishes." In fact, as the studies by Shaw et al.[7] and Todres et al.[8] demonstrate, an overwhelming majority of pediatricians and pediatric surgeons in the United States surveyed in 1977 agreed that in a case similar to that in the Johns Hopkins case, they would abide by a parental decision to omit surgery and let the child die.

One of the first significant court involvements to challenge that approach was *Maine Medical Center v. Houle*,[9] a 1974 case that involved a profoundly compromised newborn suffering from multiple maladies whose family and physician decided to forego medical treatment. Other physicians in the hospital objected and the case was brought to court. Maine Superior Court Judge David Roberts began his analysis this way: "Though recent decisions may have cast doubt upon the legal rights of an unborn child, at the moment of live birth there does exist a human being entitled to the fullest protection of the law." Then, in words which presage his order, Judge Roberts states, "The most basic right enjoyed by every human being is the right to life itself." In his view, the issue before the court was not the prospective quality of the life to be preserved, but the medical feasibility of the proposed treatment compared with the almost certain risk of death should the treatment (surgical correction of the tracheoesophageal fistula) be withheld. With that premise, the judge then asked whether there is a medical need and a medically feasible response. If these two questions could be answered affirmatively, then, Judge Roberts argued,

regardless of the quality of life, the surgery must be performed. In this case, the surgery was done, but the child, nonetheless, died.

That stark "life-at-all-cost" stance occasioned a scathing criticism in a now classic 1974 *JAMA* article by Richard McCormick entitled "To Save or Let Die: The Dilemma of Modern Medicine."[10] McCormick, the most renowned Jesuit moral theologian of his era, noted that there was no moral obligation to impose treatment on a patient who was dying or who was totally dependent on intensive measures to sustain life, nor was there an obligation to do so for a patient whose potential for relationships is nonexistent. That article, which was the first to attempt to establish practical norms or guidelines for seriously compromised newborns, has been quoted with approval by nearly every group that has subsequently tried to design standards for such decisions.

An even more frequently cited essay published by Duff and Campbell[11] a year earlier in *The New England Journal of Medicine* was the first to bring the topic of ethical dilemmas in the newborn nursery to the public's attention. In this article, the authors revealed that decisions were regularly being made in major neonatal intensive care units to forego treatment and let infants die. They reported that of 299 deaths in the special care nursery of the Yale–New Haven Hospital between 1970 and 1972, 43 (14%) were associated with discontinuance of treatment. In those cases of children with multiple abnormalities, trisomy, cardiopulmonary crippling, and central nervous system disorders, no further treatment was undertaken if the parents and physicians in a joint decision concluded that prognosis for "meaningful life" was extremely poor or hopeless. The children were left untreated and allowed to die. In Duff and Campbell's view, the decision to withhold or withdraw treatment belonged to those who bore the responsibility for the consequences of treatment—the families.

In a subsequent essay Paris and McCormick[12] had occasion to critique the Duff and Campbell position as "normless." It provided no guidelines, no standards, no norms on which to base the decision. Under the Duff and Campbell schema, a treatment decision could equally be made on concern for siblings or "family convenience" as well as on the best interests of the infant. What their approach failed to realize is that even good and caring parents acting out of fear, ignorance, or a misreading of the clinical situation can make decisions antithetical to the best interests of the child.

As illustrated in the well-known *Stinson* case, chronicled in Robert and Peggy Stinson's *The Long Dying of Baby Andrew,*[13] physicians can also err in their judgments on the value of medical intervention for a hopelessly compromised newborn. The Stinson's son, Andrew, was delivered 4 months prematurely as a "marginally viable" 800-g newborn. In the early 1980s, infants in his category had a survival rate of less than 5%. Recognizing that fact, his parents told the pediatrician not to attempt any "heroics." The doctors at Community Hospital promised that they would follow the parents' wishes.

Stinson and his wife each kept a journal of the experiences of their son's life. The journal entries reflected their initial joy at the baby's successful delivery and their fear that he might be maintained "by science-fiction means in a state of pain or hopeless deterioration." That fear was realized when Andrew developed problems in fluid adjustment and was transferred to a well-known but unidentified pediatric hospital center (now publicly acknowledged to be the Children's Hospital of Philadelphia). There the commitment to care provided at Community Hospital was transformed into a "no stops, no exit, no appeal" stance. The family was informed that "[a] baby must be saved at all costs: anything less is illegal and immoral."

When the parents asked the doctors not to use a ventilator, they were castigated for violating the sacredness of life and seeking a "return to the law of the jungle." Brain death was the only criterion the doctors would recognize as a legitimate basis for stopping treatment. With such a standard, the parents helplessly stood by as the doctors treated Andrew for brain hemorrhage, respiratory failure, necrosis of the right leg, gangrene, rickets, multiple bone fractures, retrolental fibroplasia, blindness, and finally pulmonary hypertension—an often terminal complication of severe bronchopulmonary dysplasia. Through all of this, there was no hint of a willingness to accede to the parents' repeated requests to allow Andrew to die a natural death. Only when Andrew accidentally pulled out his endotracheal tube and began breathing on his own did doctors allow "nontreatment," that is, progressive respiratory failure, to bring Andrew's life to a close.

"Babe Doe" Regulations

The attitude of the physicians in the *Stinson* case briefly became the standard in the United States in what is now known as the "Baby Doe" regulations. Those federal regulations rose from the Reagan administration's disapproval of the nontreatment in the *Bloomington Baby Doe* case.[14] There an infant with Down syndrome and a tracheoesophageal fistula was allowed to die untreated when the attending obstetrician recommended, and the family agreed to, no surgical intervention. Although three courts, including the Indiana Supreme Court, upheld the parental decision, the subsequent public outcry led to federal involvement. Under the original regulations issued by the Department of Health and Human Services, physicians were required to provide life-sustaining medical interventions to every infant. As a highly critical editorial in *The New England Journal of Medicine* stated: "The Regulations are based on the premise that *all* life, no matter how miserable, should be maintained if technically possible."[15]

Those regulations were struck down on procedural grounds by the United States Supreme Court.[16] Their legacy, however, continues in the 1984 amendments to the Child Abuse Protection Act,[17] the so called "Baby Doe Regs," which mandates that state child protective agencies, as a condition for receiving federal funding, must have procedures in place for oversight of medical neglect. Despite the fact, as Alan Fleishman correctly observes, that "[t]hese regulations … do not mandate unnecessary or inappropriate treatments," [18] more than one third of the neonatologists in a 1988 national survey stated that because of the Baby Doe regulations, they provided medical interventions for seriously compromised infants that in their judgement were not medically indicated.[19] In fact, the regulations not only allow but also direct physicians to

make treatment recommendations to the parents based on "reasonable medical judgment."

Linares and *Messenger* Cases

The test of those standards was found in the *Linares*[20] and *Messenger*[21] cases, each a highly dramatic case in which a father was charged with homicide for turning off a ventilator that was maintaining the life of his infant son.

Linares Case

In the first case, Sammy Linares—a 1-year-old child who suffered massive anoxic damage when he inhaled a balloon at a birthday party—was diagnosed as being in a persistent vegetative condition. In the words of the director of the pediatric intensive care unit at Chicago's Rush-Presbyterian—St. Luke's Medical Center, recovery "was not possible." Both the father and the treating physician agreed that, given the child's physical status, it would be medically and morally appropriate to remove the respiratory support. The hospital attorney, however, informed the physician that "while Illinois law permits hospitals to withdraw life-support mechanisms from patients who have no brain activity, there is no precedent governing those who have minimal brain activity even if they have virtually no prospect of regaining consciousness." The attorney advised the parents to seek a court order for the removal of the ventilator. In the meantime, the attending physician, understandably, declined to remove the life-sustaining machinery.

The father, rather than petitioning for a court injunction to terminate the unwanted treatment, entered the pediatric intensive care unit with a magnum .357, held it to the child's head, and threatened to kill his son if anyone approached. He himself then removed the infant from the ventilator and waited a half hour to be sure the child was dead before dropping his weapon. The district attorney sought homicide charges. One of us (JJP) wrote an "op-ed" piece for the *Chicago Tribune* on the case entitled "A Desperate Act But Not Murder,"[22] which argued that a patient in a well-diagnosed persistent vegetation state has no obligation to undergo life-sustaining interventions. The father's action, reprehensible though it might be as a way of proceeding in a medical case, was not murder; rather, the act was the freeing of his son from an unwanted medical intervention that the son had no obligation to undergo and the physician no duty to impose. The grand jury in this case agreed. It refused to return a homicide indictment against the father.

Messenger Case

Homicide charges were likewise brought in a highly publicized 1996 case against Dr. Gregory Messenger, a dermatologist from Lansing, Michigan, for removing his extremely premature infant son from a ventilator in Sparrow Hospital's neonatal intensive care unit. The newborn infant had been placed on mechanical life support despite the explicit instruction of the parents that they did not want aggressive or resuscitative measures used on their 780-g, 25-week gestational-age son.

In week 25 of the pregnancy, the mother, who suffered from hypertension, developed pulmonary edema, which in turn precipitated premature labor. Concern about a ruptured uterus led to delivery by cesarean section. Prior to delivery the parents had been told by the neonatologist that the child had a 30% to 50% possibility of survival and that if it did survive there was a 20% to 40% chance of severe intraventricular hemorrhage. The parents informed the neonatologist they did not want any extraordinary efforts undertaken, nor did they want any attempts at resuscitation. The neonatologist preferred a "wait and see" approach. She instructed her physician's assistant (PA) that if the child were "vigorous" at birth and needed ventilatory support, she was to intubate. At birth the infant was hypotonic and hypoxic, purple-blue in color, "floppy" and "appearing lifeless." He did, however, have an umbilical cord pulse of 80 to 90 bpm. The PA immediately intubated the infant.

The father informed the PA that he and the boy's mother did not want resuscitation. The PA told him that she was not authorized to withdraw treatment. The neonatologist returned to the hospital, saw the infant was pink and stable, and indicated she wanted to try surfactant to see how the child would respond before coming to any decision to remove the ventilator support.

Gregory Messenger asked to be left alone with his son and then he turned off the ventilator. Some 10 minutes later the father opened the door and indicated that his newborn son had died. The pathologist found the infant's condition was not terminal. He ruled the cause of death was respiratory failure due to the removal of the ventilatory support. The district attorney claimed that the father had failed to provide proper medical treatment for his son and charged him with manslaughter.

One of us (JJP) testified at the trial that the focus in this case, as in all treatment decisions, must be centered on the patient. It is the patient's condition and the patient's desires—not the wishes of the parents or the goals of the physician—that ought to govern these treatment decisions. The issue here was how to discern what the infant patient would want. Although some, such as the Massachusetts Supreme Judicial Court, believe that through a process of "substituted judgment"[23] we can discern the mind of the never competent, including newborn infants,[24] most commentators believe this admitted "legal fiction"[25] is so farfetched as to be judicial fantasy.[26]

As noted, the consensus now in the literature seems to be that for the "never competent" the "best interests" standard is the one that should be used. There is no doubt that if the Messengers had requested aggressive treatment for their 25-week gestational-age son, it would have been provided. The question is: Did the information given to the parents warrant a predelivery decision to withhold resuscitation and other aggressive medical interventions? Or, as the neonatologist wanted, must the parents authorize resuscitation and the use of aggressive life-sustaining measures until it becomes clear, if not certain, that the child will not survive or that if he does, he will be in such a devastated state as to justify removal of life-sustaining measures?[27]

Under any schema, a 50% to 70% risk of mortality puts a newborn into that broad area of gray in which the degree of burden and the prospects of benefit are so suffused in ambiguity and uncertainty that a decision as to whether to continue treatment properly belongs to those who bear the responsibility for the infant: the parents. That stand, as the

Hastings Center Project on "Imperiled Newborns"[28] reports, is contrary to the medical practice in the United States where physicians respond to uncertain outcome in neonatal medicine by giving "a chance" to every infant who is even potentially viable. Active treatment is then continued until it is nearly certain that the particular baby will either die or be so severely impaired that, under any substantive standard, parents would legitimately opt for termination of treatment. Then, and only then, do physicians present a choice of withdrawal of treatment to the parents.

That "wait and see" approach is appropriate in the face of complete uncertainty, that is, when decision makers have no knowledge at all about the probabilities of various outcomes. But, as the Hastings Center group put it: "It is not particularly well-suited to moral situations in which there are data on which to base predictions." The Messengers had such data. The prospect of a 50% to 70% death rate, a 20% to 40% risk of a severe brain bleed, and the probability of respiratory distress syndrome given by the neonatologist was more than sufficient evidence of the disproportionate burden that awaited this child to justify a decision to withhold resuscitation.

The jury in the *Messenger* case believed the parents' decision not to initiate ventilatory support and, once it had been initiated over the parents' objection, the decision to terminate support was morally acceptable. With minimal debate, the jury unanimously found Gregory Messenger's actions neither grossly negligent nor a breach of his legal duty to provide proper medical treatment for his son.

Miller versus HCA Case

The apparent consensus that parents have the right to refuse unwanted medical interventions for seriously imperiled infants such as extremely premature newborns, where the risk of mortality and morbidity is significant and the prospects of benefit is suffused in ambiguity and uncertainty, has been challenged by a 2003 Texas Supreme Court's ruling in *Miller v. HCA*.[29] There the Texas Supreme Court carved out an "emergent circumstances" exception to the need for parental consent to treat an infant "so premature that, despite advancements in neonatal care, has a largely uncertain prognosis." This was the first court to authorize physician resuscitation of an extremely premature infant over parental objections.

The case arose when Kara Miller arrived at Woman's Hospital of Texas in premature labor. The ultrasound assessment was an estimated fetal weight of 629 g and a gestational age of 23 weeks. Tocolytics were administered to stop the labor, but were discontinued when it was learned that the mother had a potentially life-threatening infection. Labor-inducing drugs were then begun. The attending obstetrician and a hospital neonatologist informed the parents that there was little chance of the infant being delivered alive. They also informed the parents that if the child were born alive, "it would most probably suffer severe impairments, including cerebral palsy, brain hemorrhaging, blindness, lung disease, pulmonary infections, and mental retardation."

With that background, the obstetrician and neonatologist asked the parents whether they wanted their infant daughter treated aggressively if, as anticipated, the physicians would have to induce delivery. The parents informed the doctors that they did not want any "extra-heroic measures at this time." The parents' decision was recorded in the medical record, and the obstetrician informed the medical staff that no neonatologist would be needed at the delivery.

After the parents' decision had been agreed to, someone on the nursing staff informed other hospital personnel that no neonatologist would be present for the delivery. At a meeting called to discuss objections to that decision, the administrator of the neonatal intensive care unit stated that hospital policy required resuscitation of any baby weighing greater than 500 g. Once that claim had been made, it was agreed by the staff that a neonatologist would be present at the delivery to assess the baby's gestational age and weight. Kara Miller delivered a 23.1 week gestational-age infant girl weighing 615 g. The infant was immediately "bagged," intubated, and placed on a ventilator. The Apgar scores were 3 at 1 minute and 6 at 5 minutes. At some point during the first days of life, the infant suffered a significant brain hemorrhage which, in the Court's words, "caused [her] to suffer severe physical and mental impairments," such that 7 years later she still required care 24 hours a day, a condition the court noted was not going to improve.

The Millers sued the hospital and its parent corporation Columbia/HCA Healthcare Corporation (HCA). A jury found that the hospital, without the consent of the parents, had resuscitated their infant. It also found that negligent action was the cause of their daughter's injuries. The jury awarded actual and punitive damages of $60 million. The jury verdict was overturned by the Texas Supreme Court.

The Texas Supreme Court framed the issue posed in *Miller v. HCA* as "determin[ing] the respective roles that parents and health care providers play in deciding whether to treat an infant who is born alive but in distress and is so premature that despite advancements in neonatal care, has a largely uncertain prognosis." Consent in cases involving markedly premature infants has till now been the prerogative of the parents. The state, acting as *parens patriae*, can and does intervene to protect children from neglect and abuse or to prevent parental choices that would produce such results.[30] But as long as parents choose from a professionally accepted option, the choice is rarely challenged or supervened. The Texas Supreme Court acknowledged that parental role, but in this instance the court ruled that when a doctor is confronted in a case where there are "emergent circumstances"—where death of a child is likely to result immediately unless treatment is administered—the physician may intervene even over parental objections.

The Texas court ruled that the infant "could only be properly evaluated when she was born." Consequently, in the court's view, "Any decision by the Millers before [the infant's] birth would necessarily be based on speculation." Further, the court opined, a pre-delivery decision would "not have been a fully informed one." As the Texas Supreme Court saw it, the doctor present at the delivery had to make "a split second decision on whether to provide life-sustaining treatment." In that situation, it held, "there simply was no time to obtain [the parents'] consent to treatment or to institute legal proceedings to challenge their withholding of consent without jeopardizing [the infant's] life."

Stewart-Graves versus Vaughn Case

The holding on the requirement of parental consent in *Miller* was extended in a 2007 ruling of the Washington Supreme Court in *Stewart-Graves v. Vaughn*.[31] Nichole Stewart-Graves presented at Southwest Washington Medical Center at 35 weeks' gestation following an uncomplicated pregnancy. A significant drop in the fetal heart rate led the attending obstetrician to perform an emergency caesarean section. The mother had suffered a placental abruption and infant Liam was delivered without a heart rate or respiration. The neonatologist undertook emergency resuscitation efforts for 24 minutes before the return of spontaneous circulation. The infant's mother was under general anesthesia throughout the resuscitation process and the neonatologist did not speak to the father who was in the postoperative birthing room. Like the plaintiff's daughter in *Miller*, Liam suffers from severe disabilities that require continuous care.

In the claim against the neonatologist, Dr. Vaughn, and the hospital, the parents argued that such a lengthy resuscitation without obtaining the father's consent violated Washington's informed consent requirement. The Washington Supreme Court's rejection of the claim is similar to the reasoning of *Miller*, but offers substantial grounds for distinguishing the two cases. As in *Miller*, the court in *Stewart-Graves* held that "a recognized health emergency existed in this case, as a matter of law, until the resuscitation ended." But unlike *Miller*, where the parents' decision was effectively overruled by the hospital staff, the Washington Supreme Court noted that no parental decision was ever given in *Stewart-Graves* because no legally authorized representative was "readily available," as defined in Washington law, to give consent.

The Washington court argued that the reason for the father's unavailability was not only his physical absence from the scene, but the fact that the refusal of a life-saving treatment "cannot be truly 'informed' in the context of neonatal resuscitation when the circumstances permit no more than a hasty explanation of probable outcomes by a physician whose attention must primarily focus on life-saving efforts."

Commentary

In an article on the *Miller* case, John A. Robertson of the University of Texas Law School supported the Texas Supreme Court ruling authorizing physician treatment of newborns over parental objection and extended it to claim that under the federal Child Abuse Amendments (CAA) of 1984 (the "Baby Doe rules"), there is no room for physician discretion regarding resuscitation of infants, even those at the extreme margins of viability.[32] In his words, "[o]n their face, the CAA standards leave no room for discretion. All conscious viable premature newborns must be treated, even if they are likely to have severe physical and mental disabilities."

Gone under that standard is any concern for "best interests" of the infant. Robertson would require the resuscitation of all infants born alive indifferent to predelivery assessment of gestational age and weight or concern for the outcome data on the sequelae of such births. For him, as well as the Texas Supreme Court, a nontreatment decision made before birth would be based on "speculation" and thus not legitimate. The same line of reasoning was adopted by the Washington Supreme Court where in dicta that may presage a shift on the judicial requirement for informed consent in life-or-death circumstances, the court concluded that a party was not available to give consent when "there was no meaningful opportunity for a deliberate, informed decision to refuse consent where the failure to treat meant certain and immediate death."[33]

Futility Debate

One troubling area in the dispute over extending life is the intense and ongoing debate noted by Helft and colleagues[34] on the limits, if any, to parents' claims to requested medical treatment. Before 1990 there was scant mention of the issue of physician reluctance to comply with patient or family requests for treatment. The pressing ethical concern had been to gain recognition of patients' rights to refuse unwarranted treatments. But with the U.S. Supreme Court's *Cruzan*[35] opinion and the Patient Self-Determination Act of 1990,[36] the issue that first arose with the 1976 *Quinlan*[37] case—the right of a patient, competent or incompetent, to decline unwanted medical interventions—had been definitively resolved. Patients have that right.

The focus then shifted to a little noted but increasingly difficult problem: what to do with requests for treatment believed by the physician to be futile, ineffective, or inappropriate. Until the article in the *New England Journal of Medicine* in 1990 about the by now famous "Baby L" case,[38] in which the physicians at Boston Children's Hospital who had cared for a profoundly compromised baby for some 23 months refused a mother's request to put her child once again on a ventilator, the issue had been confined to simple questions such as whether to comply with patient requests for antibiotics for viral infections or a CAT scan for routine headaches.

Although theoretically agreeing that such treatments ought not to be given, many physicians found it easier to go along with patient requests than to try to persuade them otherwise. The placebo effect would frequently convince patients that they felt better, and the insurance company or third-party payor would pay for whatever treatment the physician had ordered. That approach, however, fed a consumer mind set on the part of both patient and physician. If the patient wanted the treatment and insurance would pay for it, the doctor provides it. That attitude contributed to the erosion of physician authority and, more important, of professional responsibility. The physician was transformed from the one with the knowledge and the expertise to diagnose and prescribe into an entity whose role was to respond to whatever the patient desired.

So long as that interaction involved rather innocuous medications or relatively simple and inexpensive technologies, there was no concern on the part of medicine. But as the consumer model began to dominate, the requests escalated into demands for more and more exotic and inappropriate treatment. With that shift, the belief began to grow that informed consent and patient autonomy not only implied that patients had the right to accept or reject

proposed therapies, but they had the right to select whatever treatment they desired.

Autonomy, or the right of self-determination, was seen not only as a significant moral principle but became in the minds of some bioethicists, such as Veatch and Spicer,[39] the overriding moral principle. They believe that so long as there was financial coverage, families have a right to demand, and physicians an obligation to provide, whatever life-prolonging treatments the family requests. Veatch goes so far as to insist that if no other physician can be found who is willing to provide the desired treatment, the attending physician is obliged to do so. This holds true, he argues, even if a surrogate's request "deviates intolerably" from established standards or is, from the physician's perspective, "grossly inappropriate." Veatch's position places the physician in a terrible dilemma. It would require the physician to relentlessly impose aggressive procedures on devastated infants if requested to do so by the parents even in the face of overwhelming evidence that the interventions cannot reverse or ameliorate the child's condition.

Support for that position is found in a recent essay by Robert Truog, the director of clinical ethics at Harvard Medical School, who proposes that doctors should honor the family's choices on end-of-life care "even when we believe their decisions are wrong."[40] The problem created by that position is graphically portrayed in an article by Hacker and Hiller[41] where they described their experience with a 6-year-old child who had undergone multiple abdominal surgeries and repeated resuscitation over a 10-month period.[42] The physicians did not believe there was any hope of survival, but hospital policy required approval by the next of kin for "do not resuscitate" (DNR) status. In this case the mother refused to consider any limitation of treatment. As the authors report, "During her final resuscitation, [the patient] was asystolic for 30 to 45 minutes. Her mother was called during the course of resuscitation but would not allow it to be stopped." The physicians, subsequent to the mother's urging, succeeded in reestablishing a heartbeat in what was now a neurologically devastated child.

Such a situation has led physicians to ask if they are, in fact, obliged to do what they believe to be futile or ineffective. The so-called "futility" debate centers primarily on cardiopulmonary resuscitation (CPR) and the requirement of patient or family consent for DNR orders.[43] It is now well documented that in certain clearly defined categories of patients, there is near 100% mortality.[44] In light of these data, Blackhall[45] argues that in such circumstances, even if the family requests CPR, the physician should decline to provide it. In such instances she states, "[T]he issue of patient autonomy is irrelevant." It is irrelevant because in such cases the requested intervention will not work.

Although the medical literature continues to bombard us with articles on "medical futility,"[46] as Helft and colleagues have observed, there is no agreement on what the term means or what implications it conveys. Younger[47] has queried: Does it signify absolute impossibility? Is it purely physiological? Does it include the ability to revive heartbeat but not to achieve discharge from the hospital? How much quality of life and social value does the term embrace?

Lantos et al.[48] noted that even among physicians there is no consensus on the meaning of the term. Physicians disagree on both the chances of success and on the goals of therapy. Some invoke futility only if the success rate is 0%, whereas others declare a treatment futile with a success rate as high as 18%. Furthermore, social and psychologic factors may cloud a physician's estimate of success.[49] For example, some consider liver transplantation for an alcoholic patient futile because of the likelihood of recidivism. Others consider a treatment futile if all it can provide is a chance for a couple of days or weeks in an intensive care unit. However, as Lantos and colleagues note, "Such a goal can be of supreme value to a dying patient or the patient's family."

This lack of agreement on the meaning of the term and its already abundant misuse as a shorthand way for physicians to truncate discussions on treatment decisions make it ever more apparent that its usefulness in the medical lexicon has been short-lived. Perhaps as Truog[50] has suggested, its rapid intrusion into bioethics should be met by its equally swift demise. Jettisoning this new buzzword would be no loss. The debate on futility not only distracts, it distorts the real issue. It is not the meaning of a word but the moral basis of the participant's actions that ought to be the focus of our attention.

Approach to Resuscitation of Newborn at the Margin of Viability

At the end of their article on repeated resuscitation of a devastated child, Hackler and Hiller[41] pleaded for a better approach to the care of the hopelessly dying child. The same might be asked of the newborn at the margins of viability. It is not unrelenting aggressive interventions, but the appropriate response to the physical status and continuing interests of the newborn that commands and should direct our care.

To arrive at that response, the first question ought not be, "What should we do?" Rather it should be, "What is going on?"[51] In medicine, that approach necessitates beginning with facts. Our first task is to identify the physical findings and the data from the literature on those findings to come to a determination of the patient's medical condition. Once the diagnosis is made, the physician is to draw on training and experience to formulate a prognosis and recommendation. The patient, or in neonatology the parents, evaluate that recommendation in light of their personal psychosocial values. They can then accept or reject the recommendation, seek an alternative treatment, or decide to forego medical interventions altogether.

Society's role is to assure that the patient is not undertreated by the omission of beneficial therapies or overtreated with unwanted or unwarranted interventions. In that delicate balancing act, as the President's Commission report on *Deciding to Forego Life-Sustaining Treatment* notes, great discretion is to be afforded to parents whenever the outcome is uncertain or ambiguous.[52]

How does this apply to resuscitation and assisted ventilation for extremely low-birth-weight, early gestational-age newborns? In an article on neonatal practice, Partridge et al. [53] remind us that even as we enter the 21st century, "It is not clear which infants born at the margins of

viability should be resuscitated and provided neonatal intensive care." From their study these authors conclude that at extremely low birth weight or gestational ages, "There are no standards for appropriate levels of intervention or few factors which should be considered relevant to discussions about resuscitation at birth."

Although it is true that prognostic uncertainty for survival or long-term morbidity make antenatal counseling for parents expecting a very premature infant difficult, the failure of physicians to provide parents with the known mortality and morbidity data or an inadequate discussion of that information hinders or even precludes informed decision making. In providing that data physicians should be mindful of the findings by Tyson and the Neonatal Research Network that in addition to increasing gestational age, exposure to antenatal corticosteroids, female gender, singleton birth, and higher birth weight are associated with reduction of death and neurodevelopment impairment.[54] The National Institute of Child Health and Human Development (NICHD) now has a website in which these five factors may be entered to determine an estimated survival and neurodevelopmental disability for any given baby (http://www.nichd.nih.gov/about/org/cdbpm/pp/prog_epbo/epbo_case.cfm). Physicians who counsel parents should be aware that this data is derived from 19 NICHD centers (all large academic medical centers) and that these results may not be applicable in the local situation. Other factors such as fetal presentation, mode of delivery, and presence of amnionitis or congenital malformations may also influence outcomes.

Focus on "best interests" of the infant forces us to consider the future of the child being saved by current technology, including assisted ventilation in neonatal intensive care units. A study by Wood et al. [55] of children born at 25 or fewer weeks' gestation revealed about half of all survivors had major psychomotor development impairments at 30 months of age. One fourth of the children met the criteria for severe disability. In a startlingly frank critique of such outcomes, Battle[56] questions whether we have adequately assessed the consequences of our technologic successes in neonatology. The advances accomplished through technology, not only of keeping some babies alive but also of restoring some of these tiny infants from near certain death, is a marvel. But, as she notes, the health care professionals who achieve these miracles disappear from the life of the child and the family within days, weeks, or months. For the remaining months or years, the child and family are left to wonder about the appropriateness of those miracles as they struggle to live with or to support one of those "successes." Battle's challenge demonstrates the need to consider outcome data and long-term commitments as well as the technical ability to save infants at the margins of viability in evaluating progress in neonatology.

Mortality and Morbidity Data

What do the current studies tell us about mortality and morbidity in extremely low-birth-weight, early gestational-age infants? More importantly, what do they indicate is the practice among neonatologists regarding this class of patients? The reported outcomes from several large neonatal centers are consistent: although there is now some survival of preterm infants at the lower levels of weight (less than 500 g) and age (less than 23 weeks' gestation), the prospect for survival and, more importantly, intact survival remains exceedingly small.[57-63] For example, a study by Allen et al.[64] reveals that for infants born at 22 to 25 weeks' gestation at Johns Hopkins during the period 1988 to 1991, none of 29 infants born at 22 weeks' gestation survived, 15% survived at 23 weeks' gestation, and 56% survived at 24 weeks' gestation. Of those born at 23 weeks' gestation, only 2% survived without severe abnormalities being observed on cranial ultrasound. The data from the 2000 EPICure Study of 4004 births in the United Kingdom and Northern Ireland of all infants of less than 26 weeks' gestational age demonstrate a high mortality for extreme prematurity.[65] The survival rate to discharge from hospital ranged from 44% at 25 weeks to 11% at 23 weeks. The majority of similar studies only reported data of infants born alive and many reported only infants in whom resuscitation had been attempted or who were admitted to neonatal units. Babies deemed stillborn and those in whom resuscitation was not attempted or not successful may have been omitted, thus making survival statistics at extremely low gestational ages and birth weights even worse than reported. The only report to look at an entire population of all deliveries is the 2000 EPICure study.[65] Most of the studies report outcomes for infants born over a decade ago, but the more recent data has indicated that despite changes in neonatal intensive care and the philosophy of resuscitation, the outcomes have not changed significantly.

When weight rather than gestational age is used as the determinant of the lower margins of viability, similar bleak outcomes are found. Hack et al.[66] report that in their study of outcomes of extremely low-birth-weight infants at Cleveland's Rainbow Babies Hospital during two periods, 1982 to 1988 and 1990 to 1992, "only 8 of 159 infants of <500 gm birth weight received active delivery room treatment during the whole 9-year period, of whom 2 survived." In a 12-year historical cohort study of 1193 infants weighing less than 500 g born between 1983 and 1994 in Alberta, Canada, Sauve et al. [67] report that of the 382 born alive, neonatal care was provided in 113 cases (29.6%). Of those, 95 (84.1%) died and 18 (15.9%) were discharged alive, 5 of whom subsequently died of respiratory complications. Of the 13 (11%) survivors, 4 had no serious disabilities. The remaining 9 had one or more major disabilities including cerebral palsy, profound mental retardation, blindness, and deafness.

As the study by Allen et al.[64] demonstrates, the introduction of antenatal steroids and postdelivery use of surfactant in the early 1990s has significantly improved the prospects of these early gestational-age infants. But as Fanaroff and colleagues[68] demonstrate in their 2007 study of neonatal mortality and morbidity for very-ow-birth-weight infants born between 1997 and 2002, although the survival of infants weighing 501 to 1500 g increased by one percentage point (from 84% to 85%), survival without major neonatal mortality remained static at 70%. Further, these authors note that although "viability" as defined by a survival rate of greater than 50% would now apply to infants delivered at 24 weeks' gestational age and a birth weight of at least 600 g, this definition does not take into

account the considerable long-term neurologic deficits encountered at this weight and gestational age. For example, in the EPICure study of infants less than 26 weeks' gestational age, fewer than half the survivors were neurologically intact.

Similar neurologic outcomes are reported in more recent surveys of long-term survivors in the United States,[69] Europe,[70] and Canada.[71] The Canadian Neonatal Network survey of infants of 25 weeks' gestational age or less reports that the survival rate of this cohort without major morbidity was 23%. That figure dropped to 11% for infants of 23 weeks' gestational age. The outcome data on diminished long-term survival and the marked diminution in reproduction from an average of 50.4% for term babies to 13.9% for infants born less than 27 weeks in the longitudinal study of 1.1 million births from 1967 to 1988 in Norway presents further evidence of adverse outcomes that present throughout adulthood.[72] Data such as these on the long-term adverse sequelae in extremely premature "fetal infants" give rise to increasing concern on how to counsel parents of such infants. An even more pressing issue emerging in the literature is whether or not intensive care is justified for those born on the cusp of viability.[73,74]

New Policy Proposals

Two recent publications, the Nuffield Council on Bioethics extensive report in Britain on "Critical Care Decisions in Fetal and Neonatal Medicine"[75] and the 2007 policy statement of the American Academy of Pediatrics (AAP) on "Noninitiation or Withdrawal of Intensive Care for High-Risk Newborns,"[76] address this issue. Unlike Truog, who proposes yielding the decision to parents even over and against physicians' objections that the decision in a particular case is "wrong," the Nuffield Council and the AAP take the position that newborns are to be treated as any other patient—on the basis of their best interests. The implication is that though parents may and should continue to be involved in decision making for their children, they do not have the exclusive right to refuse—or to demand—medical treatments for the child.

Although there is a wide range of interpretations as to what might constitute "best interests" in a marginally viable newborn, the Nuffield Council Report concurs with the American Academy of Pediatrics' position that treatment decisions for these infants can be divided into three categories:

1. When early death is very likely and survival would be accompanied by high risk of unacceptably severe morbidity, intensive care is not indicated.
2. When survival is likely and risk of unacceptably severe morbidity is low, intensive care is indicated.
3. In the "gray area"—where prognosis is uncertain but likely to be very poor and survival associated with a diminished quality of life—parental desires should determine the treatment approach.

The two reports differ as to what constitutes the "gray area" with regards to extremely premature infants at the margin of viability. Although the AAP advises support of parental decisions for infants born at less than 25 weeks' gestation, the Nuffield Council would only follow parental wishes for infants born at less than 24 weeks gestation. When health professionals and parents agree on the level of care, there are no ethical problems on treatment choice. Difficulties arise when caregivers and families disagree on the intensity of care to be provided. Parents may demand continuation of aggressive treatment when in the medical team's judgment such interventions are unavailing or inappropriate. Or parents might oppose treatments that the physician believes would offer substantial benefit to the baby.

In such cases Truog advises deferring to the parents' decision or seeking court intervention to override their choice. The Nuffield Council cautions that going to court should be used only as a last resort. Even then judicial involvement should be sought only when it is believed that what is being insisted on by one of the parties is wholly antithetical to the welfare of the baby. A word of caution here is the observation that no American court has ever approved the withdrawal of a life-prolonging procedure over a family's objections.[77] Further, going to court results in a costly and cumbersome adversarial process, one that ruptures the physician-family relationship and shifts attention from the clinical situation of the infant.

To obviate clashes between parents and physicians on treatment choices, it is advisable, whenever possible, that prior to the delivery of an extremely premature infant there be a joint discussion that involves the parents and the obstetrician and a neonatologist in regard to survival rates and severity of potential disabilities. All involved should understand the provisional status of predelivery plans and the need for clinical assessment of the newborn to confirm predelivery assessments. It is important that the family receive consistent information from both the obstetric and neonatal teams.

If the circumstance of the birth precludes prior discussion, the physician has the responsibility of making a clinical assessment of the infant's condition at birth and then a judgment on whether or not to initiate resuscitation. In case of doubt, the physician should err on the side of treatment both to allow time for subsequent discussion with the parents and to formulate a more accurate evaluation of the infant's status.

In making a decision, what is called for is not rigid rules but a realistic assessment of the infant's physical prospects based on current data from the medical literature as well as the outcome data in the particular hospital. It is also important to have sensitivity to differing cultural norms and family values. As in all medical decision making, the primary consideration in treatment decisions for newborns at the margins of viability is and continues to be a commitment to act in the best interests of the patient.

Withholding and Withdrawal of Treatment

Even in cases of extremely low-birth-weight infants, the possibility of intact survival makes resuscitation, with subsequent reassessment and willingness to terminate treatment in the face of declining status, an acceptable approach. The same justification that applies to the withholding of a treatment governs its withdrawal. In fact, there is an even

greater warrant for instituting a therapy to determine whether it might work and then withdrawing it if it fails than in never having instituted it. The patient has the benefit of a trial course of the therapy, and the family has the assurance that they have tried "everything possible" on behalf of their child.

Unfortunately, as Weir[78] observes, the feeling still persists among some caregivers that the withdrawing of life-sustaining treatment is morally more significant and certainly more legally serious than withholding treatment. Several reasons contribute to this misunderstanding. It is psychologically easier not to start than to stop. Further, withdrawing a treatment once instituted gives a sense that the physician's action, rather than the underlying illness, "caused" the death. There is also a lingering misconception that the physician is duty bound to do everything possible to sustain life. From *Quinlan* in 1976 to *Cruzan* in 1990, every court of final jurisdiction that has addressed this issue has unambiguously stated that there is no moral, ethical, or legal difference between withholding or withdrawing medical interventions. Further, as the United States Supreme Court made clear in its *Cruzan* opinion—once specific state evidentiary requirements have been met—it is legitimate in the face of imminent death or irreversible loss of consciousness to withdraw life-sustaining mechanical ventilation.

The moral issue facing physicians involved in the withdrawal of medical interventions is to assure the patient and family that the withdrawal will not produce suffering for the patient.[79] This, as Civetta[80] notes, is of particular concern when ventilatory support is withdrawn. If done too rapidly or without close attention, air hunger or dyspnea may result in gagging, gasping, and struggle in the patient. Neither the patient—nor family or caregivers—should be subjected to such insensitive circumstances. To prevent that situation, physicians should take care to premedicate patients with an analgesic, usually morphine, to alleviate dyspnea and pain and a benzodiazepine for anxiety. Because the goal of these medications is symptom relief, not death, they should be titrated to the intended effect.

Although it might appear beneficial to paralyze the patient before extubation or weaning, most commentators agree that it is unethical to use neuromuscular blocking agents at the time of discontinuing a ventilator.[81] In addition to blurring the threshold between allowing to die and actively causing the patient's death, these paralyzing agents mask potential patient pain and anxiety. They are not necessary to assure absence of pain and ought not be used for that purpose.

Limiting the Use of Assisted Ventilation

Physician unwillingness to limit or omit interventions when the outcome is anything less than 100% certain, coupled with the dominant role parents have in the contemporary American setting, virtually assures that, if the parents request it, resuscitation will be attempted on nearly every infant—even those at the outer margins of viability. The ethical concern today is not whether to institute requested ventilation for infants at the margins of viability, but what happens when the prognosis of the infant shifts from uncertain to dim to dismal? In the present medical-legal environment, the tendency is still to do whatever the parents' demand.

That outcome is difficult to avoid in a culture that gives near absolute deference to patient autonomy or, in the case of neonates, to parental authority for treatment decision making. More problematic is the unwillingness of American courts to override a family's plea to continue life-prolonging interventions for a loved one even when there is unanimous agreement among the medical team of the most sophisticated medical centers that such interventions are unavailing and contrary to the standard of care. One response to that reality is a Texas statute[82] that authorizes a physician to withdraw life-sustaining interventions even over parental objections if there is support of the ethics committee for the medical team's position and if the family is unsuccessful in locating another facility within 10 days that is willing to treat the patient as the family wishes.

That statute was tested in *Hudson v. Texas Children's Hospital* (2006),[83] a case in which a child born without any prenatal care was found to have thanatropic dysplasia, a congenital problem marked by a small rib cage and underdeveloped lungs. Immediately after birth the infant was placed on a ventilator. Upon examination it became evident to the physicians that the infant had a fatal congenital abnormality. In the physicians' view, continued forced ventilation of the infant meant the child was "slowly suffocating to death." The mother, who named the boy "Sun," insisted that he was not of human parentage, but fathered by "the sun in the sky." She believed that so long as the sun continued to shine that her child would thrive. Despite the doctor's medical assessment, the mother insisted on continued ventilatory support for her baby.

Texas Children's Hospital contacted some 40 other neonatal facilities, none of which would accept the infant on transfer. The hospital, not wanting to appear callous in overriding the mother's request, sought court authorization for the removal of the ventilator. The judge who heard the case indicated that he would neither order the ventilator turned off nor would he order the hospital to maintain ventilatory support. Rather, he ruled that under Texas law, once the hospital had followed the procedures outlined in the statute—and the mother had been unable within the 10-day timeframe to locate another facility willing to accept the child on transfer—the treating physicians were free to withdraw the ventilatory support. That was done. The boy died moments later.

Other than in Texas—and Maryland, Virginia, and California, which have enacted similar statutes—what should be done when parents demand interventions the medical team believes are ineffective and unwarranted? Does the treating physician mindlessly continue providing "everything possible?" To do so, as Ingelfinger[84] pointedly reminds us in an essay on the patient-physician relationship, is to be "guilty of shirking [one's] duty, if not malpractice." Ingelfinger's position on the positive role of the physician to intervene to protect the interests of the patient even over family objections is supported by the American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Pediatrics (AAP) position that in such situations the role of parents is not absolute.[85]

Though their informed decision must be given great weight, the parents' decision is not dispositive. The "best interest" standard, as the AAP's guidelines on foregoing life-sustaining medical treatment reminds us, requires the physician to weigh the benefits and burdens of treatment from the infant's—not the parents'—perspective. Such an assessment requires calculating the chance the therapy will succeed and the degree to which it will extend life if successful; the risks, pain, and discomfort involved with the treatment or nontreatment; and the anticipated quality of life with or without the treatment."[86]

As Tyson and colleagues[87] note, although most immature infants will die without such an intervention, mechanical ventilation can make for worse outcomes—death after days or months of distress or morbidity so severe it might be considered worse than death. To avoid that outcome, Tyson proposes that treatment decisions for newborns be assessed in four categories: mandatory, optional, investigational, or unreasonable. That classification allows for a nuanced analysis of what is being done. It also broadens the decision-making process beyond merely asking the parents, "What do you want?" The categories are explained as follows:

Mandatory—If the parents ask the physician to withhold or withdraw ventilatory support that has a very high likelihood of benefiting a child, the treating physician's independent obligation to foster the best interests of the patient prohibits following the parents' request. An example would be parents who ask the physician to remove ventilation from a full-term newborn experiencing respiratory distress unless the physician can guarantee that their child will be "normal."[88]

Optional—When the risks are very high and the benefits are at best uncertain or extremely low, the parents have the option of accepting or rejecting the proposed resuscitation. In this "grey zone," the parents' decision to either accept or reject ventilatory support should be followed.[89]

Investigational—For resuscitation for babies of very low birth weight, the outcome data are such that, in the words of Lantos et al.,[90] "The best we can tell parents is that this intervention is so new or its effects on this class of patients so unproven that it is an 'innovative' or 'experimental' procedure." Such investigational procedures, as the Nuffield Council Report notes, require parental consent.[91]

Unreasonable—If the parents are demanding aggressive medical interventions when in the physician's best judgment there is no expectation of efficacy, for example, on a child born with renal agenesis or one with Herlitz subtype of junctional epidermolysis bullosa, there is no obligation to provide the treatment.[92] Such an action would be not care, but an abuse of the patient.[93]

Current Practice of Neonatologists in the Face of Failed Therapies

What is the practice of neonatologists when confronted with a deteriorating patient who is receiving life-prolonging medical interventions? A study by Wall and Partridge[94] reveals that in the face of imminent death, most neonatologists recommend the withdrawal or withholding of treatment. Some centers such as the University of North Carolina at Chapel Hill report that "in most cases death occurred after life-sustaining treatment was withdrawn."[95]

Hack and colleagues[66] found that while aggressive treatment of infants with birth weights less than 750 g did not affect mortality, it did increase the mean age of death from 72 to 880 hours. Allen[64] reports a similar frequency of late deaths in her study at Johns Hopkins. This led her to observe that "although an argument can be made in favor of keeping an infant alive long enough for the parents to say goodbye, deliberately prolonging death beyond a few hours is difficult to justify." For Allen, prolonging death is not relieving the parents of a burden, it is "prolonging suffering, not only for the infant, but also for the family and members of the staff."

Although imposing heroic suffering on one's self in the hope of a therapeutic benefit or even the altruistic advancement of science is acceptable,[96] the same does not hold for imposing that suffering on others. The lesson from the Willowbrook experiments, in which severely retarded children were subjected to hepatitis infection in the search for a cure, is that there are limits to which children may be subjected in clinical investigation.[97] The requirements for proceeding in such investigational situations are substantially higher than having parental consent.[98]

The issue in research ethics is how do we protect vulnerable populations such as children who cannot protect themselves from the injury that can occur as a result of investigational procedures. To guard their interests, we need to recast the issue in cases such as resuscitation of infants at the very margins of viability from "autonomy"—which it is not—to the rules governing research subjects. For such subjects, as Lantos noted, "[T]he effectiveness of therapy replaces patient or parent preference as the primary factor governing decisions to use or discontinue therapy."[90]

The importance of the distinction between requirements governing therapeutic and research interventions is reiterated in two *New England Journal of Medicine* articles on ethical aspects of randomized trials. In a study of the harm that can be done to patients in such trials, Alexander Capron[99] reminds us that "the lessons of the past half-century is that suffering, death, and violation of human rights can arise not only when dictators give inhumane scientists free reign to treat human beings as guinea pigs, but also when well-meaning physicians conduct research in a free and enlightened society." That reality leads Truog et al.[100] to insist that unlike conventional therapy, investigational procedures require more than informed consent; they demand heightened protection of the subject by the investigator. Such consideration must be given to vulnerable populations such as the fetus and children as proscribed by the National Research Act of 1974 (Public Law 93-348). Although the consent of the subject or proxy is a necessary prerequisite to begin an investigational procedure, they are not a sufficient basis to continue. The scientist investigator, as the Nuremberg Code makes clear, must exercise independent judgment on the safety and efficiency of the intervention under investigation.[101] In

particular, the scientist is charged with protecting the subject from "all unnecessary physical and mental suffering and injury."

This obligation continues to be the duty of neonatologists who use innovative or unproven methods to sustain life at the margins of viability. These physicians are, as Lucey notes, "engaged in a large uncontrolled experiment" in which the vast majority of infants die or, if they survive, have serious complications.[102] That neonatologists honor the obligation is seen in reports such as those of Allen and colleagues[64] at Johns Hopkins that if there is no positive response in the delivery room to bag and mask ventilation in infants with poor respiratory effort and low heart rate, no prolonged resuscitation is attempted. These physicians know from the literature and their extensive experience that additional efforts in such cases would at best only delay the inevitable outcome accompanied by painful and potentially harmful interventions. They do not engage in such action.

As the cases of *MacDonald v. Milleville*[103] and *Hall v. DeSoto Memorial Hospital*[104] show—even in the absence of a Texas-like statute—parental permission to stop the attempted resuscitation in such circumstances is not legally required. The same holds true for those infants who, despite an initial positive response to assisted ventilation, develop a physical condition as incompatible with survival as that evidenced in newborns whose heart rate cannot be increased beyond 40 to 50 bpm. The problem in these cases is not one of science. Every neonatologist knows that a 410-g, 23.0-week gestational-age infant with progressively deteriorating pulmonary function cannot survive. The problem lies not with inadequate data, but with the practice developed over the past three decades of giving parents the cruel option between continuing the now failed attempts at restoring health or letting their child die. For many parents, the latter choice is too difficult even to contemplate. Overwhelmed by anguish, they are in no position to make a reasoned choice, let alone one that will dash forever their hopes for a healthy child.[105]

Two additional problematic scenarios in attempted resuscitation of newborns are, first, how should the physician respond when an initial decision has been made to omit resuscitation on a newborn and then, after a period of waiting for the anticipated death, the parents request "everything possible" be done to save their child? The resuscitation of a cold acidotic infant is the guarantee of a neurologically devastated child. And, in the American scene, it is almost inevitable that there will also be a lawsuit against the physicians for the injuries incurred by the delay in providing intensive care to the infant. The decision to forego attempted resuscitation ought to be made only after careful assessment of the newborn's condition. Once made, it ought not be reversed.

A second issue is how long should an attempt at resuscitation of a newborn be maintained. The AAP's *Textbook of Neonatal Resuscitation* notes that, "Current data indicate that after 10 minutes of asystole, newborns are very unlikely to survive, or the rare survivor is likely to survive with severe disability."[106] In the absence of factors that might be compromising the attempted resuscitation, the AAP advises that after 10 minutes of no heartbeat, "discontinuation of resuscitation efforts may be appropriate."

Conclusion

When all of the available choices fail and thereby cease to be options, no choice should be offered. The words we use when undertaking an investigational procedure, "We will initiate the process and see how the child declares himself," should be followed. If, as sometimes happens, a newborn receiving assisted ventilation evidences pulmonary insufficiency incompatible with survival, the parents should be informed that though "everything possible" has been tried, the efforts have not succeeded. The most we can do now for such infants is to keep them comfortable and be with them in the last moments of their life.

In an editorial on care of extremely small infants in a 1986 issue of *The New England Journal of Medicine,* Gordon Avery advised, "Do not continue with intensive care in the face of accumulating evidence of hopelessness."[107] In blunt words he exhorted his colleagues to "[T]ake a stand." Two decades later Avery's plea to physicians to provide care appropriate to the infant's physical condition continues to be an imperative in neonatology.

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6 Pulmonary Care

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In addition to establishing and maintaining the artificial airway, the clinician must demonstrate a working knowledge of the multiple supportive pulmonary care skills that are essential for optimal care of the intubated and ventilated neonate. This chapter presents the principles and guidelines required for the safe intubation and successful pulmonary care of these critically ill infants. Some of the guidelines addressed will reflect significant changes in cardiopulmonary resuscitation (CPR) of the newborn presented in the revised Neonatal Resuscitation Program (NRP) (see Chapter 4).[1] With the "explosion" of new information available regarding the care of the neonate who requires assisted ventilation, we attempt to focus the discussion in this chapter on pulmonary care. The reader will be referred to other chapters of the book for a more in-depth presentation of specific topics.

All caretakers involved in the management of these babies need to be aware of the safety issues with regard to the transmission of pathogenic organisms by bodily fluids and closely follow the Occupational Safety and Health Administration (OSHA) standards outlined in Appendix 30.

Indications for Intubation

Resuscitation at Delivery

The neonatal resuscitation guidelines published jointly by the American Academy of Pediatrics (AAP) and the American Heart Association provide a comprehensive stepwise algorithm for the assessment and resuscitation of the newborn infant at delivery.[1] Ongoing reassessment of the infant's response as resuscitation proceeds is a major feature of this algorithm. Endotracheal intubation may be warranted at any of several points during resuscitation, and the timing of intubation may be influenced by the skill and experience of the operator as well as the clinical circumstances. Indications for endotracheal intubation during delivery room resuscitation include (1) tracheal suctioning for prevention of meconium aspiration; (2) need for prolonged positive-pressure ventilation; (3) administration of prophylactic surfactant; (4) presence of obstructive upper airway lesions requiring an artificial airway; and (5) cases in which air distention of the gastrointestinal (GI) tract is undesirable, such as with congenital diaphragmatic hernia.

Aspiration of meconium before or during delivery can lead to an aspiration pneumonia, and plugging of airways with particulate meconium may cause air trapping and subsequent pneumothorax. Early uncontrolled trials suggested that immediate endotracheal intubation and tracheal suctioning was warranted for all babies born through meconium-stained amniotic fluid in order to prevent meconium aspiration and its consequences.[2] However, more recent multicenter prospective trials have shown that this approach offers no benefit to infants who are vigorous at birth.[3] A vigorous infant is defined as one who has good respiratory effort, good muscle tone, and a heart rate (HR) of less than 100. Current guidelines suggest that an infant born through meconium-containing amniotic fluid requires immediate endotracheal intubation and suctioning only when the infant is not vigorous at birth.[1] If the infant is intubated to suction meconium from the trachea, a meconium aspirator should be attached to the endotracheal tube to provide appropriate suctioning. If meconium is recovered, intubation and suctioning can be repeated if the infant is not bradycardic; if the infant is bradycardic, positive-pressure ventilation should be provided without further attempts at tracheal suctioning.

Positive-pressure ventilation should be initiated during neonatal resuscitation when the infant is bradycardic (HR less than 100) or apneic despite stimulation or when there is persistent cyanosis despite supplemental oxygen administration.[1] Under these circumstances, positive-pressure ventilation should be initially provided with a resuscitation bag and mask. Intubation for positive-pressure ventilation should be considered if bag and mask ventilation is ineffective or if the need for positive-pressure ventilation continues beyond a few minutes.

Intratracheal surfactant replacement therapy, administered via the endotracheal tube, has been an essential component of the prevention and treatment of respiratory distress syndrome (RDS) in premature infants since the early 1990s (also see Chapter 22). Multiple trials have compared prophylactic surfactant administration, usually given within the first 10 minutes of life in the delivery

room, with later rescue treatment of established RDS in infants at substantial risk for the development of RDS. A meta-analysis of these trials demonstrated that prophylactic surfactant administration leads to significant reductions in the risk of air leak complications and death.[4] These benefits are most pronounced in those infants born at less than 30 weeks of gestation who have not been exposed to antenatal steroids.[5,6] Current recommendations from the AAP Committee on the Fetus and Newborn suggest that prophylactic surfactant be considered for those premature infants at highest risk for RDS.[7] However, use of prophylactic surfactant is quite variable in neonatal units across the country.[8] One reason for this variation in practice is widespread interest in early application of nasal continuous positive airway pressure (CPAP), rather than prophylactic intubation and surfactant treatment, for the prevention and early treatment of RDS (see Chapter 8). Early nasal CPAP may have the potential to reduce the incidence of bronchopulmonary dysplasia without an increase in other morbidities.[9] However, a recently concluded randomized, controlled trial demonstrated that early nasal CPAP, as compared with early intubation, did not significantly reduce the rate of death or bronchopulmonary dysplasia.[10]

Certain anatomic lesions may cause obstruction at the level of the nasopharynx, larynx, and upper trachea and may necessitate endotracheal intubation of affected neonates during initial resuscitation.[11] Beginning at the nasal level, these lesions include bilateral or severe unilateral choanal atresia or stenosis; pharyngeal hypotonia; and micrognathia, such as may be seen in the Robin sequence (which may include cleft palate and glossoptosis). At the level of the larynx, obstructive problems may include laryngomalacia (or laryngotracheomalacia), laryngeal web, bilateral vocal cord paralysis, and congenital subglottic obstruction. In addition, critical airway obstruction may be secondary to other lesions that may compress the airway and impair normal respiration. These may include cystic hygroma, goiter, or hemangioma. Many of these lesions, particularly those causing significant fixed obstruction at the level of the larynx or below, may render endotracheal intubation extremely difficult and may require emergency tracheostomy (see Chapter 25).

Infants born with congenital diaphragmatic hernia frequently require positive-pressure ventilation at delivery because of respiratory distress with cyanosis. Provision of positive-pressure ventilation with bag and mask will drive large amounts of air into the upper GI tract, causing distention of bowel that has herniated into the chest. Such bowel distention will cause further lung compression and compromise respiratory function. For this reason, infants with diaphragmatic hernia should be promptly intubated in the delivery room if resuscitation is required.[1] Some clinicians also advise that these infants should be paralyzed with a muscle relaxant to prevent spontaneous breathing from causing bowel distension. An orogastric tube should also be placed to evacuate any air that does enter the stomach. The diagnosis of diaphragmatic hernia is often confirmed by antenatal ultrasound studies and should be suspected in any infant with a scaphoid abdomen, unilaterally diminished breath sounds, and persistent respiratory distress.

Postnatal Respiratory Failure

Infants in the neonatal intensive care unit may require endotracheal intubation and positive-pressure ventilation because of respiratory failure related to a variety of causes. Two common scenarios that merit particular consideration include preterm infants with worsening respiratory distress syndrome and infants with postextubation respiratory failure.

A variety of competing factors will influence the decision to intubate an infant who has worsening respiratory distress syndrome. The symptoms of untreated RDS will tend to worsen during the first 48 to 72 hours of life, until the infant begins to make significant amounts of endogenous surfactant. Therefore, an infant with moderately severe respiratory insufficiency and distress during the first 24 hours of life may merit intubation and ventilation in anticipation of worsening disease, whereas an infant with comparable disease severity at 3 or 4 days of life may avoid intubation in anticipation of spontaneous improvement. Surfactant treatment of established RDS has been shown to decrease the incidence of air leak complications and death.[12]

Although the optimal timing of surfactant administration for treatment of RDS is controversial, the available data suggest that early treatment is more effective, and this observation may thus lead to earlier intubation. On the other hand, positive-pressure ventilation delivered through an endotracheal tube is well known to cause lung injury, particularly if large tidal volumes are used. Some centers that make extensive use of nasal CPAP to avoid intubation and mechanical ventilation have reported very low rates of chronic lung disease.[9] However, this finding was not duplicated in a recent randomized controlled trial.[10] Different practitioners will weigh these competing factors differently, and the indications for intubation of an infant with RDS will vary depending on the clinical circumstances and local practices.

Postextubation respiratory failure is a common occurrence in preterm infants, occurring in as many as one third of infants. Causes of respiratory failure in these infants include central or obstructive apnea, respiratory insufficiency leading to progressive atelectasis, and early chronic lung disease. Early application of nasal CPAP following extubation has been shown to reduce the need for additional ventilatory support, but it may fail in 25% to 40% of infants.[13,14] Some evidence suggests that nasopharyngeal positive-pressure ventilation may be more effective in preventing postextubation respiratory failure, but this modality is also not universally effective.[15] Other techniques to avoid re-intubation include the use of methylxanthines, use of ventilation through nasal prongs, and frequent postextubation chest physiotherapy.[16] Indications for re-intubation include progressive respiratory acidosis, significant oxygen requirement, or severe apnea.

Routes of Intubation

Intubation can be performed orally or nasally. The choice of route depends on the circumstances and the preference of the clinician. Both oral and nasal endotracheal

intubation have their unique complications and share a few as well.[17-19] Oral intubation is easier, faster, and less traumatic to perform, and it may be preferable in an emergency. Available data have failed to demonstrate statistically significant differences between oral and nasal intubation with respect to tracheal injury, frequency of tube retaping, or tube replacement.[20] However, a higher incidence of postextubation atelectasis has been noted in nasally intubated patients, especially in preterm infants with birth weight less than 1500 g; atelectasis was associated with a marked reduction in nasal airflow through the previously intubated nares and stenosis of the nasal vestibule.[21,22] Midface hypoplasia has been reported to be associated with long-term intubation for bronchopulmonary dysplasia.[23]

On the other hand, proponents of nasal intubation believe that fixation of the tube to the infant's face is easier and more stable because it minimizes the chance for accidental dislodgment and decreases tube movement, which can result in subglottic stenosis. Prolonged oral intubation can result in palatal grooving[24] and defective dentition.[25] Furthermore, there is evidence that acquired subglottic stenosis is increased in patients who were orally intubated and whose birth weight was less than 1500 g. The same study and one other offer evidence that the nasotracheal tube is easier to stabilize than an oral tube and that extubation occurs less frequently than in oral intubation.[19,26] Acquired subglottic stenosis secondary to oral intubation may be a sequela of tracheal mucosal damage from the endotracheal tube itself or from repeated intubations. Most significantly, severe damage can occur from the up-and-down movement of the endotracheal tube.[20] Even with perfect fixation of the tube, up-and-down movement of 7 to 14 mm has been reported owing to the varying degrees of flexion of the neck. The caretaker team can minimize palatal grooving and defective dentition by rotating the fixation site from side to side during periodic retaping. Devices are available commercially that serve as palate protectors for prolonged intubation of very-low-birth-weight infants (Gesco Pla-nate®, MedChem Products, Woburn, Mass). Continuing attention to the quality of fixation, together with stabilization of the infant's head position, minimizes tube shifting and accidental extubation with the oral approach. However, both the oral and nasal techniques will continue to have a place in the care of the ventilated neonate. Problems associated with oral and nasal endotracheal tube use are summarized in Box 6-1.

Box 6-1 PROBLEMS IN NEWBORN INFANTS WITH ORAL AND NASAL ENDOTRACHEAL TUBES

Common Problems
- Postextubation atelectasis—more common with nasal endotracheal tubes
- Pneumonia/sepsis
- Accidental extubation
- Intubation of mainstem bronchus
- Occlusion of tube from thickened secretions
- Tracheal erosion
- Pharyngeal, esophageal, tracheal perforation
- Subglottic stenosis

Problems Unique to Nasal Endotracheal Tubes
- Nasal septal erosion
- Stricture of the nasal vestibule

Problems Unique to Oral Endotracheal Tubes
- Palatal grooving
- Interference with subsequent primary dentition

From Spitzer AR, Fox WW: The use of oral versus nasal endotracheal tubes in newborn infants. J Cal Perinatol Assoc 4:32, 1984.

Equipment

The equipment needed for intubation is listed in Box 6-2, and the guidelines for choosing the correct tube size and suction catheters are listed in Tables 6-1 and 6-2.[1]

The use of tubes of appropriate size minimizes trauma, airway resistance, and excessive leak around the tube. A standard kit containing all of the equipment, as listed in Box 6-2, can be prepared and stocked, but it must be checked regularly to ensure that all of the necessities are present. The infant should be placed under a radiant warmer for endotracheal intubation. A laryngoscope with a Miller no. 0 or no. 1 blade should be used to visualize the vallecula, epiglottis, and glottis. The no. 0 blade is used for almost all newborns. The no. 1 blade is used for infants who are several months old or newborns whose birth weight is greater than 4 to 5 kg.[1,27] A Miller "00" blade has been touted for use in extremely low-birth-weight infants because its smaller blade is more easily accommodated in

Box 6-2 EQUIPMENT NEEDED FOR INTUBATION

- Laryngoscope with premature (Miller no. 0) and infant blades (Miller no. 1); Miller no. 00 optional for extremely premature infant
- Batteries and extra bulbs
- Endotracheal tubes, sizes 2.5, 3.0, 3.5, and 4.0 mm ID
- Stylet
- Suction apparatus (wall)
- Suction catheters: 5.0, 6.0, 8.0, and 10.0 French
- Meconium aspirator
- Oral airway
- Stethoscope
- Non–self-inflating bag (0.5 L), manometer, and tubing; self-inflating bag with reservoir, manometer optional for self-inflating bag
- Newborn and premature mask
- Source of compressed air/O_2 with capability for blending
- Humidification and warming apparatus for air/O_2
- Tape: ½-inch pink (Hytape)
- Scissors
- Magill neonatal forceps
- Elastoplast (elastic bandages)
- Cardiorespiratory monitor
- Carbon dioxide monitor or detector
- Pulse oximeter (SpO_2)

TABLE 6-1 Selecting the Appropriate-Size Endotracheal Tube

Tube Size (inside diameter in mm)	Weight (g)	Gestational Age (wk)
2.5	<1000	<28
3.0	1000-2000	28-34
3.5	2000-3000	34-38
3.5-4.0	>3000	>38

From Kattwinkel J (ed): Neonatal Resuscitation Textbook, 5th ed. Elk Grove Village, Ill., American Academy of Pediatrics and the American Heart Association, 2006. Used with permission of the American Academy of Pediatrics.

TABLE 6-2 Selecting the Appropriate-Size Suction Catheter

Endotracheal Tube Size (mm)	Catheter Size (French)
2.5	5 or 6
3.0	6 or 8
3.5	8
4.0	8 or 10

From Kattwinkel J (ed): Neonatal Resuscitation Textbook, 5th ed. Elk Grove Village, Ill., American Academy of Pediatrics and the American Heart Association, 2006. Used with permission of the American Academy of Pediatrics.

the mouths of micropreemies. However, because the light source is set back farther from the blade tip, some clinicians believe the visualization is not as good as with the "0" blade.

In cases where the baby requires bag-and-mask ventilation prior to intubation, a ventilation bag with a manometer and the appropriate-sized mask should be used. The mask should be clear and have a soft, form-fitting cushion that extends around the circumference. The alternative is the rigid but anatomically shaped Rendell-Baker/Soucek mask, which may have less dead space but has been demonstrated to be more difficult to use, often resulting in ineffective ventilation.[28]

Two different types of resuscitation bags or manual resuscitators are available to provide assisted ventilation via mask or endotracheal tube: the self-inflating bag and the non–self-inflating or "anesthesia" bag.[1] The non–self-inflating bag is also commonly referred to as a flow-inflating bag.[1] Both come in a wide variety of configurations, but all configurations share some basic attributes, including an oxygen inlet, patient outlet, flow-control valve, and pressure manometer attachment site. The self-inflating bag, as the name implies, reinflates after squeezing and does not require the flow of oxygen to reinflate. However, this bag with an oxygen source can deliver only about 40% oxygen because as the bag reinflates, room air is drawn into the bag and mixes with 100% oxygen from the oxygen source. A reservoir will not allow room air to come into the bag; therefore, the self-inflating bag attached to an oxygen source with a reservoir is able to deliver 90% to 100% oxygen to the baby.

Two other important characteristics of most self-inflating bags are a "popoff valve," which is "set" at 30 to 40 mm Hg, and a non-rebreathing valve, which is built into the bag and prevents the reliable delivery of free-flow oxygen.[29] In order to deliver free-flow oxygen, the operator needs to disconnect the oxygen tubing from the bag and hold the oxygen tubing close to the nose of the baby. In contrast, the non–self-inflating bag is an excellent source of free-flow oxygen, especially with the use of the appropriate-sized mask attached to the bag. Finally, both of these bags require a pressure manometer in order to provide safe and effective ventilation to the newborn.[29] Table 6-3 compares the two ventilation bags (or manual resuscitators).

TABLE 6-3 Neonatal Manual Resuscitators

	Self-Inflating Bag	Non–Self-Inflating Bag
Types	Laerdal, Hope II, PMR II, and a host of disposable equivalents	"Anesthesia bag" with spring-loaded or variable-orifice bleed port
Operator	Requires education on bag characteristics	Requires both experience and knowledge of bag characteristics for adjustment of flow and bleed
Oxygen-air source positive F_{IO_2} delivery	Operates with room air	Requires compressed gas
	Efficacy of O_2 delivery dependent on correct use of closed reservoir system and closure of popoff valve (use of open reservoir or popoff valve reduces F_{IO_2})	Delivers F_{IO_2} of gas source unambiguously
	Many brands deliver room air on spontaneous breaths (in-house verification of brand performance is recommended)	Oxygen delivery same on spontaneous breaths as it is on mandatory breaths
Pressure delivery	Having excessive trust in popoff feature is unwise; occlusion of popoff valve and use of manometer allow performance equal to that of non–self-inflating bags	With manometer attached, any pressure can be easily given
Comments	Relatively complex mechanism with possibility of failure, particularly when reusable units are reassembled	Simple, reliable mechanism dependent on gas supply
	If popoff pressure is adequate, allows removal of bulky manometer for transport	Manometer is bulky

Types of Tubes

The endotracheal tube should be made of a nontoxic, thermolabile, nonkinking material that molds to the airway. The tube should meet the standards of the American Society for Testing and Materials F1242-89 and be radiopaque or have a radiopaque line. Cuffed endotracheal tubes are not routinely used in neonates because the bulk of the cuff may prevent the practitioner from inserting as large a diameter tube as would otherwise be possible. There is always a serious concern that the inflated cuff may damage the very sensitive airway mucosa of the small baby. If sealing the space around the tube becomes a priority, cuffed tubes are now available (Sheridan, Inc., Argyle, NY, USA).

The type of endotracheal tube used most commonly is the Murphy endotracheal tube (Fig. 6-1). The Murphy tube is preferred for long-term ventilation. Most often, Murphy tubes have centimeter markers to show the overall depth of the tube, as well as vocal cord guide markers near the tip. These markers, under laryngoscopic visualization, show the clinician the depth within the trachea. Standard default markers should be used with caution because of the range of anatomic variation. In one review of the length of the black area at the tip of endotracheal tubes produced by four major manufacturers, the marker length varied by 10 mm in 2.5-mm internal-diameter tubes.[30]

A Murphy tube has a tip bevel that allows smooth passage through the nares and a side hole whose purpose is to allow ventilation even if the tip is partially obstructed or is placed in the right mainstem bronchus. Some clinicians avoid using side-hole ("Murphy eye") tubes for prolonged ventilation because of anecdotal evidence that these tubes can abrade the trachea and cause scarring. Exclusive use of these endotracheal tubes in one institution was associated with an increased incidence of subglottic stenosis that ended when use of the tubes was discontinued. It can be adequately maintained in the correct position if the lip marker is placed on the tube at the lip level and it is fixed to the face. After proper placement is determined, the marker can be used as a reference to ensure that the tube's position remains constant. The Murphy tube is pliable (and becomes even less firm when it is allowed to remain under a radiant warmer while preparations are made for resuscitation). Many clinicians prefer to use an obturator or stylet to facilitate insertion. The stylet should not extend beyond the distal tip of the tube to avoid tracheal damage from the insertion process.

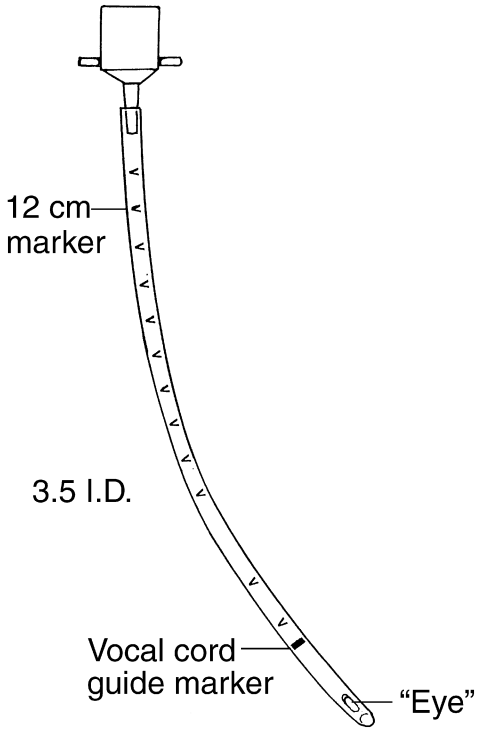

Figure 6-1 ■ Murphy-type endotracheal tube. The Murphy type is straight and relatively soft, with markings to show depth of insertion in the airway and in the trachea. An "eye" is present at the tip.

The vicious cycle of asphyxia is frequently in progress in the critically ill neonate who requires emergent tracheal intubation. The process of intubation in such an infant can exacerbate the difficulties that he or she is already experiencing. Intubation is associated with severe bradycardia, hypoxia, and elevation of arterial blood pressure and intracranial pressure.[31]

Techniques

There are a number of methods for performing endotracheal intubation in newborns, but the technique outlined in the NRP textbook should be considered the technique of choice[1] and "a common sense approach."[32] The steps are as follows, with other acceptable techniques included in parentheses:

- Stabilize the baby's head in the "sniffing position." A shoulder roll placed under the shoulders can help maintain the baby's head in the correct position.
- Deliver free-flow oxygen during the procedure and suction the mouth and pharynx before sliding the blade into the mouth.
- Slide the laryngoscope over the right side of the tongue, pushing the tongue to the left side of the mouth, and advance the blade until the tip lies just beyond the base of the tongue.
- Lift the blade up slightly; raise the entire blade, not just the tip. The blade should be placed in the vallecula and, as the blade is raised, the epiglottis and the glottis with the vocal cords should be visualized. (Some clinicians slide the blade and raise the epiglottis to visualize the vocal cords.)
- Look for anatomic landmarks; suction as necessary for visualization.
- If the vocal cords are closed, wait for them to open. Insert the tip of the tube from the right side of the mouth until the vocal cord guide is at the level of the vocal cords. Avoid placing the tube into the blade groove during the insertion because that will block the vision of the glottis and vocal cords.
- Hold the tube firmly against the baby's hard palate while removing the laryngoscope once the tube has been placed. Hold the tube while removing the stylet as well.

The NRP textbook states that the procedure should be completed in 20 seconds,[1] but timed video recording of trained teams have shown the procedure may take 30 to 40 seconds even with skilled practitioners. This time allotment does not include setting up all of the equipment and getting the team together to help with the resuscitation.[1] Heart rate and pulse oximetry should be monitored during the intubation procedure and the infant ventilated with bag and mask prior to starting and between attempts. Recovery should be allowed between intubation attempts as indicated by improving vital signs and pulse oximetry. The practitioner can improve O_2 tension during intubation by taping a suction catheter connected to a low-flow O_2 source along the laryngoscope blade.[33] Other investigators have maintained a flow of O_2 (3 to 5 L/min) through the endotracheal tube during intubation in an attempt to prevent drastic changes in oxygenation. At least two laryngoscopes have been designed with an O_2 port alongside the blade.[34]

There is a developing consensus that premedications should be used with nonemergent intubations to minimize pain, reduce bradycardia, and prevent increases in intracranial pressure. Medications such as atropine, succinylcholine, pancuronium bromide, and analgesics have been recommended although there is no standard formula. In some respects, atropine could be helpful in decreasing the volume of secretions and blocking a bradycardia secondary to a vagal response, a muscle relaxant might be helpful in decreasing movement of the baby, and analgesics can be safely used to reduce the discomfort of the procedure.

Nasotracheal Intubation

Nasotracheal intubation may be more time consuming and technically more difficult than orotracheal intubation for the less experienced practitioner. A nasotracheal tube is inserted into one of the nares and guided into the posterior pharynx along the floor of the nose. A laryngoscope is placed into the mouth and the glottis is visualized. A Magill forceps is held in the right hand and introduced into the mouth along the right side of the laryngoscope blade. The nasotracheal tube is grasped a short distance from its tip with the forceps. The tip of the tube is elevated until it is at the level of the glottis and is advanced between the vocal cords and into the trachea. An assistant may be needed to grasp the exterior (or distal) end of the endotracheal tube and assist with its advancement. Care should be exercised in using the Magill forceps so that the soft tissues of the oropharynx are not damaged. Experienced operators may successfully accomplish nasotracheal intubation without the Magill forceps. In addition, cooling a Murphy tube with a predetermined bend prior to intubation may facilitate the procedure.

Digital Intubation

Direct digital intubation of the trachea is considered to be an alternative method, which is performed using the index finger as a guide and using no laryngoscope or visualization.[35] The technique is well described by Hancock and Peterson[35] and is summarized as follows (Fig. 6-2):

- The operator may stand on either side or at the foot of the child; gloves are recommended.

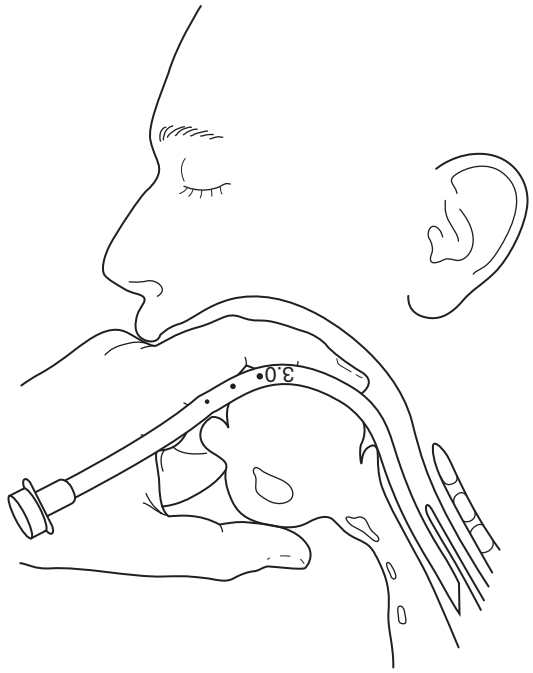

Figure 6-2 ■ Finger intubation technique. (From Hancock PJ, Peterson G: Finger intubation of the trachea in newborns. Pediatrics 89:325-327, 1992.)

- Moisten the tube and the gloved finger with sterile water to facilitate the procedure; (a slight crook in the end of the tube may be helpful; use of a stylet may also be helpful, at least until the operator becomes familiar with the procedure).
- The index finger of the nondominant hand slides along the tongue until the finger tip passes the epiglottis and identifies the aryepiglottic folds at the opening of the trachea.
- Slight cricoid pressure may be applied using the thumb of this hand.
- The endotracheal tube is then advanced with the thumb and index finger of the dominant hand holding the tube like a pencil and using the index finger of the dominant hand as a guide.
- The endotracheal tube is passed into the trachea and advanced the appropriate distance; a slight tightening about the tube is felt and placement is confirmed by feeling the secure position and by palpation of the trachea and tube.
- The tube is then secured if intended to be left in place.

Depth of Tube Insertion

In addition to direct visualization of the tube as it passes through the glottis, there are a number of different suggested "rules of thumb" for initial estimation of proper depth of tracheal tube placement. These rules use the centimeter markings on the side of a standard Murphy tube to gauge the depth of placement. The most common rule uses birth weight and a simple formula, the rule of 7-8-9. An endotracheal tube is advanced 7 cm to the lip for a 1-kg infant, 8 cm for a 2-kg infant, and 9 cm for a 3-kg infant. The rule of 7-8-9 is not appropriate for infants

with hypoplastic mandibles (e.g., those with Pierre Robin syndrome) or short necks (e.g., those with Turner syndrome).[36] Similarly, nasotracheal tube insertion can be governed by adding 1 cm to the 7-8-9 rule.

Determination of Placement

Placement of the endotracheal tube after intubation is determined first clinically and then by chest radiograph. Clinical determination includes the following:

- Improvement or maintenance of heart rate in the normal range
- Good color, pulses, and perfusion after the intubation
- Good bilateral chest wall movement with each breath
- Equal breath sounds heard over both lung fields
- Breath sounds heard much louder over the lung fields than are heard over the stomach
- No gastric distention with ventilation
- Presence of vapor in the tube during exhalation
- Direct visualization by laryngoscope of the tube passing between the vocal cords
- Presence of exhaled CO_2 as determined by a CO_2 detector and/or an end-tidal CO_2 monitor or capnography[37]
- Tip to lip measurement: Add 6 to the newborn's weight in kilograms (rule of "7-8-9")

The chest radiograph should be performed to demonstrate that the tube is in the mid trachea. Tube position can change during the x-ray procedure if the infant's neck is in a flexed or extended position. Endotracheal tube position can be confirmed on x-ray by following both of the mainstem bronchi back to the carina and cephalad to the tip of the tube.[1] Occasionally a lateral radiograph is necessary to confirm placement in the trachea.

Tube Fixation

Secure fixation of the endotracheal tube is important, not only to prevent accidental extubation but also to minimize tube movement during ventilation and other interventions such as suctioning or chest physiotherapy (CPT). Accidental extubation and repeated intubations have been demonstrated to be associated with the development of subglottic stenosis, as well as increased mortality.[17,18] The likelihood of accidental extubation also has been found to be associated with younger gestational age, higher level of consciousness, higher volume of secretions, and slippage of the tube.[18] It also is clear that there is no consensus as to which tube fixation method is most effective. The technique shown in Figure 6-3 represents a modification of the method originally described by Gregory[38] and is similar to what is used at the authors' institutions. The exception is that tincture of benzoin is no longer used, especially in "micropreemies." Also, some of these techniques can be used to secure nasotracheal tubes (Fig. 6-4) without the use of tincture of benzoin. Several devices for fixation of neonatal endotracheal tubes are available from various manufacturers. (See also discussion in Chapter 7.)

Acquisition and Maintenance of Intubation Skills

Intubation of the trachea is a complex psychomotor skill taught to a variety of health care professionals. Although

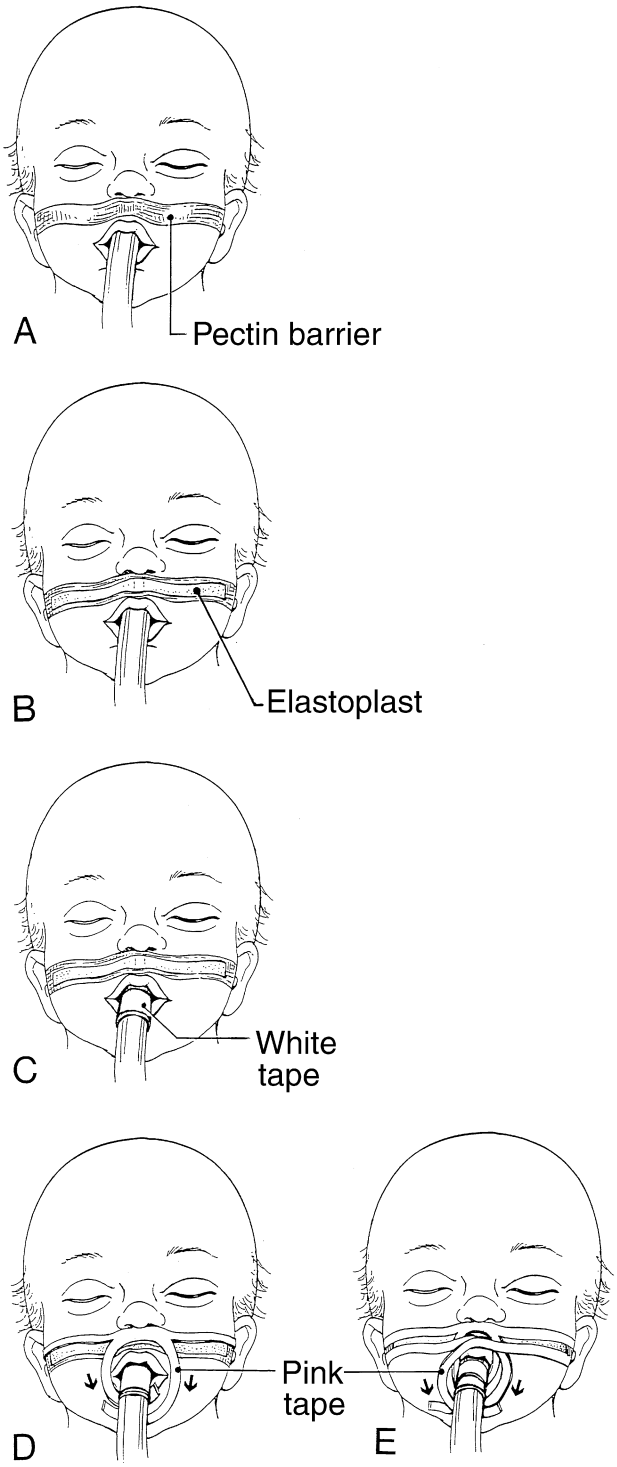

Figure 6-3 ■ Technique for securing an endotracheal tube. **A,** Pectin barrier is applied to the infant's face from ear to ear and over the upper lip. **B,** A ¼-inch width of an elastic bandage (Elastoplast) is applied over the pectin barrier. **C,** A short strip of cloth tape or elastic bandage is wrapped around the tracheal tube to mark its point of passage at the mouth. The centimeter marking under the tape should be charted. **D,** Pink tape cut in the shape of an H is applied over the elastic bandage, with its ends extending beyond the bandage. The lower arms of the H are then wrapped around the tube. **E,** Single, ¼-inch strips of pink tape are secured over the lower part of the elastic bandage and wrapped around the tube. As an alternative to using an H-shaped piece of tape, the entire taping procedure can be done with a series of single strips of tape.

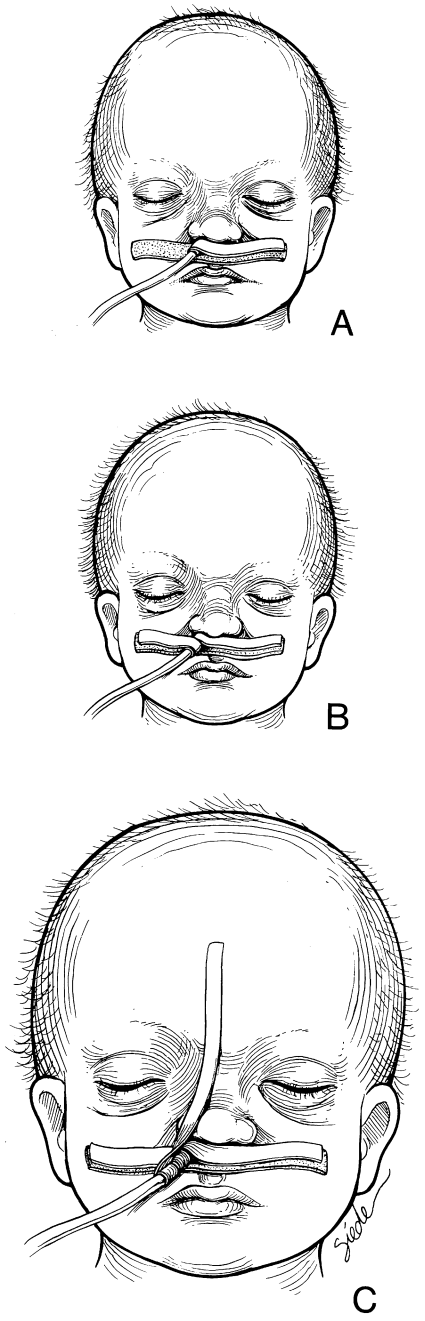

Figure 6-4 ■ Technique for securing a nasotracheal tube. **A,** A ¼-inch strip of elastic bandage is applied over the upper lip, and a ¼-inch strip of Hytape (pink) is applied from the right side of the face and around the tube. **B,** A second piece of tape is applied from the left side of the face and around the tube. **C,** A third piece of tape is applied down the bridge of the nose and around the tube.

ventilation can be accomplished successfully using a bag and mask, there are many instances when neonatal tracheal intubation is required. The challenge is maintaining a high skill level for a procedure that may be performed only sporadically by individual providers.

Depending on the clinical setting, intubation skill may be required of attending physicians, residents, nurses, respiratory therapists, and paramedics. Institutional or departmental policies may require or expect that certain individuals be proficient at intubation yet may be unable to provide opportunities to maintain proficiency. The challenge is that, without regular practice, individual intubation skill level decreases over time[39] and the complications from an unskilled intubation may be severe.[40,41]

Initial training in intubation often occurs in a Clinical Skills Lab using plastic manikins made specifically for the purpose of intubation. This is typically the first exposure to the skill of intubation for medical students as well as for other disciplines. Courses such as the Neonatal Resuscitation Program and the Pediatric Advanced Life Support course include intubation education, practice, and testing on a manikin. The fact that students are "tested" on their ability to intubate a plastic manikin airway model may lead some to think that they are now "proficient." It is important to emphasize that such courses provide only limited exposure to the intubation skill and that the ability to intubate a plastic manikin does not immediately translate to the bedside. However, recent improvements in the manikin, especially the anatomy and "feel" of the airway, make this simulation experience more readily transferrable to actual clinical situations.

Studies have shown that, over time, cognitive knowledge remains but the actual hands-on skill level declines[42] and that ongoing review and proctored skills practice is needed to maintain a level of proficiency.[43] A 10-year study of neonatal intubations performed by pediatric residents at one institution showed that median success rates varied from 33% for PL 1 residents to 40% for PL 2 and PL 3 residents. Success rates for residents with greater than 20 intubation attempts was 49%, whereas those residents with less than 20 attempts had a 37% success rate.[44] These same pediatric residents may go on to take positions where they are expected to and need to have intubation proficiency, yet the study showed that they did not have the opportunity during their training to achieve a high level of success at the procedure. Another study found that, although pediatric residents stated that they felt confident with neonatal intubation skills, objective findings showed that they did not meet the study-specified definition of technical competence.[45]

Neonatal and Pediatric Transport Teams typically use a combination of registered nurses, respiratory therapists, paramedics, and physicians, and there are many teams that run primarily as nurse-therapist or nurse-paramedic. Because team members are expected to perform advanced level skills, team training generally includes skills such as intubation, umbilical line, and needle aspiration/chest tube insertion. In addition to a didactic and skills practice orientation, transport team members should attend regular update and competency sessions. In the book *Risk Management Techniques in Perinatal and Neonatal Practice,* the authors state that team members need an adequate number of transports to maintain skills and, if the number of transports is low, there must be other mechanisms to simulate transport team function.[46]

Over the last 25 years there have been many changes related to the indications for intubation of the neonate. Historically, all newly born infants with meconium staining of the amniotic fluid require intubation and suctioning. The latest Neonatal Resuscitation Program recommendations call for intubating only those infants

with meconium staining who are not vigorous. Newer oxygen delivery methods, such as high-flow nasal cannula and nasal CPAP, allow more infants to be cared for without the need for intubation. Ready availability of High-Risk Perinatal Units and Neonatal Intensive Care Units ensures that more critically ill neonates are born at a center with high-level skills. All of these advances are good for the neonate, but they have resulted in a decreased number of intubations available for pediatric residents and other practitioners. When a neonate (or any other patient) needs an airway emergently, competence is important.

Health care educators need to be creative in providing the initial intubation education and also in monitoring and facilitating the continuing education of those individuals expected to respond to a neonatal emergency. A blended learning approach can integrate online learning with supervised manikin practice. Although expensive, animal intubations (usually cats) can provide an excellent practice model, but must be done adhering to the NIH Office of Animal Care and Use (OACU) guidelines. The airline industry has long been using simulators for initial training and for continuing education and competency evaluation. The simulator manikin set-up is expensive but provides an excellent learning model that functions in real time. Patient simulations are generally enjoyed by students (generic and professional) and are perceived by the students to be of benefit.[47,48] The newest neonatal simulator manikins, although expensive, provide an excellent resource for this training.

Looking to the future, educators should consider the use of virtual reality simulation. Virtual reality simulators are available to teach trauma assessment and skills and also diagnostic bronchoscopy. In one study the virtual reality bronchoscopy simulator was used to train new students in doing a diagnostic bronchoscopy. With minimal time practicing on the simulator, the new students were able to attain a level of proficiency similar to that of more experienced bronchoscopists.[49] Virtual reality simulation can be used for initial education and practice and at regular intervals to reinforce skills.

Alternatives to Endotracheal Intubation: Use of the Laryngeal Mask Airway

The laryngeal mask airway (LMA) has been available for a number of years as an alternative to endotracheal intubation in babies, infants, children, and adults.[1] It is mentioned but not recommended for routine use in the new NRP textbook,[1] and a variety of papers discuss its use in various clinical scenarios, including the following:

- In neonatal resuscitation of term and larger preterm infants (size 1 LMA) (see Fig. 4-9)
- In the difficult airway, such as in the Robin sequence, and other situations when micrognathia is profound
- As an aid to endotracheal intubation
- As an aid in flexible endoscopy
- In surgical cases in place of endotracheal intubation[50-53]

The success rate of insertion of the LMA has been reported to be greater than 90% in a number of descriptive studies of small series of infants and children[54] (see Chapter 4 for further discussion of LMA use).

Humidified High-Flow Nasal Cannula

Avoiding ventilator-induced lung injury is a common goal of neonatal intensive care and has led to considerable interest in less invasive means of providing effective respiratory support. Neonates who might require respiratory support short of intubation and mechanical ventilation include those with apnea of prematurity, mild to moderate respiratory distress syndrome, and atelectasis caused by respiratory insufficiency, as well as recently extubated infants at risk for postextubation respiratory failure. Nasal CPAP has traditionally been a widely used support modality in these infants. It has the advantage of being well studied and is known to improve pulmonary mechanics and to stabilize the upper airway.[55] However, nasal CPAP devices are bulky, may cause nasal trauma, and can be difficult to properly maintain in position.

Recently, humidified high-flow nasal cannula (HHFNC) devices have come into widespread use in neonatal intensive care units. These devices differ from traditional nasal cannula therapy in that the gas flow to the patient is warmed and humidified up to the point of patient contact, allowing the use of higher gas flows without causing nasal drying, mucosal trauma, and patient cooling. Gas flow rates used in neonatal HHFNC therapy may range between 2 and 8 L/min. The higher gas flows that can be attained with HHFNC have led many to view this therapy as a viable alternative to nasal CPAP that is less bulky and easier to maintain.

The level and consistency of CPAP that can be attained with HHFNC has been examined in several small case series reports, with variable results.[56-59] There is general agreement that HHFNC can produce a clinically significant level of CPAP, particularly at higher flow rates. However, several variables appear to play an important role in determining the level of CPAP attained, including patient size,[56] cannula diameter,[60] and whether the mouth is open or closed.[56] In some instances, particularly when the nasal cannula completely occludes the nares, dangerously high levels of CPAP may be produced.[60] It should be noted that unlike nasal CPAP devices, HHFNC devices at this time do not incorporate a safety popoff valve in their design, raising the possibility that very high pressures could be transmitted to the lungs. Until better safety and efficacy data are available, HHFNC should be used with caution and not be viewed as a substitute for nasal CPAP devices.

The indications for HHFNC use in neonates are not well defined at present, and the manufacturers of the devices used in HHFNC therapy do not make any specific recommendations about clinical applications.[61] When used in newly extubated infants to prevent extubation failure, a single-center study using historical controls found that HHFNC was as effective as nasal CPAP.[62] A small randomized crossover trial found that HHFNC was more effective than "standard" high-flow cannula therapy in preventing extubation failure.[63] When used as a primary mode of respiratory support, HHFNC has been shown in a retrospective study to be more effective than nasal CPAP in preventing intubation for respiratory failure.[64] In all of these studies, HHFNC appeared to be well tolerated.

However, the variability of the patient populations in these studies, the small numbers of patients studied, and the absence of any large-scale, randomized, controlled trials do not allow delineation of a clear role for HHFNC at this time.

Safety concerns related to HHFNC use mainly relate to the level of CPAP generated and the potential for barotrauma, as discussed above, and to infectious risks. Reports of infections caused by *Ralstonia* sp. associated with the Vapotherm® HHFNC device led to the recall of that device from the marketplace in January 2006.[61] That device has since been returned to the marketplace, with new instructions for its use designed to minimize the possibility of infection. However, this incident highlights the potential for waterborne infections originating in the humidification apparatus of HHFNC devices, and close surveillance of infection rates associated with these devices seems prudent until more data is available.

Monitoring During Conventional and High-Frequency Ventilation

Electrocardiography, respiratory impedance tracings, and serial arterial and/or capillary blood gases have been the traditional mainstays of bedside monitoring of the newborn, and they still have an important role. In general, the emphasis on noninvasive monitoring has resulted in the development and availability of new technologies that allow close monitoring without invasive procedures. The following is a list of those instruments:

- Transcutaneous monitoring of P_{O_2} and P_{CO_2}
- Pulse oximetry to provide continuous measurement of hemoglobin saturation with O_2
- End-tidal CO_2 monitoring

See Chapters 7 and 17 for a more in-depth discussion of these noninvasive monitoring techniques.

For infants on high-frequency ventilation (HFV), pulmonary care involves new technology and keen observation.[65,66] These critically ill babies require a definite team approach, including an experienced respiratory therapist and nurse, and the traditional tools, including cardiorespiratory monitoring, intermittent arterial blood gases (from an arterial line), and "wiggle" assessment. A sample of a protocol used in the Infant Special Care Unit at our institution includes the following:

Assessments every 1 hour:

- Vital signs from monitors, including heart rate, arterial blood pressure, body temperature
- Vibration (or wiggle) assessment (scale +1 to +3)
- Capillary refill
- Comfort level

Assessments every 4 hours—"Hands-on assessment":

- Auscultation of breath sounds on oscillator
- Palpation of pulses
- Nasogastric tube placement can be assessed without having to take the baby off of the ventilator

Assessments every 8 hours—Ventilator is turned off but the patient remains on the circuit or back-up rate (high-frequency jet ventilation [HFJV]):

- Heart rate, position of point of maximum intensity (PMI) of heart, presence or absence of a heart murmur
- Bowel sounds
- Other assessments:
  - Arterial blood gases after initiation of HFV: hourly for 6 hours, every 2 hours for 6 hours, every 4 hours and as needed thereafter
  - Chest radiograph schedule: just prior to being placed on HFV, within 1 hour after initiation of HFV, every 12 hours twice, then daily and as needed
  - Continuous monitoring of oxygen saturation using the pulse oximeter

Airway Management After Artificial Airway Placement

The keys to optimal management of the airway after placement of an endotracheal tube include knowledge of the potential problems, close monitoring of clinical parameters, thoughtful use of the technology listed previously, and intervention if problems arise. This level of care is the responsibility of all members of the team caring for each baby.

Humidification and Warming

The endotracheal tube bypasses the normal humidifying, filtering, and warming systems of the upper airway; therefore, heat and humidity must be provided to prevent hypothermia, inspissation of airway secretions, and necrosis of airway mucosa. Filtration of dry gases before humidification also is needed because of the contamination sometimes found in medical gas lines. A heated water humidifier is necessary to ensure that inspired gases are delivered at or near body temperature (37° C) and that they achieve near-total saturation with water vapor. A minimum dead space hygroscopic condenser (Hudson/RCI, Temecula, Calif, USA) should be considered for use during transport or short-term ventilation. In the past, nebulizers were used in some applications, particularly in oxygen administration by head hood after extubation. Use of this system has been discarded because of impairment in oxygenation and the possibility of water intoxication caused by excess delivery of particulate water droplets and the presence of excessive noise. Sterile distilled water rather than saline is used in continuous therapy.

It should be noted that water packaged "for irrigation" exceeds standards established for water packaged "for respiratory therapy" and costs less.

A modern servocontrolled heated humidifier, with its high and low temperature alarms and heated wires that prevent accumulation of condensation, should provide adequate humidification with proper operation. O'Hagan et al.[67,68] observed wide variation in the delivery of relative humidity, even when the temperature was maintained above 34.7° C; this variation resulted in failure to meet the American National Standards Institute guidelines for humidifier performance.[69] This may account for the findings of O'Hagan et al.,[68] who observed a significant increase in morbidity when temperatures below 36.5° C were maintained at the airway. These studies have led to the recommendation that relative humidity, as well as temperature, be monitored continuously. Miyao et al.[70] suggest

that even maintenance of the Institute's standards (70% humidity at 37° C) may be inadequate, particularly if heated wire circuits are used. Use of circuits with heated wires was adopted primarily because of the frequency with which condensation needed to be drained and because of infection control considerations. The heated wire circuits were intended to enable the clinician to heat the gas inside the circuit to a temperature above that at which it left the humidifier, ensuring adequate absolute humidity without condensation in the circuit. This feature, which results in delivery of a hot gas with a lower relative humidity, may have caused the problems noted earlier.[70]

The increased temperature of a gas shifts the isothermal boundary (the point at which the gas completes equilibrium to body temperature and humidity levels) to a point closer to the airway opening. At first glance, this seems beneficial because less mucosa is exposed to the humidity deficit of the gas. However, because the effect of a given humidity deficit is concentrated on a smaller area of the mucosa, there is the potential for a greater degree of damage. Moreover, use of higher airway temperatures means that, even with lower humidity, there is relatively less opportunity for humidified air from within the lung to recondense some of its humidity upon exhalation. The result is an increase in the humidity deficit (the difference in total water content of inspired gas and the water content it achieves within the lung). The potential for adverse effects with use of the heated wire circuit is exacerbated by inadequate monitoring of humidity levels. If the wire is so hot that the circuit is dry, it is not known whether the relative humidity is 70% (the nominally acceptable American National Standards Institute value) or less.[68]

Traditionally, probes for monitoring inspired gas have been placed as close as possible to the patient connection so that the effect of the trip down the inspiratory line on the inspired gas can be monitored. Unfortunately, in some neonatal circumstances, the probe is continuously in the presence of a heated field and may register the effect of this heat by radiation and/or convection, totally apart from the effect of the inspired gas. If this temperature is sensed by a servocontroller, the humidifier and the heated wires may automatically heat less because the temperature is actually being controlled by another heat source (Fig. 6-5). An extension adapter, which is provided by most manufacturers, allows the probe to be placed outside of the heating field, thus remedying this problem. This extension does not need to incorporate heated wires because the gas temperature is maintained by the heated field on entry.

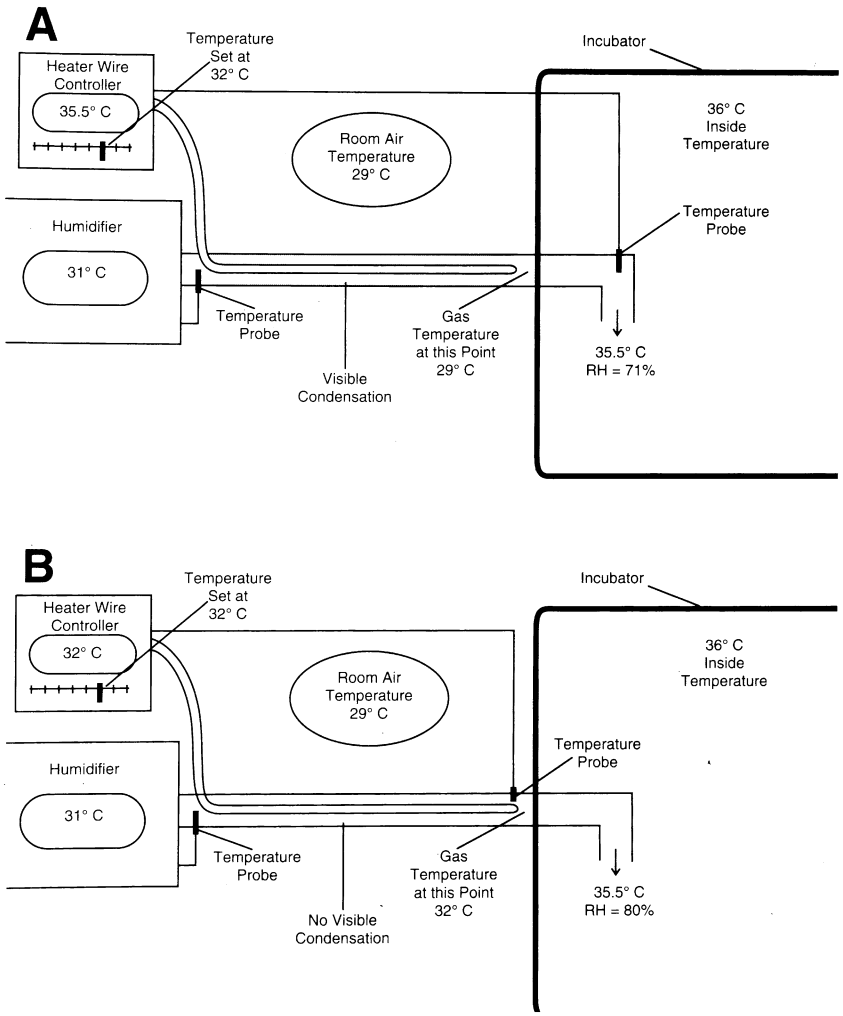

Figure 6-5 ■ **A**, Temperature probe located inside a heated field tends to indicate a heat representative of the heated field rather than of the inspiratory gas before entry into the field. The humidifier does not provide the heat that is being detected by the wire controller. The heat source is particularly difficult to assess because most heated wire circuits operate with humidifiers that do not provide a display of the temperature of the gas immediately after it leaves the humidifier. **B**, Proper placement of the probe. If the probe is only slightly outside a radiant warmer field, it may need to be shielded, particularly if phototherapy is in use. (From Chatburn RL: Principles and practice of neonatal and pediatric mechanical ventilation. Respir Care 36:560, 1991.)

An additional set of problems associated with heated wire circuits has been reported by the Emergency Care Research Institute (ECRI)[69] and the US Food and Drug Administration (FDA; see Appendix 31). Generic circuits that are not always compatible with the humidifier and its power source have been manufactured, leading to melting or charring of circuit components. Use of such circuits must be preceded by careful compatibility testing. In addition, the ECRI emphasizes that the circuits must never be covered by bed linens or drapes and that they must never be activated in the absence of flow through the system; otherwise, melting or charring may result. If a nonheated wire system is used, the temperature must be monitored by a thermometer placed inline to ensure proper temperature ranges. Use of inline water traps is recommended for decreasing the resistance to flow caused by condensate and for ensuring stability of oxygen concentrations. Despite all of the hazards and limitations of the current generation of heated wire circuits, their use has become widespread in most neonatal intensive care units. The clinician should adopt the following precautions specified by the ECRI and the FDA (in addition to the previously mentioned standards):

1. Temperature monitoring must take place before gas enters the heated field.
2. Temperature must be maintained at 36° to 37° C.
3. At least some visible condensation must be present on the inspiratory limb, despite previous beliefs to the contrary.

Bronchopulmonary Hygiene

The clinician must keep the chest clear of secretions in the conducting airways, and he or she must keep the artificial airway patent by ensuring proper humidification and suctioning of the endotracheal tube. These procedures may be done as needed but normally are performed routinely on a schedule, followed by administration of aerosolized medications.[71] The frequency of suctioning should depend on the patient's need, because this and other methods of bronchopulmonary hygiene may have detrimental side effects, especially in the very-low-birth-weight infant.

CPT involving postural drainage in concert with percussion or vibration has been shown to be beneficial in removing secretions and preventing atelectasis in recently extubated neonates.[72] It also has been shown to result in removal of more secretions from intubated neonates.[73] Furthermore, oxygenation has been shown to be enhanced after completion of CPT.[72] The benefit of this procedure may lie in the periodic redistribution of the gravity-dependent regions of the lung, rather than in the physical removal of secretions. On the other hand, CPT has not gained universal acceptance. Its use should be individualized in each baby because as noted earlier, use of these techniques has been associated with a variety of negative effects, especially in infants born weighing less than 1000 g. This group of extremely low-birth-weight infants frequently is on a minimal stimulation plan of care for the first 3 to 5 days of extrauterine life, thus minimizing any pulmonary care interventions.[74] The paucity of airway secretions in this group of infants during this time has led some clinicians to suction only on an "as needed" basis or not at all.

Positioning of the Patient

Postural drainage involves the use of various positions in which the different mainstem bronchi are positioned vertically so that drainage from the smaller bronchi moves into the larger bronchi (Figs. 6-6 to 6-13). The two forces at work during this procedure are gravity and airflow. Any area of the bronchial tree that is to be drained (with the exception of the medial basal segment) must be uppermost.[75] These positions may not be practical for implementation in critically ill babies who have chest tubes or endotracheal tubes, who have undergone surgery, or who are at great risk for intraventricular hemorrhage. Optimally, the infant should be monitored during CPT; potential monitors include transcutaneous O_2 or CO_2, or pulse oximeter. Significant oxygen desaturation during the procedure should cause the caretaker to pause and initiate measures necessary to correct hypoxemia.

Percussion and Vibration

Two types of hand pressure can be applied to the neonatal chest to expedite adequate drainage: percussion and vibration. Percussion in the neonate can be performed with small plastic cups with padded rims or with soft circular masks with their adapters plugged so that the air pockets are maintained. The chest is percussed over the area to be drained for 1 to 2 minutes. Percussion may be reserved for infants who weigh more than 1500 g and are older than 2 weeks of age because of the potential risk for intraventricular hemorrhage.

The traditional view of vibration is that it is effective only during exhalation because it causes secretions to move from the periphery of the lungs with the outflow of air. This technique requires careful observation of chest movements. For vibration, the wrist is extended and the arm muscles are contracted in a manner similar to that used for isometric exercises. The result can be described as a controlled quiver. The placement of fingers flat against chest walls of infants suffices. A light touch with rapidly vibrating fingers has been considered effective in mobilizing secretions in neonates.[76] Because few practitioners feel comfortable with this technique, vibrations can be done with a padded electric toothbrush, a small hand vibrator, or a commercially available pulmonary vibrator.

Vibration is tolerated by a greater number of patients than is percussion. The duration of vibration therapy is subject to the infant's tolerance and can be monitored on the basis of the parameters discussed previously.[76]

Optimization of Drug Delivery

The common practice of administering aerosolized medications before bronchopulmonary hygiene and suctioning is based on custom more than scientifically verified practice. The pharmacology of drug action is discussed in Chapter 21.

Although delivery of aerosolized medication has a number of advantages over systemic dosing, recent

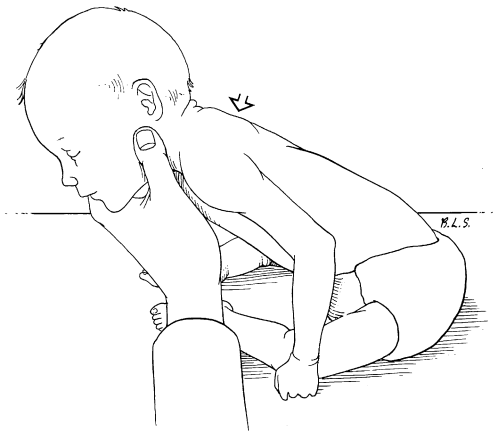

Figure 6-6 ■ Drainage of the posterior segments of the upper lobe. The infant is leaned over at a 30-degree angle from the sitting position. The clinician claps and vibrates over the upper back on both sides.

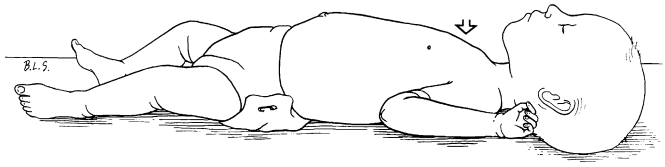

Figure 6-7 ■ Drainage of the anterior segments of the upper lobe. While the infant is lying flat on his or her back, the clinician claps and vibrates between the nipples and the clavicle on both sides.

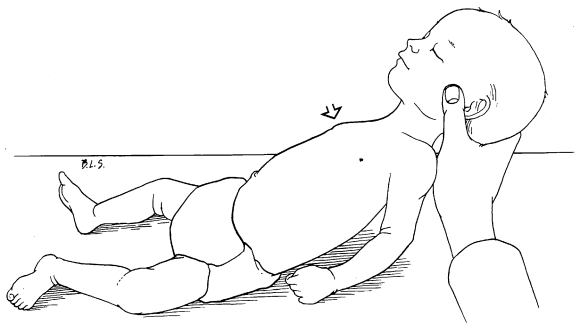

Figure 6-8 ■ Drainage of the apical segment of the upper lobe. The infant is leaned backward about 30-degrees from the sitting position, and the clinician claps or vibrates above the clavicle on both sides.

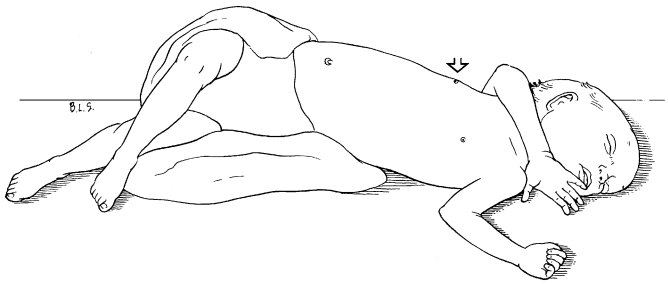

Figure 6-9 ■ For drainage of the right middle lobe, the caregiver elevates the hips to about 5 inches above the head. He or she rolls the infant backward one-quarter turn and then claps and vibrates over the right nipple. For drainage of the lingular segments of the left upper lobe, the caregiver places the infant in the same position but with the left side lifted upward; he or she then claps and vibrates over the left nipple.

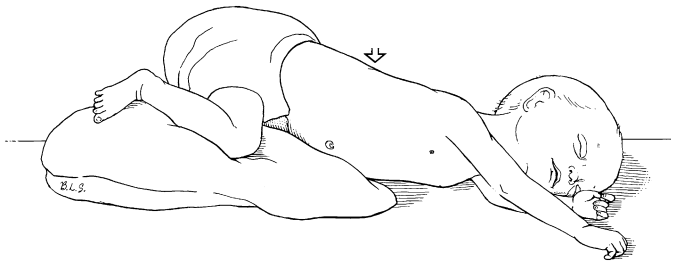

Figure 6-10 ■ Drainage of the lateral basal segments of the lower lobes. The caregiver places the infant on the left side with the hips elevated to a level about 8 inches above that of the head. The caregiver rolls the infant forward one-quarter turn and then claps or vibrates over the lower ribs. Note that the position shown is for draining the right side. For draining the left side, the same procedure is followed, except that the infant is placed on his or her right side.

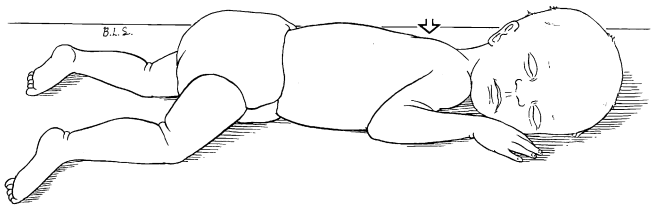

Figure 6-11 ■ Drainage of the superior segments of the lower lobe. The clinician places the infant flat on the stomach and then claps or vibrates at top of the scapula on the back side of the spine.

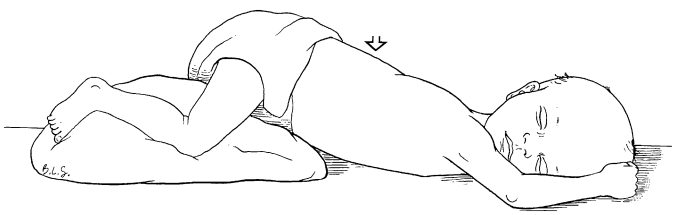

Figure 6-12 ■ Drainage of the posterior basal segments of the lower lobe. The clinician places the infant on the stomach with the hips at a level 8 inches above that of the head. He or she then claps and vibrates over the lower ribs close to the spine on both sides.

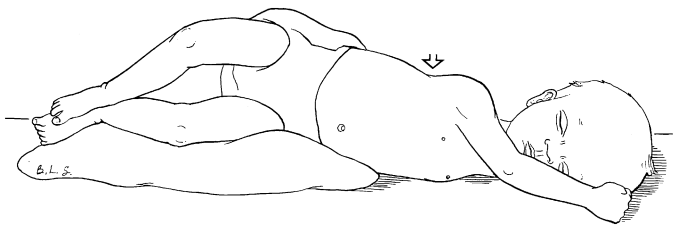

Figure 6-13 ■ Drainage of the anterior basal segment of the lower lobes. The caregiver places the infant on the left side with the hips at a level about 8 inches above that of the head. He or she then claps and vibrates just beneath the axilla. Note that for drainage of the opposite anterior basal segment, the infant is turned on the right side.

Box 6-3 OVERVIEW OF FACTORS THAT INFLUENCE NEONATAL AEROSOL DELIVERY AND DEPOSITION

Host-Related Factors

- Anatomic (nasal breathing, size of oropharynx, airways, lung development)
- Physiologic (breathing pattern, inspiratory flow rate, tidal volume, pulmonary mechanics)
- Pathophysiologic (inflammation, mucus, atelectasis, fibrosis)

Aerosol System–Related Factors

- Characteristics of the medication (particle size, shape, density, output)
- Generator [pressurized metered-dose inhaler (pMDI) or nebulizer]
- Delivery devices–patient interfaces (face mask or endotracheal tube)
- Conditions (ventilatory, environmental)
- Provider technique (optimum use of pMDI with spacer)

Data from Cole C: The use of aerosolized medicines in neonates. Neonat Respir Dis 10:4, 2000.

Box 6-4 THE IDEAL AEROSOL DELIVERY SYSTEM

- High efficiency in aerosol delivery
- Predictable and reproducible (in same patient and different patients)
- Easy to use and maintain
- Efficient to administer
- Convenient
- Cost-effective
- Environmentally safe

Data from Cole C: The use of aerosolized medicines in neonates. Neonat Respir Dis 10:4, 2000.

information has helped in the design of a few reliable aerosol delivery systems (Boxes 6-3 and 6-4 and Table 6-4).[71] The basic fundamental characteristics of factors that influence neonatal aerosol delivery and deposition are listed in Box 6-3. These factors can be divided into two groups: host-related factors and aerosol system–related factors.[71] Box 6-4 lists the characteristics of "the ideal aerosol delivery system." Table 6-4 compares the advantages and disadvantages of the three most frequently used aerosol delivery systems: the pressurized metered-dose inhaler and the jet and ultrasonic nebulizers.[71] However, even with the progress being made in the design of aerosolized medication delivery systems, the clinician may need to test a variety of delivery devices and decide which system is most efficacious for each individual patient. The same may have to be done with the type and dose of aerosol medication[77,78] in order to establish a bronchodilator dose, that is, measuring a patient's response to a specific drug and dose using bedside pulmonary function methods detailed in Chapter 18 rather than using predetermined dose tables. In addition, it is important to understand the variables unique to the aerosol route that can affect the drug delivery device. The small internal diameter and high resistance of the neonatal endotracheal tube impair aerosol delivery in the intubated patient compared with the nonintubated patient. In studies with animals, humans, and bench models, from 0.19% to 2.14% of the total drug amount in the nebulizer cup was administered to the lung or lung model when conventional jet nebulizers were used[77,78] compared with 10% of the total dose that was shown to be deposited in the lungs of nonintubated patients.[79]

With currently available methods, the placement and operation of a nebulizer are important for maximizing drug delivery to the lung. The nebulizer should be placed

TABLE 6-4 Advantages and Disadvantages of Aerosol Generators in Neonates

Aerosol Generator	Advantages	Disadvantages
Pressurized metered-dose inhaler (pMDI)	• More consistent aerosol particle size and output • Less time-consuming • Less preparation time • Less contamination • Less expensive than single-use nebulizers • Some HFA formulations have more optimal aerosol particle size	• Technique problems • Lack of pure medications • Not all medications available in pMDI • New hydrofluoroalkane (HFA) formulations need clinical studies
Jet nebulizer	• Tidal breathing • Passive cooperation • Can be used for long periods to deliver high doses • Wide range of medications	• Expensive and inconvenient • Inefficient and highly variable aerosol output • Numerous environmental factors affect aerosol particle size and output • Poor aerosolization of suspensions and viscous solutions • Preparation time • Time-consuming to administer • Contamination potential • Requires compressed gas
Ultrasonic nebulizer	• Potentially more efficient than jet nebulizer and pMDI • Tidal breathing • Passive cooperation • Can be used for long periods to deliver high doses	• Expensive and inconvenient • Requires power source • Contamination potential • Limited medications available for use • Preparation time • Time-consuming to administer

Data from Cole C: The use of aerosolized medicines in neonates. Neonat Respir Dis 10:4, 2000.

at least 5 inches upstream from the patient connection (not directly on the ventilator Y), and the humidifier should be bypassed for the duration of medication delivery.[71] If the nebulizer itself can provide the necessary flow for operation of a time-cycled pressure-limited ventilator, source flow other than the nebulizer should be eliminated if dilution of medication is to be prevented; however, the nebulizer flow should not be permitted to back up into the ventilator.[80] On the other hand, for more sophisticated ventilators in which this technique would trigger an alarm, nebulizers that prime the inspiratory tubing while running only in the expiratory phase are under development.[81]

Suctioning

Standards for suctioning protocols vary among institutions and usually are not based on physiologic principles or the results of current research.[82] The role of endotracheal suctioning is important, but the potential risks are many.[83] Use of a closed "inline" suctioning system has been promoted to decrease respiratory contamination and pulmonary infections. Disadvantages of these systems include increased expense and potential increase in air leaks. Suctioning should be performed by experienced personnel because complications from the trauma of this procedure may lead to hypoxemia,[82-84] cardiovascular embarrassment, barotrauma, and intraventricular hemorrhage. However, with care, patience, and appropriate anticipation, suctioning is a highly effective method of clearing the airway. The interval should be individualized and documented at the bedside; an example is illustrated in Figure 6-14. Following are a few suggestions on how to optimize benefits and prevent complications (see Table 6-5 and Figs. 6-13 and 6-15 for additional information):

- Anticipate when setting up for suctioning by having the proper equipment available.
- Be aware of ventilatory parameters and F_{IO_2}.
- Perform noninvasive monitoring of oxygenation before, during, and after suctioning.
- Have two people available (two-person job).
- Have the proper suction catheter size (see Tables 6-1 and 6-2 and/or Figs. 6-14 and 6-15). Ensure the external diameter of the suction catheter is not more than two thirds the internal diameter of the endotracheal tube.
- Individualize suctioning interval, catheter size, and depth of instillation of suction catheter as outlined in Tables 6-1 and 6-2.
- Prepare settings for vacuum pressure, from 60 to 100 mm Hg.

FRONT

ET TUBE PLACEMENT AND SUCTIONING RECORD

Baby's Name _____ Weight (gm) _____

Date Tube Inserted _____

Tube Position _____ cm Above Carina

ET Tube Size _____ Catheter Depth _____ cm

BACK

INTERTECH / OHIO		
TUBE SIZE	CUT (cm)	CATHETER DEPTH (cm)
2.5	11	14.5
3.0	13	17.0
3.5	13	17.0
4.0	14	18.0

Figure 6-14 ■ Bedside "suction card" with values to be re-verified after every chest radiograph has been obtained. Values are based on tube position relative to the carina. Suction depth must be reduced if the tip is not 2 cm above the carina. The table on the back of the card allows compensation for the extra length of the endotracheal tube's 15-mm adapter.

TABLE 6-5 Endotracheal Suctioning in Newborn Infants

	Hodge	Hagedorn et al.	Fletcher and MacDonald
Irrigation solutions	Saline, but not routinely	Saline	Saline
Amount for irrigation	0.1-0.2 mL/kg	0.25-0.5 mL	Not specified
Catheter size	0.5-0.66 of tube diameter	Not specified	0.5 of tube diameter
Depth of insertion	Length of tube only	Length of tube only	1 cm beyond tip of tube
Hyperinflation	PIP 10%-20% above baseline	Match PIP	PIP or PIP plus up to 10 cm H_2O
Hyperventilation	Equal total respiratory rate	Equal to ventilatory rate	Rate 40-60 breath min with long inspiratory time
Oxygen enhancement	10%-20% above baseline	If clinically indicated	10% above baseline
Suction pressure	50-80 cm H_2O	80-100 mm Hg	"Lowest possible"
Duration	Not specified	5-10 sec	15-20 sec disconnect time
Intermittent vs continuous	Not addressed	Continuous on withdrawal	Not addressed
Head turn	No	No	Turn head for selective bronchial suction

Data from Hodge D: Endotracheal suctioning and the infant: A nursing care protocol to decrease complications. Neonat Network 9:7, 1991; Hagedorn MI, Gardner SL, Abman SH: Respiratory diseases. In Merenstein GB, Gardner SL (eds): Handbook of Neonatal Intensive Care. St. Louis, CV Mosby, 1989, p. 381; Fletcher MA, MacDonald MG: Atlas of Procedures in Neonatology, 2nd ed. Philadelphia, JB Lippincott, 1993, p. 292.
PIP, Peak inspiratory pressure.

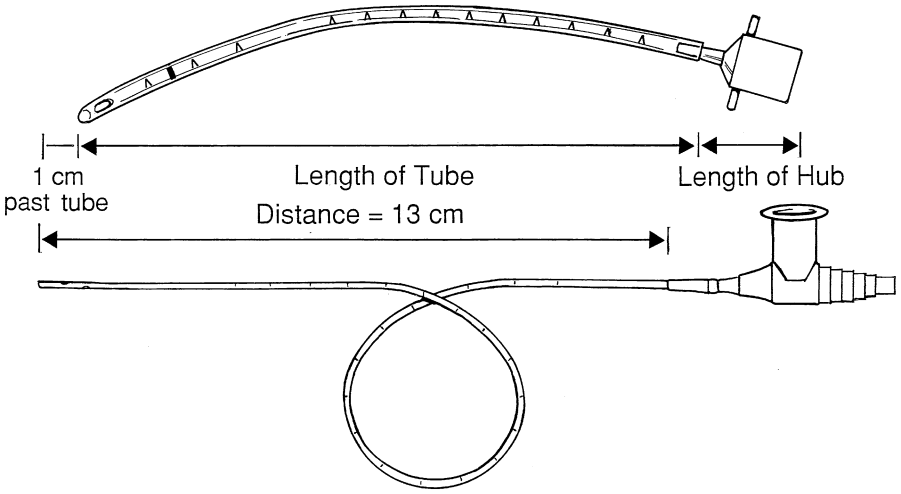

Figure 6-15 ■ Method for determining the length of catheter advancement in an endotracheal tube. Knowledge of the placement of the tube and of the length of the tube can be applied to the use of a calibrated suction catheter for providing consistent catheter advancement to a level 1 cm above the carina.

- Use normal saline for irrigation, 0.1 to 0.5 mL/kg ONLY if secretions are deemed to be thick and tenacious upon assessment.

The once routine practice of instilling normal saline has become a "PRN" habit. With the present focus on VAP (ventilator-associated pneumonia), studies that have shown a marked increase in the number of bacteria present in the lower airway after normal saline administration versus no normal saline have forced nurses and respiratory therapists to re-evaluate suction procedures (see Chapter 24).[85,86] The purpose of the normal saline instillation is to thin out tenacious secretions or to loosen dried secretions within an endotracheal tube, and assist in their removal. Studies have shown that mucus is not miscible with saline, even with shaking.[87] Attention must be paid to ensure adequate humidity in the ventilator circuit. Other studies have demonstrated the need for increasing positive end-expiratory pressure in infant animal models after normal saline instillation and suctioning.[88] Efforts to decrease the stimulation of premature infants, especially the extremely low-birth-weight patients, require the NICU staff to constantly assess the need for suctioning. A review of the literature and scientific evidence suggests an absence of positive effects from normal saline instillation.

Remember, suctioning technique looks easy when it is performed by skilled neonatal intensive care unit nurses and respiratory therapists, but the dangers are many, including hypoxemia, bradycardia, accidental extubation, and possible intraventricular hemorrhage. Close attention to the changes in the baby and adherence to suction technique are necessary to be of benefit to the sick infant. (See also discussion in Chapter 7.)

Surfactant Administration

This section addresses the technical aspects of surfactant administration, including dosage forms, amounts, and administration techniques. Other aspects of surfactant treatment are discussed in Chapter 22.

The surfactant pool size in lungs of healthy, full-term neonates is about 100 mg/kg.[89] Infants with RDS have a surfactant pool size that is approximately 10% of that seen in the healthy, full-term lung.[90] Surfactant doses for prevention or treatment of RDS are aimed at achieving a surfactant pool size comparable to that in the full-term lung while also allowing for some uneven distribution of exogenous surfactant and surfactant inactivation by protein exudates. Thus surfactant doses in the range of 50 to 200 mg/kg have been used in various clinical studies.[91] Currently available commercial surfactant preparations contain varying amounts of phospholipids, but the recommended dosage amounts give 100 to 200 mg/kg of phospholipids per dose (Table 6-6). All currently available surfactant preparations are obtained by extraction from animal lungs and are available in a liquid form for intratracheal instillation, although a new, completely synthetic surfactant (lucinactant) may be available by the time this text is published. Differences in recommended dosage volume may lead the clinician to favor a particular surfactant preparation in certain clinical situations.

Recommended modes of surfactant administration are based on those used in research protocols, but there are limited human data comparing different techniques of sur-

TABLE 6-6 Surfactant Preparations

Surfactant	Source	Phospholipid Content, mg/mL	RECOMMENDED DOSE (mL/kg)	
			Initial	Repeat
Infasurf	Calf lung	35	3	3
Survanta	Cow lung	25	4	4
Curosurf	Pork lung	80	2.5	1.25

Data from package inserts. See references 90, 99, 100.

factant administration. Surfactant is generally administered through a small-bore catheter inserted into the endotracheal tube, although the Infasurf package insert suggests instillation through a side-port adapter.[92] Animal data suggest that administering surfactant by bolus or rapid intratracheal infusion results in more even distribution of surfactant than giving the surfactant by very slow continuous intratracheal infusion.[93] Surfactant doses are typically divided into 2 or 4 aliquots. The infant is positioned before each aliquot so as to ensure even distribution of surfactant throughout both lungs, although there are limited data regarding the efficacy of this practice.[7] Very limited data suggest that delivery of surfactant by nebulization might result in improved distribution of surfactant,[94] but this approach requires further study.

Extubation

There is no single reliable physiologic parameter or pulmonary function test in neonates that determines readiness for extubation. The optimal time for extubation is determined by a variety of parameters, including mean airway pressure, oxygen requirement, ventilatory requirements (see Chapters 9 and 10 on modes of ventilation), estimation of negative inspiratory force, static compliance, and most importantly, the appearance of the baby. Gillespie et al.[95] have suggested placing the infant on endotracheal CPAP for 10 minutes while monitoring the spontaneous minute ventilation. The ability of the infant to spontaneously generate at least 50% of the minute ventilation that was seen during assisted ventilation predicted readiness for extubation and shortened the time to successful extubation. The clinician may also use intermittent bagging of the infant to get a sense of the compliance of the lung. The baby's primary problem and the clinical course and duration of assisted ventilation can provide helpful information regarding the appropriate timing for extubation. Some experts believe that a transition period from assist mode, pressure support, and/or extubation to nasal prong or nasopharyngeal continuous positive airway pressure (CPAP) is an excellent way to facilitate extubation. Sometimes a methylxanthine is used during the weaning process because its effects include "reminding the newborn to breathe" and increasing the efficiency of the diaphragm, especially in very-low-birth-weight infants.[96,97] If the infant has been on assisted ventilation for several days and there is concern about edema and inflammation in the upper airway, one or two doses of dexamethasone, given 24 to 48 hours prior to extubation, may be helpful.

Extubation Technique

Many authors advise extubation with positive pressure to avoid atelectasis.[38] Some clinicians, however, use negative pressure to suction the airway during the extubation process. To the best of our knowledge, no controlled clinical study has yet established the advantage of extubating with positive or negative pressure.

Postextubation Care

The extubated infant requires frequent clinical assessment during the postextubation period. Frequent observation of breathing patterns, auscultation of the chest, and monitoring of vital signs, pulse oximetry (continuous), transcutaneous CO_2 levels, and/or blood gases are all of value. Other interventions, including bronchopulmonary hygiene,[98] can be started in an attempt to prevent or reverse atelectasis, most often seen in the right middle and upper lobes. Racemic epinephrine may help open up the airways by decreasing edema of the airway, although reviews of its efficacy have been negative.[16] After extubation, if there is a clinical concern, a chest radiograph can be obtained. If the baby continues to deteriorate, other techniques to consider include initiation of CPAP using the nasopharyngeal technique (NPCPAP), intermittent manual bagging using the correct-sized mask and non–self-inflating bag, racemic epinephrine, and/or corticosteroids (inhalation or parenterally) if signs of upper airway obstruction are noted. The risk-benefit ratio for corticosteroids should always be considered before use.

If the baby is unable to maintain adequate ventilation despite interventions, then reintubation and suctioning should be accomplished. There are multiple reasons for extubation failure; Box 6-5 provides a comprehensive list. Extubation failure should prompt a search for a cause that can be corrected before the next extubation attempt.

Box 6-5 MAJOR CAUSES OF EXTUBATION FAILURE

I. Pulmonary
   A. Primary disease not resolved
   B. Postextubation atelectasis
   C. Pulmonary insufficiency of prematurity
   D. Bronchopulmonary dysplasia
   E. Eventration or paralysis of diaphragm
II. Upper Airway
   A. Edema and/or excess tracheal secretions
   B. Subglottic stenosis
   C. Laryngotracheomalacia
   D. Congenital vascular ring
   E. Necrotizing tracheobronchitis
III. Cardiovascular
   A. Patent ductus arteriosus
   B. Fluid overload
   C. Congenital heart disease with increased pulmonary flow
IV. Central Nervous System
   A. Apnea (extreme immaturity)
   B. Intraventricular hemorrhage
   C. Hypoxic ischemic brain damage/seizures
   D. Drugs (phenobarbital)
V. Miscellaneous
   A. Unrecognized diagnosis (e.g., nerve palsy, myasthenia gravis)
   B. Sepsis
   C. Metabolic abnormality

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7 Nursing Care

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Newborns receiving assisted ventilation and neonatal intensive care require a multidisciplinary group of care providers. Professional nurses, physicians, respiratory therapists, social workers, developmental specialists, occupational and physical therapists, pharmacists, and clinical dieticians comprise the team who work in the neonatal intensive care unit (NICU). In this chapter, nursing care for the newborn requiring assisted ventilation is explored, including issues regarding nasal continuous airway pressure (NCPAP), airway management, prevention of nosocomial respiratory infections, targeted oxygen saturation monitoring for premature infants, and care during technologies such as high-frequency ventilation and inhaled nitric oxide.

Nursing Assessment

Neonatal nurses provide hour-by-hour care of each patient in the NICU. The experienced NICU nurse serves as the infant's link to the environment, often serving as "interpreter" for the infant through the careful assessment of physiologic data and infant behavioral responses to determine each individual infant's response to treatment. Because each nurse will generally be responsible for only one to three patients at any given time, nurses remain in constant proximity to their patients, often making important observations and assessments that are then reported to the health care team. Such observations may stimulate further evaluation by the medical team and may result, for example, in additional laboratory work and other diagnostic evaluations.

Nurses assess their patients during their admission to the NICU and also at regular intervals each day. This assessment includes evaluation of physical characteristics such as color, neuromuscular tone, skin integrity, vascular perfusion, and edema. Evaluations of the cardiovascular, respiratory, gastrointestinal, genitourinary, neurologic, musculoskeletal, and integumentary systems are made and documented in the medical record at least once every shift. Auscultation of the chest is performed regularly to evaluate quality of breath sounds and determine whether a heart murmur is present. Special attention is paid to the work of breathing and chest wall movement for the infant receiving assisted ventilation. Color and volume of secretions retrieved while clearing the oropharynx and endotracheal tube are carefully noted.

Monitoring for disease processes such as necrotizing enterocolitis or gastrointestinal perforation includes measuring abdominal girth and observing for discoloration of the abdomen, gastric residuals, and frank blood in stools. Sepsis monitoring involves assessment of hypothermia or hyperthermia, hypoglycemia, increased apnea and bradycardia, lethargy, hypotonia, and poor feeding. Other assessment activities include measuring and recording daily weights, intake and output, temperature of the infant and environment, heart rate and electrocardiogram, respiratory rate and quality of breathing as noted previously, blood pressure and perfusion, and oxygen saturation monitoring. Neurobehavioral and developmental status includes the assessment of pain and discomfort in relation to the treatments being received, as well as the effect of other environmental stimuli.

Assessment of the overall skin condition involves evaluating all skin surfaces, head-to-toe, daily or more frequently. Risk factors for skin injury include gestational age less than 32 weeks, edema, adhesives applied to the skin to secure tubes, lines and monitoring equipment. Although pressure sores are very rare in neonates, they may occasionally be seen on the ears or occiput of critically ill neonates on high frequency ventilation or extracorporeal membrane oxygenation unless frequent repositioning and use of gel pillows or mattresses is employed.

Another aspect of assessment involves evaluating the technology used to support the infant. This includes checking the patency and functioning of all intravascular devices, evaluating the security of endotracheal tubes, CPAP and cannula prongs, and assessing the placement and security of all other invasive tubes such as chest tubes and nasogastric tubes. The presence and appropriate functioning of all respiratory equipment, monitoring devices, intravenous pumps, thermoregulatory devices, and emergency equipment such as bag, mask, and suctioning equipment should be confirmed with appropriate documentation.

Assessment of the family is an important responsibility shared with social workers and physicians. Nurses assist families as they come into contact with their infants, helping them understand the infant's medical problems, the type of equipment that is being used, and the infant's unique responses to his or her environment. Nurses often can identify behaviors in families that are commonly seen such as relunctance to touch or handle the baby or noticeable lack of visitation, during this vulnerable period, and they stay alert for behaviors that may signify the possibility of later attachment disorders or behaviors that may

indicate the need for immediate crisis intervention. They also integrate parents and other caregivers into the daily care of the infant from the first days of hospitalization, and assess how well the family is able to assume physical and emotional caregiving for their infant. This should be accomplished well before discharge to home.

Nursing the newborn requiring assisted ventilation and intensive care is complex and challenging. Nurses provide a vital link between the patient and the rest of the multidisciplinary team as a result of their knowledge, proximity to the patient, and skill at interpretation of physiologic, behavioral, and technical information.

Respiratory Care

Monitoring of ventilation equipment, oxygen delivery systems, and patient oxygenation are ongoing activities and essential components of nursing care for infants receiving assisted ventilation; many of these activities are shared responsibilities with respiratory therapists in the NICU. Special concerns while caring for infants requiring assisted ventilation include providing nasal CPAP, maintaining targeted oxygen saturation parameters, maintaining a secure and patent airway, detecting and intervening in cases of sudden respiratory deteriorations, and management of the infant on high-frequency ventilators and inhaled nitric oxide.

Nasal Continuous Positive Airway Pressure

The widespread and increasing use of noninvasive forms of ventilatory support, such as nasal continuous positive airway pressure (NCPAP) and nasal intermittent mandatory ventilation, has provided a number of challenges to direct care providers in the NICU (see Chapter 8). A major factor contributing to success or failure with NCPAP lies in the comfort level and knowledge of the nurses providing the care.[1] One study reported significant improvements with the success of early NCPAP over a 4-year period, indicating a substantial learning curve for all professionals involved, including nurses, respiratory therapists, and physicians; extensive and ongoing education included information on how and why CPAP works and on complications and trouble-shooting.[2]

Maintenance of continuous flow and appropriate CPAP pressures is affected by the infant's position and overall comfort. The prongs or mask interface need to be properly positioned, and the infant's mouth closed to ensure appropriate CPAP. Repositioning is essential for a numer of reasons, including respiratory stability and neurodevelopmental outcomes, and is recommended every 3 to 6 hours.[1] Placing an infant on assisted ventilation in the prone position increases oxygenation, tidal volume, and lung compliance and reduces energy expenditure when compared to the supine position. Prone positioning has become an important therapeutic intervention for adults or children with acute respiratory distress syndrome (ARDS): it allows ventilation of formerly dependent areas of the lung. Similar effects from prone positioning may also improve ventilation of the neonatal lung. Prone positioning may also be beneficial in infants receiving NCPAP because lying prone seems to aid in keeping the infant's mouth in a closed position, decreases abdominal distention, and also keeps the infant calmer. Offering a pacifier and providing containment using swaddling or nesting techniques can be beneficial in both promoting comfort and improving respiratory support. The use of a chin strap may prevent air leaks and loss of pressure.[12]

Complications from NCPAP range from pneumothorax to excessive abdominal distention, airway blockage with secretions, and injury to the skin and nasal septum. Careful auscultation of breath sounds is needed, as well as attention to the pressure limits on the CPAP delivery device. Excessive abdominal distention is addressed by gastric decompression with an orogastric tube, although this complication may often hinder the advancing of enteral feedings and lead to numerous abdominal x-rays. One study documented that gastric emptying was delayed in infants receiving NCPAP.[13]

Administration of oxygen under pressure through nasal prongs can be excessively irritating to nasal mucosa, resulting in increased production of secretions. The use of warmed, humidified gas is imperative. Although there is currently no empirical evidence for exactly how best to care for the airway of infants on NCPAP,[1] nursing care does involve regular suctioning of the nares to maintain patency. Although it may cause trauma, suctioning is necessary, but using techniques such as round-tipped plastic suction devices can minimize trauma from mucosal bleeding and swelling.

One of the biggest challenges faced while caring for the infant on NCPAP is protecting the nasal septum and surrounding structures from injury. The nasal septum is fragile, and the interfaces between the infant's nose and the CPAP system, either prongs or mask, may cause pressure. A study comparing different CPAP devices found no significant differences between "bubble" CPAP systems with prongs, infant flow driver interface, or nasopharyngeal prongs in terms of nasal injuries.[14] A review of studies involving the various CPAP devices and pressure sources reported that short binasal prongs are better than nasopharyngeal prongs and that the optimal pressure source has not been determined.[15] There is no data about the effect of using CPAP masks in premature infants, although many NICUs have adopted the use of masks alternating with nasal prongs in an effort to reduce nasal trauma. Diligence in ensuring the appropriate positioning of prongs relative to the nose and frequent repositioning is necessary. Careful inspection to detect any skin and tissue injury is accomplished by removing the nasal prongs or mask every 3 to 4 hours; providing a "blow-by" break for 10 to 15 minutes is also helpful if the infant can tolerate it . A checklist with all the steps necessary to prevent complications for patients on NCPAP has been useful in some NICUs to improve the consistency of care ( ).

Despite meticulous care practices, tissue injury may occur on the philtrum of the lip or the nasal septum ( ).[16] Hydrocolloid "shields" have been devised to protect skin, but have variable results because pressure is often the problem, rather than friction. Once the skin barrier has been injured, use of these products may promote further breakdown.[1] Application of an antimicrobial ointment such as mupirocin may be beneficial to reduce the risk of infection through this portal of entry.

TABLE 7-1 Nursery Management of Nasal Continuous Airway Pressure (NCPAP)

Date:	**Day Shift**		**Evening Shift**		**Night Shift**	
Infant's Weight:						
	Yes	**No**	**Yes**	**No**	**Yes**	**No**

Check Infant's Position

☐ Blanket and neck rolls used to ensure head is kept in neutral position
☐ NCPAP prongs not pulling on nose

Check Positioning of Tubing and Hat

☐ *Pressure* tubing separated and placed under Velcro straps
☐ *Exhalation* tubing free or under Velcro center strap to give best positioning fit
☐ Tubing is secure and bed/tubing level with middle of isolette porthole
☐ Check that hat is positioned at brow and nape of neck
☐ Patient has correct hat size according to color code on tape
☐ Absence of indentations on cheeks from straps
☐ Removal of hat to assess placement/positioning
☐ *(Circle if present)* "Squished"/folded ears/head molding

Check Nares

☐ Prongs are in nares, not on upper lip/bridge of nose
☐ Feeding tube is placed in mouth instead of nares
☐ *(Circle if present)* Creases at pressure points; reddened, rawness
☐ Use otoscope/penlight to check for breakdown in nares and secretion build-up in back of throat
☐ Use 8 10 Fr catheter to suction oropharynx PRN
☐ ***Only if needed***, suction nares ***gently*** with BBG nasal aspirator tip

"Blow-by Breaks"

☐ BBB given every shift and tolerance documented
☐ Percent F_{IO_2} during "break" documented

Comments:

NOC resource (RN/RT) _____
Days resource (RN/RT)_____
PM resource (RN/RT)_____

From Children's Hospital and Research Center, Oakland, California.

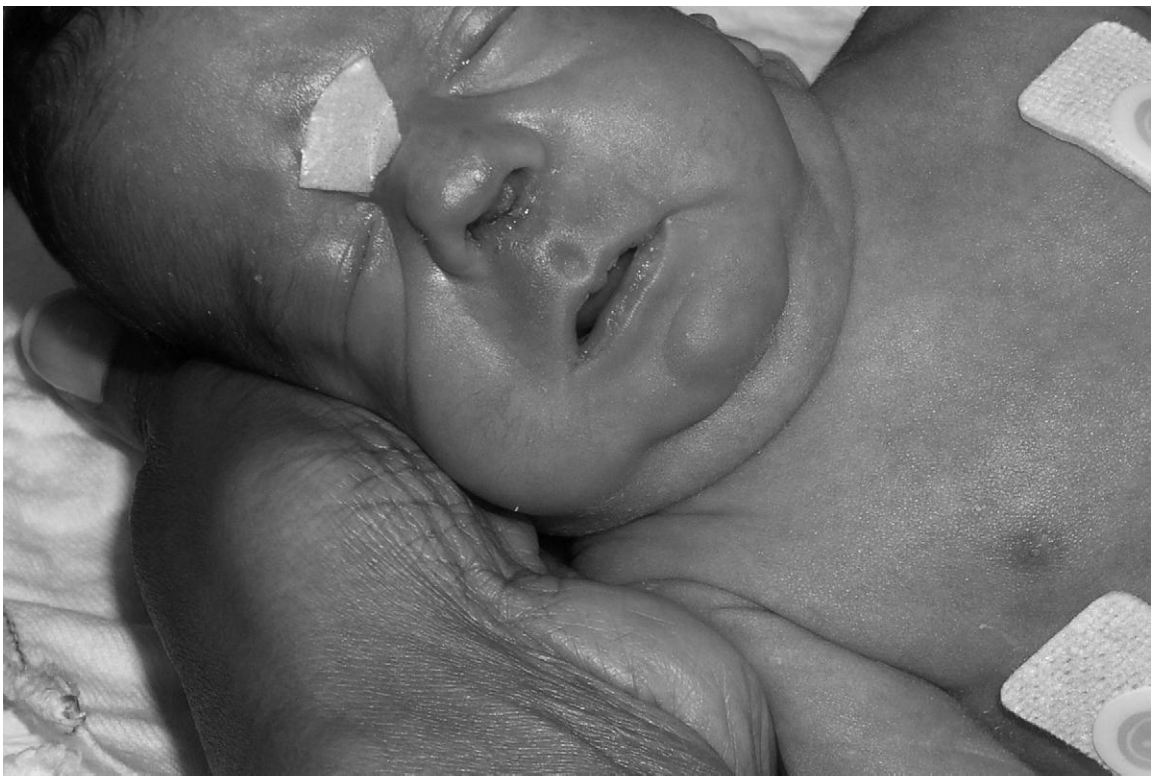

Figure 7-1 Photo of tissue damage to nares caused by nasal continuous positive airway pressure (CPAP).

Assessment of infants on NCPAP also includes overall evaluation of respiratory status including retractions and respiratory effort, breath sounds, oxygenation and pCO_2 levels. Although there may be retractions and PCO_2 levels in the range of 45 to 65 torr, if the infant generally appears comfortable, he can be maintained on NCPAP. Signs of distress include PCO_2 greater than 65, FIO_2 requirement greater than 60% consistently, and increased retractions, tachypnea, and apnea. These signs may be indications that the infant is failing NCPAP, and that intubation and assisted ventilation is needed. Risk factors that have been associated with failure of early NCPAP in very-low-birth-weight infants (less than 1500 g) include use of positive-pressure ventilation in the delivery room, severe RDS on initial x-ray, and an alveolar-arterial oxygen tension gradient of 180 mmHg or greater on the first arterial blood gas.

High-Frequency Ventilation

Nursing care for the infant on high-frequency ventilation (see Chapter 11), either via oscillator or jet ventilators, requires a different set of knowledge and skills.
Assessment of the infant receiving high-frequency ventilation is frequent and extensive, differing from routine nursery assessment related to the absence of tidal breathing. It is not possible to auscultate the chest for either breath sounds or apical pulse while the infant is on high-frequency ventilation, and therefore skill in observing and palpating for chest "wiggle" and other parameters of ventilation adequacy are employed. Use of transcutaneous monitors for assessment of transcutaneous partial pressure of carbon dioxide (transcutaneous carbon dioxide tension [$TcPCO_2$]) trends is becoming more common, especially for infants on high-frequency ventilation. In many cases, the infant's condition while undergoing high-frequency ventilation can change very rapidly because of both the infant's underlying pulmonary pathology and the device in use. It is possible to interrupt or pause the ventilator briefly during the assessment process to auscultate breath sounds and listen for heart murmurs; however, this can also destabilize the infant. Coordination among multidisciplinary team members is recommended for these assessment periods, so that the time during which the patient is removed from high-frequency ventilation is kept to a minimum.

The concern about minimizing periods when the infant is not connected to the ventilator circuit is primarily related to efforts to prevent the mean airway pressure from falling, which would allow the alveoli to collapse. Closed suctioning, using inline devices described in the section on suctioning, is used to prevent disconnecting the infant from ventilation during suctioning. Many NICUs use in-bed scales, weigh infants infrequently, or simply do not weigh patients receiving high-frequency ventilation to prevent destabilizing the respiratory system. Depending on which high-frequency ventilator is used, positioning and turning infants on high-frequency ventilation may require two persons, one to rotate the infant while another caregiver briefly disconnects the ventilator circuit while the ventilator itself remains in a fixed location. Some units have devised ways for parents to hold infants while they are on high-frequency ventilation,[90] although many still do not allow holding for these infants. lists assessment and care practices specific to high-frequency ventilation.

TABLE 7-2 Nursing Interventions in Infants Receiving High-Frequency Jet and High-Frequency Oscillatory Ventilation

Intervention	HFJV	HFOV
ET suctioning	Suction catheter inserted into ETT, continuous suction applied. Avoid manual bagging. Adjust HFJV or CMV setting to facilitate recovery.	Performed on HFOV. Suction with closed, inline suction system; reconnect to HFOV. Hand bagging is avoided. MAP increased if needed to facilitate recovery.
Positioning	Patient can be placed in all positions. Limited by short, but flexible, length of "jet" tubing to patient box. Patient box sits next to head. Can move patient while connected to HFJV.	Positioning on HFOV limited by rigid tubing that delivers bias flow. Turning "head-to-toe" by moving the baby 180 degrees while the circuit remains fixed is the most common technique. Infants must always remain elevated above the rigid circuit tubing to prevent aspiration of condensed humidity.

Adapted from Karp T: High frequency ventilation: Life in the fast lane? Presented at Neonatal Nurses National Conference, Nottingham, England, September 25, 1993, and adapted from Inwood S: High frequency oscillation and Karp T: High frequency jet ventilation. In Nugent J (ed): Acute Respiratory Care of the Newborn (Monograph). Petaluma, Calif, Neonatal Network, 1991; Avila K, Mazza LV, Morgan-Trujillo L: High-frequency oscillatory ventilation: a nursing approach to bedside care. Neonatal Network 13:23, 1994.

CMV, Conventional mechanical ventilation; *ETT,* endotracheal tube; *HFJV,* high-frequency jet ventilation; *HFOV,* high-frequency oscillatory ventilation; *MAP,* mean airway pressure.

Pressure Ulcers and Skin Breakdown

Although the incidence of ischemic injury related to pressure ulcers is low in NICU patients compared to adults, infants at risk for this complication include those on high-frequency ventilation and extracorporeal membrane oxygenation because they are more difficult to turn or move. In addition, they are generally critically ill and may be hypotensive, which can lead to peripheral tissue hypoperfusion, and may be edematous because of leaking capillaries or the need for excessive fluid or blood products to maintain blood pressure. Paralyzing medications such as pancuronium, vecuronium, or high levels of sedation create poor tone and decreased movement,[104] which increases the risk of skin breakdown.

Sites for pressure ulcers in newborns on assisted ventilation include the occiput of the head and the ears, because of the heavy weight of the infant's head compared to the body. In addition, the circuit connected to the endotracheal tubes is often secured to avoid displacing the tube, and thus the infant cannot turn or move the head without assistance.

Prevention of pressure ulcers to the head and ears involves using surfaces that alleviate pressure points. These include water mattresses or pillows, air mattresses,[108] and gelled mattresses, pillows, and wedges, which equalize the pressure around the head and ears. Turning the infant a minimum of every 4 hours is necessary, along with careful inspection of skin surfaces. Even when turning side-to-side is not feasible, lifting the head, shoulders, and hips and supporting these areas with pressure-reducing surfaces is helpful. Once a pressure ulcer occurs, wound care is necessary using moist healing techniques and principles.

Inhaled Nitric Oxide

The use of inhaled nitric oxide (iNO) is now commonplace for newborns receiving assisted ventilation (see Chapter 14). Following approval by the Food and Drug Administration for treatment of pulmonary hypertension in term newborns in 1998, use of this selective pulmonary vasodilator has become mainstreamed in many NICUs for this indication. More recent studies showing a reduction in the incidence of bronchopulmonary dysplasia (BPD) in premature infants treated with iNO during the first month of life[112] and fewer respiratory problems in the first year of life[113] have expanded the use of this treatment in premature infants in the NICU.

Care of the infant receiving iNO requires comprehensive knowledge of physiology, pathology, and treatment regimens.[114] Nursing care of the newborn receiving inhaled nitric oxide includes careful monitoring of the gas administration and preventing any interruption of iNO administration during hand ventilation, turning, moving, or suctioning; closed suctioning systems are recommended. Monitoring of methemoglobin levels, suggested in studies of full-term infants treated with iNO for pulmonary hypertension (especially those on higher concentrations), was not found to be necessary in the premature infants treated with iNO for BPD.[111] Gradual weaning of iNO is necessary even in patients who are "nonresponders" because of the down-regulation of the patient's endogenous nitric oxide production during treatment with iNO and the potential for destabilizing patients with marginal oxygenation and reserves.

Airway Security

Accidental dislodgment of the endotracheal tube can result in serious complications including acute hypoxia, bradycardia, and potential damage to the trachea or larynx. Preventing accidental extubations is an important responsibility for nurses and respiratory therapists. Factors associated with accidental extubations include the length of time intubated, agitation, endotracheal tube (ETT) suctioning, weighing, turning the patient's head, chest physiotherapy, loose tape, short ETTs, and retaping the ETT.[18] The incidence of accidental extubations reported in the literature is variable[19,20] but approximates 5 events per 100 ventilator days.

Many different techniques have been described to secure ETTs, ranging from adhesives with bonding agents[21,22] or pectin barriers,[23,24] suturing the tube to tape, and using metal or plastic bows to prevent slipping of the ETT.[25] Some commercially available products for securing neonatal ETTs have incorporated similar ideas in their products. Because the common link in all these methods is the use of adhesives, an in-depth review of adhesive application and removal in the neonate is described below.

Adhesive Application and Removal

Not only is the uppermost layer of the epidermis of the skin, the stratum corneum, histologically thinner in premature infants, fibrils that connect the top two layers of the skin, the epidermis and the dermis, are fewer and more widely spaced in the premature infant compared with term infants.[26] Thus premature infants are more vulnerable to stripping of the epidermis when adhesives are removed, because the adhesives may be more firmly attached to the epidermis than the epidermis is to the dermis. The traumatic effects of adhesive removal have been documented on premature infants and include reduced barrier function, increased transepidermal water loss, increased permeability, erythema, and skin stripping ( ).[,28] Skin barrier function is also altered in adults with tape removal, but occurs only after repeated strippings.[29]

Solvents are not recommended for adhesive removal in newborns because these contain hydrocarbon derivatives or petroleum distillates that have potential toxicity when absorbed. The risk of toxicity from absorption is greater in premature infants due to their immature stratum corneum, and in newborns in general due to their larger surface area to body weight. In addition, skin irritation and injury have been reported related to the use of a solvent in a premature infant.[30]

Pectin-based skin barriers such as Hollihesive™ and Duoderm™ are used between skin and adhesive and mold well to curved surfaces while maintaining adherence in moist areas. Although studies initially described less visible trauma to skin from pectin barriers, a study using direct measurements of skin barrier function found that pectin barriers caused a degree of trauma similar to that of plastic tape.[28] Despite this finding, pectin barriers and similar hydrocolloid adhesive products continue to be used in the NICU because they mold well to curved surfaces and adhere even with moisture. Several hydrocolloid products for securing ETTs are commercially available.

The use of bonding agents, such as tincture of benzoin or Matisol,™increase the adherence of adhesives and may result in skin stripping and damage because they cause the adhesive to adhere more tenaciously to the epidermis than the fragile bond between epidermis and dermis, especially in the premature infant. An alcohol-free plastic polymer skin protectant, Cavilon™ (3M), has been shown to reduce measurable damage from adhesives in adults[32] and reduce visible disruption in newborns[33]; it is approved for use in infants greater than 30 days of age.[34] The effect of repeated applications of barriers films on adherence or in moist environments has not yet been studied.

Preventing trauma from adhesives can be accomplished by minimizing use of tape when possible, dabbing cotton on tape to reduce adherence, and using hydrogel adhesives for electrodes. However, hydrogel adhesives are not adequate when attaching life support devices such as endotracheal tubes. Delaying tape removal may be helpful, because many adhesives attach less well to skin when in place for

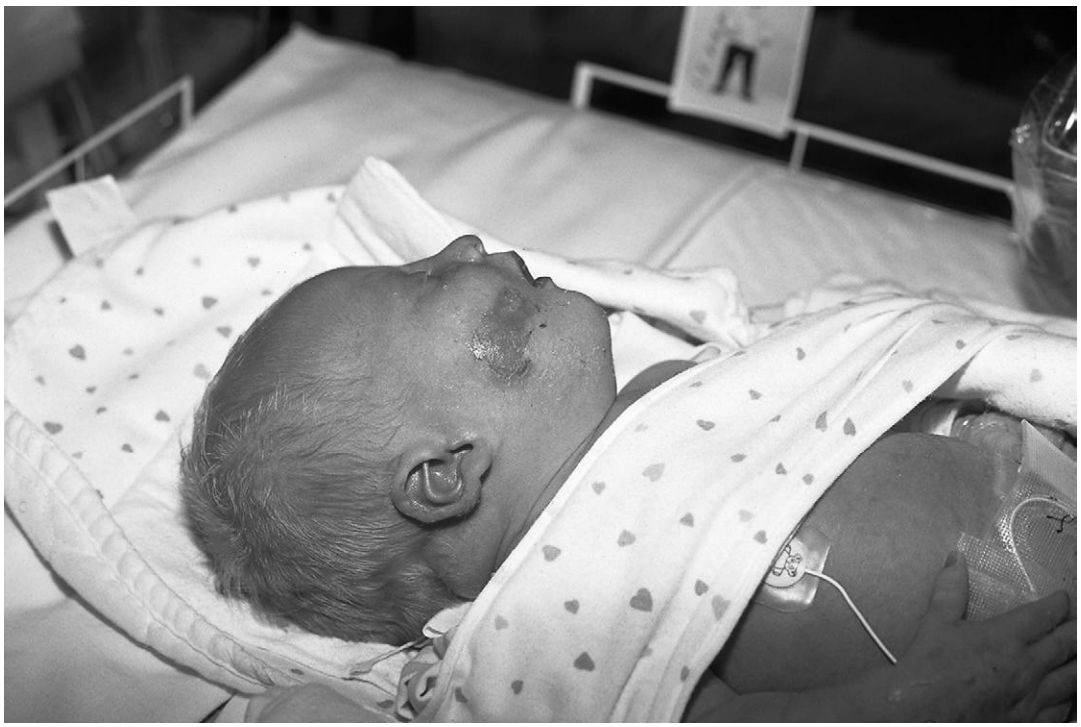

Figure 7-2 Photo of damage caused by adhesive removal.

over 24 hours. Remove adhesives slowly and carefully, using water-soaked cotton balls and pulling the adhesive parallel to the skin surface, folding the adhesive onto itself.[35] Removal also can be facilitated using emollients or mineral oil if reapplication of adhesives at the site is not necessary.

No research exists that identifies the "best practice" for ETT taping. It is imperative that each NICU develop a standard practice that is consistently used to avoid confusion during intubations and ETT retaping, and that all members of the multidisciplinary team agree on the method that is selected. A card specifying the depth that the ETT is inserted should be posted at each bedside, with the centimeter marking that is at the patient's lip displayed. Adhesion of the ETT taping should be inspected often, and the ETT retaped whenever necessary to prevent accidental dislodgment. Regular monitoring of unplanned extubations can be incorporated into quality improvement audits, and practices to reduce the number of untoward events should be implemented (see Chapter 19).

ETT Movement and Malposition

Position of the ETT may be altered with inadequate fixation of the tube, changes in patient position, and flexion and extension of the head. Because the trachea of a term newborn is quite short (mean 57 mm) and even shorter in premature infants, small movements of the ETT can result in displacement, causing the tube to move into the right mainstem bronchus with flexion, or into the neck with extension ( ).[36,] In addition to potentially altering ventilation and blood gas parameters and causing tracheal damage, ETT movement can result in misinterpretation of the ETT position on x-rays. The infant's head should be carefully positioned when obtaining x-rays, placed in a "neutral" position to avoid extension or flexion. Some authors have even devised plastic forms to keep the infant's head in place during x-rays[38] to avoid the unrewarding activity of pushing the ETT in further, only to have to withdraw it with the next x-ray. The ETT should be positioned with the bevel in an anterior placement to avoid having the bevel abut against the tracheal wall with head movement or position changes ( ).[39]

Suctioning

The presence of an ETT causes irritation to tissue and increased secretions. It is necessary to clear this artificial airway periodically to maintain ventilation for the infant. ETT suctioning has been associated with a number of complications in infants including hypoxemia,[40,41] bradycardia,[41,42] atelectasis,[43] mucosal trauma, and pneumothorax.[44] Systemic adverse effects are also of concern, including increased blood pressure,[45,46] changes in cerebral blood volume, and reduced oxygenation in cerebral blood flow.[46,] Infection is also a concern, both in terms of nosocomially acquired pneumonia and introduction of microorganisms into the bloodstream through injured mucosa.

Important considerations in ETT suctioning for NICU patients includes frequency of suctioning, depth of suctioning, use of instillates such as normal saline, and use of closed suction devices. Because hazards are associated with suctioning, many NICUs suction intubated patients only when it is assessed to be needed, that is, when breath sounds are moist or congested, when secretions are visible, or when the infant is either hypoxic or agitated with no known cause. During high-frequency oscillatory or jet ventilation (HFV), it is not always obvious when suctioning is needed, and some nurseries implement routine suctioning every 4 to 8 hours for patients on HFV.

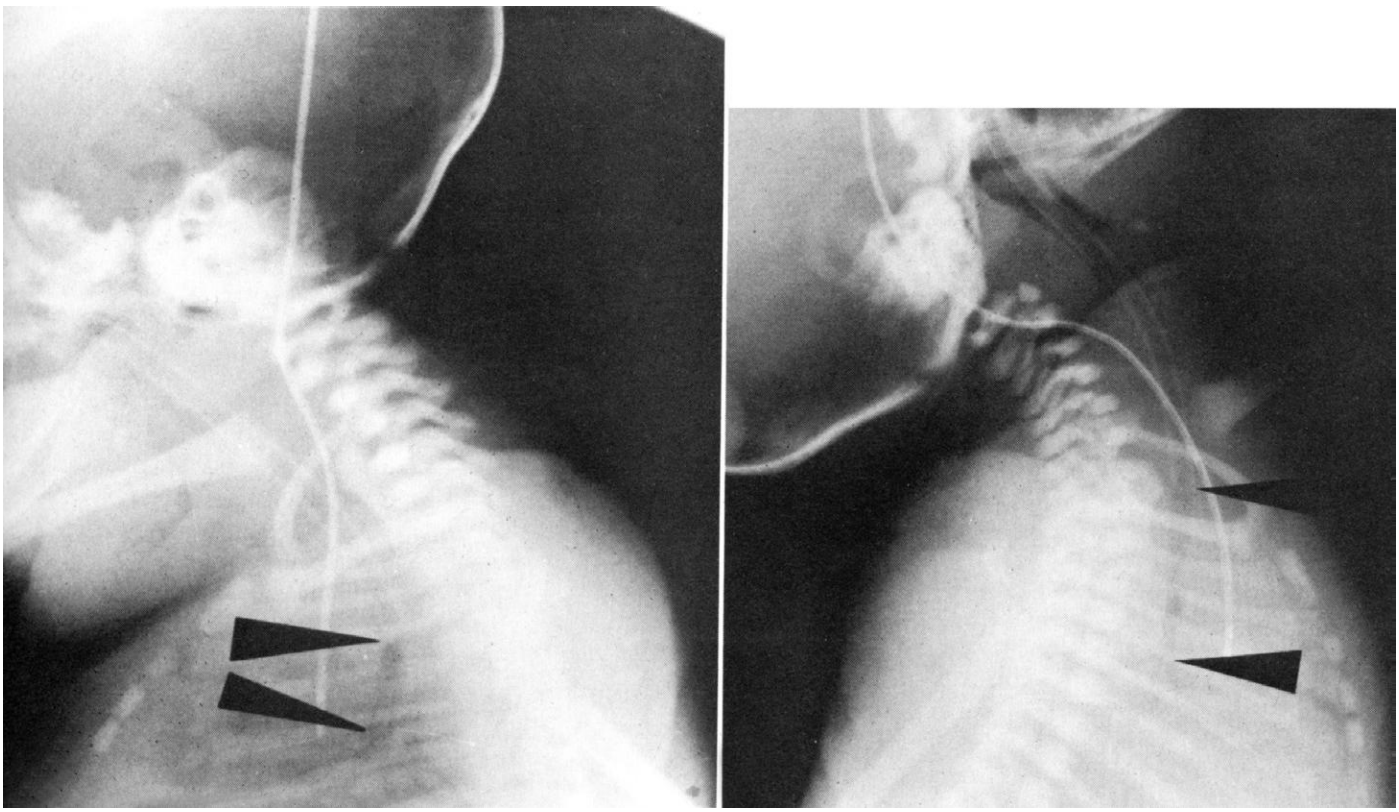

Figure 7-3 Reprint of x-ray photos showing endotracheal tube position changes with head position changes. (From Todres ID, deBros F, Framer SS, et al: J Pediatr 89:126-127, 1979.)

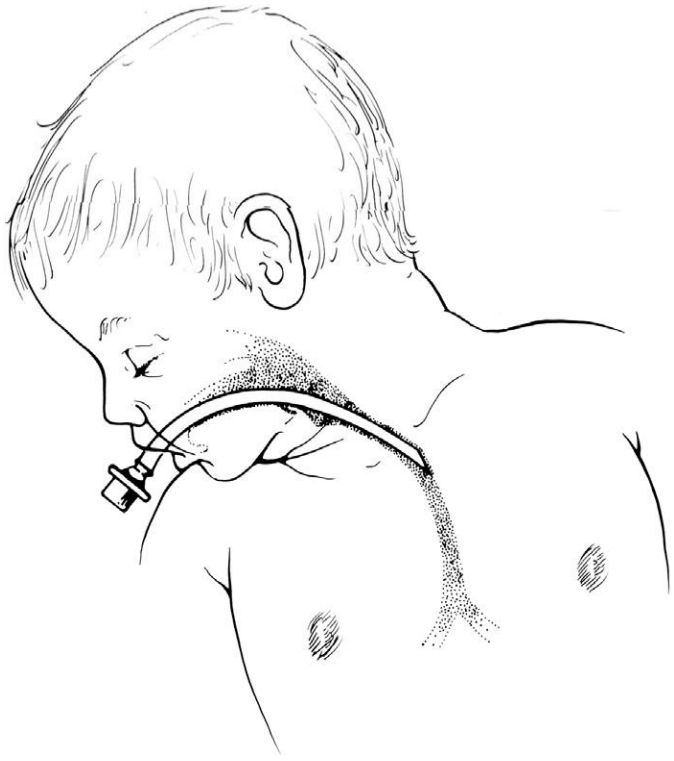

Figure 7-4 Illustration of endotracheal tube bevel abutment. (From Brasch RC, Heldt GP, Hecht ST: Radiology 141:387-391, 1981.)

Suctioning to the end of the ETT, to a premeasured depth that includes the ETT and adaptor, is also common practice in an effort to reduce trauma to the tracheal mucosa and to decrease the possible introduction of microorganisms through injured mucosa[48] and avoid bronchial perforation.[49] Although regular use of small volumes of normal saline (0.25-0.5 mL) to lubricate the ETT have previously been shown to not have deleterious effects in some studies,[50,51] other studies report potential adverse effects on oxygenation.[52,53] In addition, there is concern that saline instillation does not lead to increased secretion recovery and may be a risk factor in ventilator-associated pneumonia by way of moving the biofilm that occurs in the ETT further into the distal airway (see Chapter 24).

Closed suctioning systems that are placed inline with the ETT and ventilator circuit have become popular in many nurseries. Small studies support the reduction in transient hypoxemia and bradycardia with closed suctioning versus open suctioning methods.[54,55] A comparison of closed and open suctioning systems in small premature infants indicates that closed suctioning reduces physiologic disruption resulting from disconnection of the ventilator and does not increase bacterial colonization of the airway, frequency of suctioning, or incidence of nosocomial pneumonia.[56] Other potential advantages to closed suctioning include ease of use, with only one person needed, and reduced contamination with microorganisms. Although maintenance of lung volumes during suctioning

has been mentioned as an advantage during closed suctioning because positive pressure is maintained from the ventilator, this was not seen in bench test evaluation of these systems. The manufacturer recommends that the closed suction system shown in be replaced daily. (See also discussion in Chapter 6.)

Preventing Ventilator-Associated Pneumonia

Preventing nosocomial infection in the NICU and in other hospitalized patients, including ventilator-associated pneumonia (VAP) and catheter-related bloodstream infection, is now mandated by the Joint Commission of Accreditation of Hospitals. The assumption is that these complications are preventable by measures undertaken by care providers in the NICU. Many controversies remain regarding the diagnosis of VAP in neonates (see Chapter 24), and little evidence exists about how to best prevent VAP in the NICU. Yet many NICUs are undertaking quality improvement initiatives to reduce their incidence of VAPs by tightening criteria for diagnosis of VAP and instituting practices modeled on adult VAP prevention strategies.

Adult VAP prevention strategies are based on bacterial colonization of the airway and digestive tract and aerosolization of contaminated water, inhaled medications, or equipment leading to aspiration of contaminated secretions into the lower airway, resulting in bronchiolitis and focal or multifocal bronchopneumonia. Prevention strategies include using noninvasive ventilation whenever possible, using oral ETT instead of nasal, avoiding repeated intubations, changing the ventilator circuit only when visibly contaminated, keeping the head of bed elevated 30 to 45 degrees, using special ETTs that allow suctioning of the pharynx prior to deeper ETT suctioning, and giving special attention to oral hygiene to reduce bacterial colonization.

Oral colonization in premature infants has been reported in one small study.[61] Infants of 30 to 34 weeks' gestation who were not on antibiotics were colonized primarily with alpha hemolytic streptococcus, *E. coli*, and *Klebsiella* bacteria, whereas infants of 30 to 34 weeks' gestation receiving antibiotics were colonized with non–*E. coli* gram-negative bacteria. Infants of less than 30 weeks' gestation were colonized primarily with coagulase-negative *Staphylococcus aureus* (CONS). Thus the role of oral hygiene in neonates is not clearly understood, and interventions are not well researched at this time.

Some of the empirically based VAP prevention strategies for neonates on assisted ventilation include the following: (1) avoid breaking into respiratory circuit at all times, (2) use gloves with any contact (suctioning, etc.), (3) maintain separate ETT suctioning tubing and oral suctioning tubing ( ), (4) wipe oral cavity with normal saline, (5) avoid saline instillation with ETT suctioning, and (6) suction ETT only when visible secretions are noted or a change is noted in breath sounds or respiratory status. Although these interventions have not yet been rigorously studied, many NICUs are attempting to reduce their VAP rate by bundling similar interventions in the hope of potential benefit (see Chapter 24).

Oxygen Saturation Monitoring

The importance of monitoring for both hypoxemia and hyperoxemia cannot be overemphasized. The potential detrimental effects of hyperoxemia in premature infants

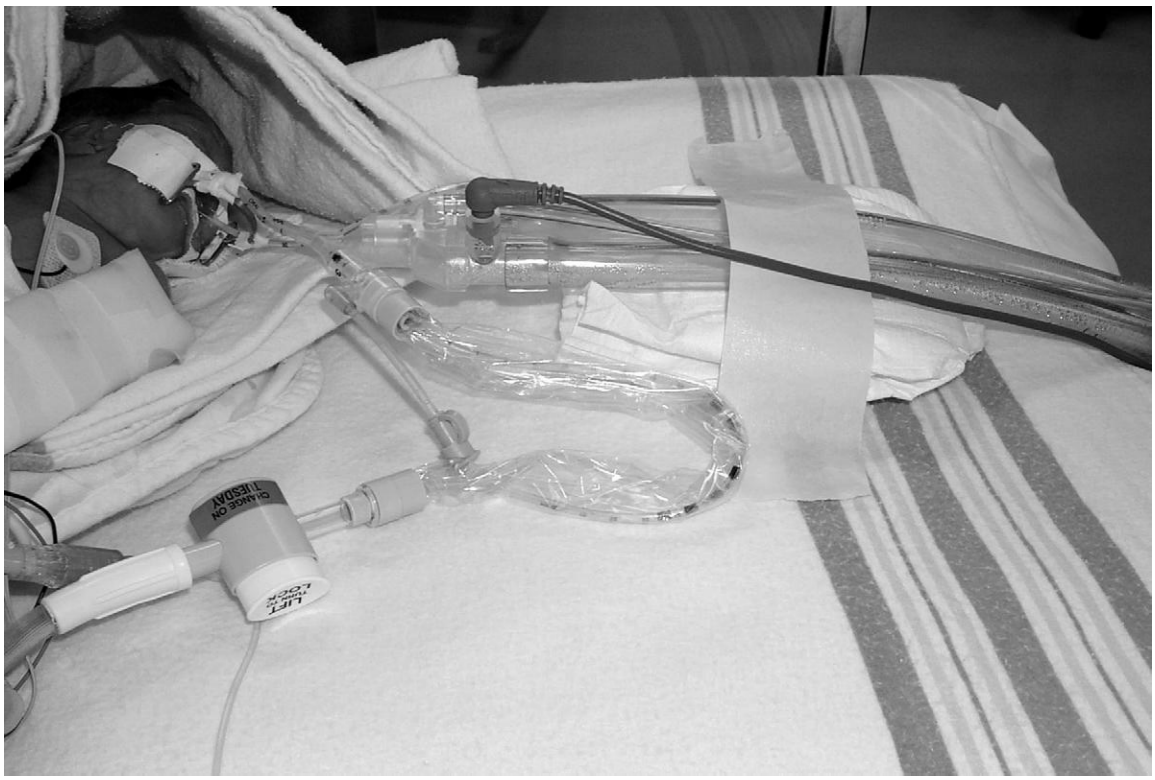

Figure 7-5 Photo of inline closed suction system.

Figure 7-6 Photo of system to separate suctioning tubing for endo tracheal tube and oral suctioning.

less than 32 weeks' gestation as a result of the overuse of oxygen include retinopathy of prematurity and bronchopulmonary dysplasia.[65,66] Oxygen saturation monitoring, now considered the fifth vital sign, successfully detects hypoxemia but cannot adequately monitor for hyperoxemia.

Reducing the targeted oxygen saturation ranges in premature infants to between 85% and 94% substantially decreased rates of grades III and IV retinopathy[62] and is now the recommended practice in NICU care. However, changing practices to prevent hyperoxia with the same vigilance that nurses acted to prevent hypoxia for many years has been challenging. An anonymous survey of NICU nurses documented significant, clinically relevant variability in oxygen saturation limits that are set during care of extremely low-birth-weight infants.[68] A multicenter study reported that, although lower alarm limits were set correctly 91% of the time, higher alarm limits were set correctly only 23% of the time, with 76% of the limits set too high and 24% of the limits found to be 100%.[69] The AVIOx study group also found that study infants were outside of targeted oxygen saturation ranges more than half of the time. These studies underscore the challenge of implementing this clinically essential practice change.

Multidisciplinary dedication, as well as changes in the attitudes and interventions of staff, is needed. One study reported that, instead of achieving a sudden decrease in the incidence of severe retinopathy after lowering the targeted oxygen saturation parameters, a more gradual decline in severe disease was seen over a 4-year period.[62] The authors describe an initial resistance to change among staff, difficulties in consistency in implementation on different shifts, acceptance by some staff whereas others continued to resist, and the need for initial training, followed by retraining, education, and sharing evidence about the dangers of hyperoxia. Finally, a signed statement from each staff member acknowledging their understanding of the policy and the mandate to comply was needed to ensure the connection between policy and practice.

Among the challenges of maintaining the targeted oxygen saturation parameters is the significant lability displayed by ventilated premature infants related to their disease conditions, responses to environmental stimuli, and need for ongoing interventions such as suctioning and other invasive procedures. In addition, until this effort to lower targeted oxygen saturation ranges was undertaken, clinical staff used their own individual judgment on how to respond to labile oxygenation, many choosing to dial the inspired oxygen levels up or down in response to changes in oxygen saturation. More explicit and detailed protocols were needed, with guidance on where to set alarm limits, how long to wait before responding to lower saturation levels, even how to respond, using incremental changes in FIO_2 of 2% to 5% instead of 10% or higher.[62,] Many NICUs have tightened their protocols, no longer allowing staff to "use their own judgment" in regard to responding to lower than desired oxygen saturation levels. Some NICUs have developed "campaigns" to remind staff of the need to carefully monitor oxygen saturation and maintain much tighter control of parameters, avoiding hyperoxia in infants at high risk of retinopathy of prematurity ( ). Carefully evaluating the number and types

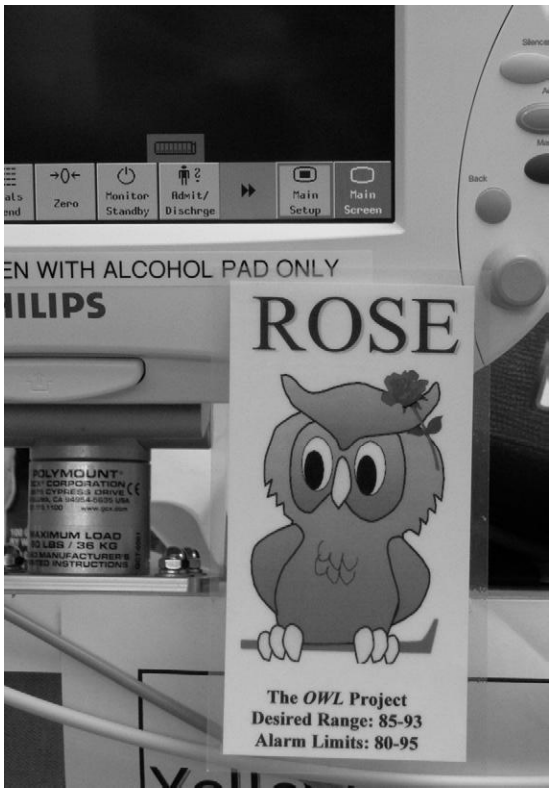

Figure 7-7 Photo of sign posted by the pulse oximeter to remind staff of the need to stay within oxygen saturation targets.

of procedures that a ventilated neonate receives is also necessary to reduce episodes of hypoxia and resulting hyperoxia when increased F_{IO_2} is administered.

Oxygenation and Behavioral Reactions to Procedures

Premature and seriously ill neonates are continually bombarded by procedures to improve their physiologic status or monitor their condition. With continuous monitoring using pulse oximetry, the effects of routine procedures on oxygenation, including heelstick blood sampling, intubation, suctioning of the endotracheal tube, chest physical therapy, weighing, bathing, changing diapers, and even social interaction were revealed; these procedures often resulted in significant and prolonged reductions in oxygenation. The extent of hypoxemia and overall distress can be dramatically reduced when personnel modify their caregiving according to the infant's responses.

Careful observations of oxygenation and behavioral reactions in ventilated infants with appropriate, individualized interventions can reduce the amount of stress the infant experiences. Supporting the infant's body position can also reduce the stressful effects of procedures and other interventions. Swaddling, rolls, and the use of other containment techniques have been shown to improve physiologic and behavioral organization during weighing, suctioning, and heelsticks, [,80] and provide comfort from pain.[81] One study reports a decrease in the frequency of hypoxemic episodes when ventilated premature infants were cared for in the prone position,[4] possibly by increasing lung compliance and decreasing asynchronous chest wall movements. Positioning the ventilated NICU infant has many potential benefits, including improved comfort and ventilation and prevention of postural deformities,[82] and should be approached with knowledge about how positioning goals can be best accomplished ( ).

Infants requiring assisted ventilation must undergo invasive procedures such as heelstick, endotracheal suctioning, IV placement, venipunctures, and adhesive removal on a daily basis. A descriptive study showed that infants under 31 weeks' gestation averaged a mean of 142 painful procedures during their NICU stay[83]; the authors encourage neonatal units to question the need for each and every potentially harmful invasive procedure. Interventions such as containment and offering a pacifier have been shown to reduce overall crying time and behavioral response to pain and discomfort. Oral sucrose has been shown to reduce crying when offered to newborns during painful procedures such as heelstick blood sampling.[85] Dipping a pacifier in sucrose or sterile water was also shown to significantly reduce pain responses in premature infants.[84]

Administration of Opiates and Sedatives

Routine administration of opiates and sedatives for ventilated infants remains controversial (see Chapter 21).[86] Use of opiates for ventilated infants during routine caregiving procedures such as weighing, bathing, and suctioning reduced hypoxemia and associated distress in one small study. However, the calming effects of medications, while reducing patient movement and promoting sleep, may also interfere with the infant's own respiratory effort and prolong weaning from assisted ventilation.[88] In a large randomized trial, there were no benefits seen with the continuous administration of morphine to ventilated preterm infants; infants treated with intermittent doses of morphine had lower pain scores, but infants who received "open label" boluses of morphine in addition to blinded continuous morphine infusions had an increased incidence of severe intraventricular hemorrhage.[89] Medications are best used judiciously, taking into account the stage of illness, therapeutic goals, and individual infant characteristics. Other causes of agitation should be considered, including inadequate ventilation. In many cases, patient comfort is often the best indicator of the appropriateness of selected ventilatory support modes, perhaps more useful than blood gases.

Box 7-1 INTERVENTIONS TO POSITION NEONATES

1. Change positions every 2 to 3 hours for extremely ill or immature infants.
2. Promote hand-to-mouth behavior by allowing the hands to be free when caregiver is present; side-lying positioning also assists in this goal.
3. "Nest" the infant by using blanket rolls or other position ing aids.
4. Place rolls under the hips when infant is prone to prevent hip abduction.
5. Roll shoulders gently forward with soft rolls when both prone and supine to prevent shoulder extension.
6. Use water- or air-filled pillows under the head to minimize cranial molding; frequent position changes (every 2-3 hours) from side to side; midline also facilitates this goal.
7. Support soles of feet with rolls to prevent ankle extension.
8. Swaddle with blankets or buntings when infant is stable to promote flexion and self-regulatory behavior.
9. Consider gentle massage to promote skin blood flow in infants with neuromuscular blocking agents; reposition every 2 hours to prevent pressure sores.
10. Position with right side down or prone to promote gastric emptying; prone position is best for minimizing effects of gastroesophageal reflux.
11. Elevate head of bed after feedings to reduce pressure of full stomach against the diaphragm and improve respiratory capacity.
12. Hold stable infants, even when on the ventilator; holding is soothing and provides vestibular stimulation similar to fetal experience.

Comfort Care

Another source of comfort for stable ventilated infants is to be held by their parents ( ). In recent years, holding infants who require assisted ventilation has become more common in many NICUs, as staff became cognizant of the importance of holding for the parents and developed the necessary skills and comfort level themselves in assessing and handling the ventilated infant. Some nurseries have even developed techniques that allow parents to hold their infants even when they are on high-frequency oscillatory ventilators.[90] A special type of holding, skin-to-skin or "kangaroo holding" is now practiced in many nurseries, even for ventilated infants ( ).[91]

During skin-to-skin holding, the mother (or father) holds the infant clothed only in a diaper, against the skin of his or her chest; the infant is then covered with a blanket or the parents clothing. Practical issues during skin-to-skin holding includes transfer techniques from bed/incubator to parent, selecting chairs that support mother and infant comfortably, and monitoring during holding. Transfer techniques include carefully moving the baby to the seated mother or having the mother stand while the infant is placed on her chest; then the mother carefully lowers herself with the infant onto the chair. Other nurseries have invested in special lounge or reclining chairs that can be raised to the level of the infant's incubator, which then provide a comfortable way for the mother to relax during holding for prolonged periods. Continuous monitoring of heart rate, oxygenation, and skin temperature is necessary to determine each individual infant's tolerance during holding.

Benefits of early skin-to-skin holding on the psychological state of the mother, improved lactation, and parent-infant bonding have been demonstrated.[92,93] A number of studies have evaluated the effects of skin-to-skin holding on the infant with sometimes conflicting results seen in temperature stability[94,95] and other physiologic parameters. A recent prospective study of 53 premature infants with mean weight at study of 1253 g (range 631-1700 g), including five ventilated infants, found the infants remained clinically stable with more efficient gas exchange, with no risk of hypothermia even for infants weighing less than 1000 g.[98] Adverse effects of skin-to-skin holding were reported by another study, including a significant increase in the frequency of bradycardia and hypoxemia, which may be due to an increase in temperature.[99] Careful monitoring of all physiologic parameters is necessary during skin-to-skin holding to assess each infant's response to this valuable experience and to determine when nursing intervention is needed.

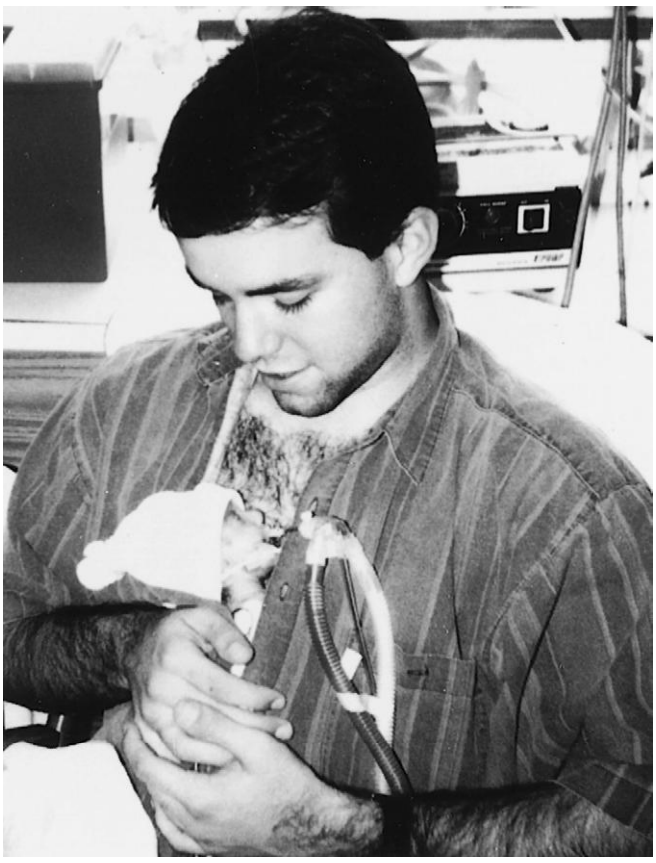

Figure 7-9 Photo of parent holding infant skin-to-skin.

Figure 7-8 Photo of parent holding ventilated infant.

Sudden Deterioration

A sudden deterioration can occur as a result of a multitude of factors in the ventilated neonatal patient. NICU nurses are often the first to detect the change and are prepared to respond to each situation. Among the causes of acute decompensation are malpositioned ETTs, plugging of the ETT, and pulmonary air leaks. (See Chapter 9.)

The cause of acute deterioration is not always apparent. Often the assessment and problem solving of these events occurs during resuscitation. Hand ventilation with a resuscitation bag connected to a manometer is initiated immediately, and F_{IO_2} increased until oxygen saturation reaches 90% to 95%. Breath sounds are immediately auscultated; if equal bilaterally, the tube is likely in proper position and free from thick secretions. If the tube falls below T4 and into the right mainstem bronchus, breath sounds are audible only on the right side. If the breath sounds are distant, or if air entry is detected in the gastric areas accompanied by distention, or an audible cry is heard, the ETT may have slipped into the esophagus. An end tidal CO_2 monitor or detection device will show an absence of CO_2 during expiration. The ETT should be immediately removed and bag and mask ventilation provided until the infant is

reintubated. Once replaced, the ETT should be securely taped at the same place as the previous tube, and an x-ray is obtained to confirm appropriate ETT position.

If the breath sounds are louder on the right side, the ETT may have slipped into the right mainstem bronchus. A chest x-ray can confirm this diagnosis, or perhaps identify an air leak in the left lung. If the ETT extends into the right bronchus, the left lung may appear to have atelectasis on x-ray. The appropriate adjustment to the ETT position is determined by measuring the tube position from the x-ray and then repositioning and taping the ETT securely.

If the ETT is plugged with secretions, breath sounds may be diminished bilaterally, with decreased rise of the chest wall during hand ventilation. Initially, the ETT is suctioned to attempt to remove the secretions. If this measure is unsuccessful, the ETT is removed and bag and mask ventilation initiated until the ETT is replaced.

An extremely serious and potentially life-threatening cause of sudden deterioration is tension pneumothorax. The immediate clinical presentations are cyanosis, bradycardia, decreased blood pressure, and narrowing pulse pressure, as well as a shift in the point of maximal impulse of the heart and breath sounds diminished or absent on the affected side. Once the decompensation is detected, the patient is hand ventilated. The diagnosis may be confirmed with transillumination of the chest with a high-density fiberoptic light source, or with a chest x-ray. Sometimes the situation is so severe that the chest is decompressed with needle aspiration before the diagnosis is confirmed radiographically. Once the air is evacuated and the patient stabilized, a chest tube is inserted. It is then attached to a drainage system with vacuum set at 10-20 cm of negative pressure to assist in air removal. An algorithm that describes interventions for acute deterioration for infants on assisted ventilation is shown in Figure 9-8 in Chapter 9.

Summary

In conclusion, the daily care of newborns who require assisted ventilation involves knowledge that extends beyond pulmonary anatomy, physiology, and technology. The nursing care for these infants demands advanced knowledge of multiple organ systems, precision in caregiving, and creative problem solving. Also critical to successful outcomes are attention to developmental care and family-centered care during this vulnerable period for infants and their families.

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8 Noninvasive Respiratory Support

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Noninvasive respiratory support (NRS) is becoming increasingly more popular as a method of respiratory support in sick newborn infants. NRS refers to respiratory support provided without use of an endotracheal tube. This support consists of continuous positive airway pressure (CPAP), continuous negative expiratory pressure (CNEP), and noninvasive positive-pressure ventilation (NIPPV). Oxyhoods and nasal cannulae may also provide NRS and are briefly discussed in this chapter as well.

Confusing terminology has evolved as this rapidly developing field has expanded, resulting in a veritable alphabet soup of acronyms used to describe various methods of NRS. Unfortunately, such variations can result in confusion among readers of the neonatology literature. In Table 8-1 we have compiled the diverse group of acronyms we have encountered that relate to this topic. In Table 8-2 we list the acronyms we prefer, which are used throughout this chapter. These reflect what we believe to be the most commonly applied terms.

Continuous distending pressure (CDP) is a general term defined as the maintenance of an increased transpulmonary pressure during the expiratory phase of respiration. CPAP, PEEP, and CNEP are each types of CDP. The basic goal when one treats with any form of CDP is to help provide distension of the lungs, thereby preventing collapse of the alveoli and terminal airways during expiration.

The acronym CPAP reflects a positive pressure applied throughout the respiratory cycle to the airways of a spontaneously breathing baby. Positive end-expiratory pressure (PEEP) refers to the positive pressure applied during the expiratory phase of respiration to a mechanically ventilated neonate. Continuous negative expiratory pressure (CNEP) may also be applied transthoracically to similarly distend distal airways. However, it is a technique rarely used in infants during the past four decades. A variety of CDP devices available today allow "breaths" to be delivered above the baseline CPAP pressure; such breaths may be synchronized or nonsynchronized to the infant's own breaths. The goal of these devices is to enhance CO_2 removal and stimulate breathing. Various CDP devices provide an adjunct to weaning infants off mechanical ventilation after they have been extubated and also help manage apnea of prematurity. They are used for a variety of other respiratory conditions associated with (1) decreased functional residual capacity; (2) atelectasis; (3) right-to-left cardiac or intrapulmonary shunting; (4) ventilation-perfusion mismatch; (5) alveolar edema; (6) aspiration of noxious substances; (7) increased airway resistance; (8) chest wall and airway instability; and (9) obstructive apnea.

In this chapter, we have attempted to present a broad overview of the current status of NRS. As part of this review, we refer to relevant Cochrane Collaboration reviews. For readers unfamiliar with the Cochrane Collaboration, it is an organization in which members perform systematic reviews of randomized, controlled trials in order to produce unbiased and precise estimates of the effect of a treatment on outcomes of clinical importance. A number of such reviews have been completed concerning NRS. Readers interested in the various reviews concerning neonates may go to the following website to peruse the topics: ***http://www.nichd.nih.gov/cochrane/cochrane.htm***. This website is provided for free by the National Institute of Child Health and Human Development, a division of the National Institutes of Health (NIH).

Background and Historical Aspects

The history of NRS is largely the history of CPAP. Although many neonatologists believe this technique to be a relatively recent innovation, it was described for use in newborn infants almost a century ago.[1] In his 1914 textbook on diseases of the newborn infant, Professor August Ritter von Reuss describes an apparatus (Fig. 8-1, *A*) that is virtually equivalent to the "bubble CPAP" that is used today (Fig. 8-1, *B*). We are uncertain why this concept was abandoned from the care of neonates during the ensuing 60 years. The application of positive airway pressure in the clinical management of adult patients with lung disorders dates back to the 1930s. Poulton and Oxon,[2] Bullowa,[3] and Barach et al.[4] described use of positive pressure via face masks for acute respiratory insufficiency, pneumonia, and pulmonary edema, respectively.

During the 1940s, positive pressure was introduced for high altitude flying. Because of the recognition of potential complications of CDP caused by its effects on major blood vessels,[5] during the ensuing two decades it was used, but only sporadically in clinical practice. In 1967 PEEP was added to mechanical ventilation in conjunction with peak inspiratory pressure to treat hypoxemia in adults with acute respiratory distress syndrome (ARDS).[6] In neonates that were mechanically ventilated during the 1960s, it was a common practice to allow the positive pressure at end-expiration to fall to 0 cm H_2O.

TABLE 8-1 Confusing Status of Acronyms Concerning Continuous Distending Pressure*

Acronym	Definition
BiPAP	Bi-level positive airway pressure
CDP	Continuous distending pressure
CNEP	Continuous negative expiratory pressure
CPAP	Continuous positive airway pressure
DPAP	Directional positive airway pressure
ETCPAP	Endotracheal tube continuous positive airway pressure
HFNC	High flow nasal cannulae
IFD	Infant flow driver
NC	Nasal cannulae
NCPAP	Nasal continuous positive airway pressure
nCPAP	Nasal continuous positive airway pressure
N-CPAP	Nasal continuous positive airway pressure
n-CPAP	Nasal continuous positive airway pressure
NEEP	Negative end-expiratory pressure
NHFV	Nasal high frequency ventilation
NIPPV	Nasal intermittent positive-pressure ventilation
NPCPAP	Nasopharyngeal continuous positive airway pressure
NP-CPAP	Nasopharyngeal continuous positive airway pressure
NP-CPAP	Nasal prong continuous positive airway pressure
NPPV	Noninvasive positive pressure ventilation
NPSIMV	Nasopharyngeal synchronized intermittent mandatory ventilation
NP-SIMV	Nasal prong synchronized intermittent mandatory ventilation
NP-SIMV	Nasopharyngeal synchronized intermittent mandatory ventilation
NSIMV	Nasal synchronized intermittent mandatory ventilation
NSIPPV	Nasal synchronized positive-pressure ventilation
NV	Nasal ventilation
PDP	Positive distending pressure
PEEP	Positive end-expiratory pressure
SNIPPV	Synchronized nasal intermittent positive-pressure ventilation

*Note that different acronyms are used to mean the same thing, and sometimes the same acronym is used to mean different things.

A classic clinical finding in nonintubated premature infants with respiratory distress syndrome (RDS) is an expiratory grunt. Widespread alveolar collapse is the predominant pathophysiology of that disorder. Harrison and colleagues[7] recognized that the grunt was produced by the infants who would close their glottises during expiration in an attempt to increase pressure in the airways and maintain dilatation of their alveoli. Limited air escaping through the partially closed glottis produced the audible grunt. In a landmark report in 1971, Gregory and colleagues[8] described the initial clinical use of CPAP to maintain alveolar stability (via either an endotracheal tube or a head box) in premature infants with RDS.

Use of CPAP in neonates during the 1970s was welcomed with enthusiasm as the "missing link" between supplemental oxygen and mechanical ventilation to treat RDS.[9] During this decade a simple approach to providing CPAP was widely used, application via binasal prongs, known as nasal CPAP (NCPAP).[10,11] Alternative methods of providing CPAP were occasionally described (see subsequent section on delivery of CPAP). During the 1970s, it was commonly believed that air leaks (such as pneumothoraces) were more common with CPAP than with mechanical ventilation. Gastric distension during CPAP was frequently observed too. The hard nasal prongs often were not tolerated by neonates. In addition, intermittent mandatory ventilation (IMV), first described in the early 1970s, quickly became the standard of care for supporting the lungs of sick newborn infants, and remained so for three decades. For these reasons the use of CPAP fell out of favor during this period.

Exogenous surfactant therapy has clearly decreased the mortality rate of very-low-birth-weight (VLBW) neonates with less than 1500 g birth weight. Other chapters in this textbook describe additional ways of ventilating infants that were developed during the 1980s and 1990s, such as high-frequency ventilation and patient-triggered ventilation, in an attempt to further improve pulmonary outcomes. To date, however, none of these techniques have substantially improved either morbidity (e.g., air leaks and chronic lung disease) or mortality. Over the past 15 years, there has been a resurgence of interest in CPAP as a gentle way of maintaining patency of alveoli and allowing sufficient gas exchange.

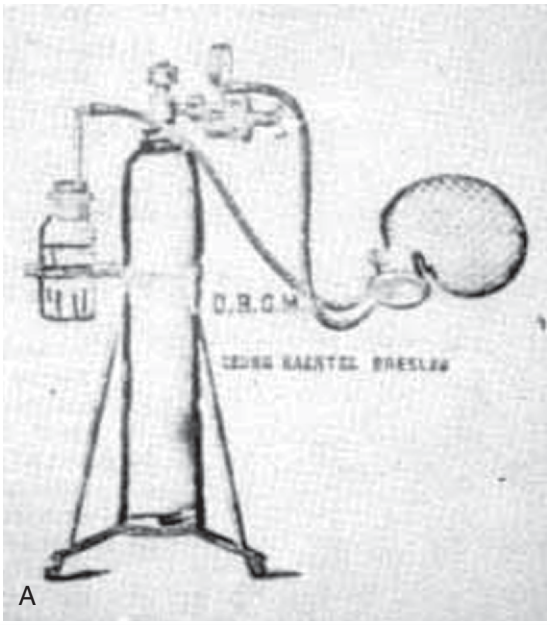
Atelectotrauma is both a cause and consequence of lung injury.[12] It is a process of individual lung units collapsing and then requiring higher pressures to reopen. Unfortunately, some areas of the lungs may remain collapsed, whereas others become overventilated. The collapse of some lung units, as well as the overexpansion of others, may injure lung parenchymal elements and the alveoli themselves. The process of closing and reopening, particularly when there is excess alveolar distension, may lead to inflammation and the release of cytokines. This process has been termed *biotrauma*.

Volutrauma is regional overdistension of the lungs resulting from large tidal volume breathing. Such breaths may damage the pulmonary capillary endothelium and the basement membranes. As a consequence, fluid, protein, and blood may leak into the airways and alveoli. This

TABLE 8-2 Preferred Acronyms Concerning Continuous Distending Pressure*

Acronym	Definition
BiPAP	Bilevel positive airway pressure
CDP	Continuous distending pressure
CNEP	Continuous negative expiratory pressure
CPAP	Continuous positive airway pressure
ECMO	extracorporeal membrane oxygenation
HFNC	High-flow nasal cannulae
HHNC	Humidified, high-flow nasal cannulae
IFS	Infant Flow system (variable flow nasal CPAP)
NC	Nasal cannulae
NCPAP	Nasal continuous positive airway pressure
NHFV	Nasal high frequency ventilation
NIPPV	Nasal intermittent positive-pressure ventilation
NPCPAP	Nasopharyngeal continuous positive airway pressure
NPSIMV	Nasopharyngeal synchronized intermittent mandatory ventilation
NRS	Noninvasive respiratory support
NSIMV	Nasal synchronized intermittent mandatory ventilation
NV	Nasal ventilation
PEEP	Positive end-expiratory pressure
VFD	Variable flow driver

*Acronyms presented in this table are used in this chapter.



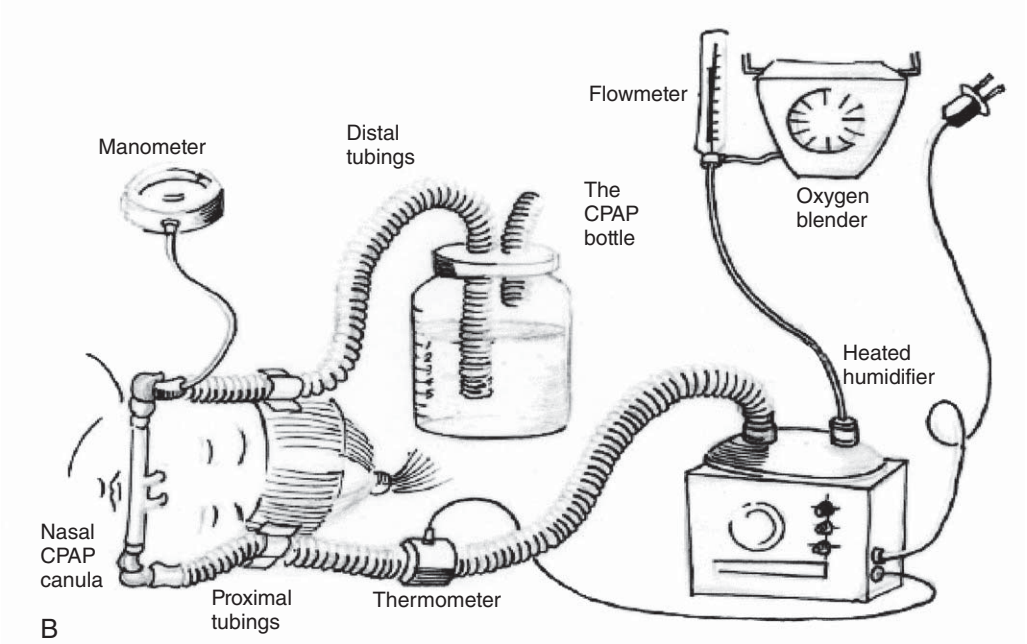


Figure 8-1 ■ **A,** A CPAP apparatus described in von Reuss's 1914 textbook *Diseases of the Newborn*. Note the tubing that leads from the oxygen tank to the equivalent of a mask and bag device. A valve regulates oxygen flow. The distal tubing leaves the mask and is placed in a bottle of water to regulate the pressure. The apparatus is strikingly similar to "bubble CPAP" used in the current era. **B,** A schematic of the "bubble CPAP" set-up. A source of blended gas is administered to the child, in this case via Hudson prongs. The distal tubing is immersed in fluid to a depth of the desired level of CPAP. (**A** from Arch Dis Child 65:68, 1990; used with permission. **B** from Pediatrics 108:759-761, 2001; used with permission.)

process also promotes lung inflammation. It does not take much to initiate the cascade of lung injury. In preterm animals, as few as six manual tidal ventilations of 35 to 40 mL/kg administered to preterm lambs before surfactant treatment resulted in lung injury and decreased response to exogenous surfactant.[13]

The term *barotrauma* refers to purported injury from the pressure used to inflate the lungs. Although barotrauma was once thought to be a major factor in producing lung injury, atelectotrauma, volutrauma, and biotrauma are currently believed to be the key elements. An extensive discussion of the pathophysiology of chronic lung disease can be found in Chapter 23.

Optimal lung inflation is defined as the lung volume at which the recruitable lung is open but not overinflated.[12] The art of medicine in the newborn intensive care unit (NICU) is to achieve optimal lung volume in neonates with respiratory disorders. CPAP is one method many clinicians believe best achieves optimal lung inflation with resultant good oxygenation and ventilation, without the

use of an endotracheal tube. Using CPAP, care must be taken not to decrease the distending pressure below the closing pressure of the majority of the alveoli, but instead to achieve the lowest possible pressure that will maintain open alveoli without overdistension.

Reviews of NCPAP over the past two decades will refer to the 1987 publication of Avery et al.,[14] who surveyed eight NICUs to assess the incidence of chronic lung disease (CLD). The frequency of CLD in that report was lowest at Babies and Children's Hospital, Columbia University, New York. That center reportedly used NCPAP considerably more often than the other seven NICUs. Many clinicians have been influenced by the "Columbia" approach in which "bubble CPAP" is used early in the course of respiratory distress of both premature and term-gestation infants.

As part of this strategy, clinicians often accept hypercapnia with $PaCO_2$ levels up to 65 mm Hg (8.7 kPa) or higher, PaO_2 levels as low or lower than 50 mm Hg (6.7 kPa), and pH values as low as 7.20. This general approach has been used in that institution for more than 30 years.[14] Despite the promulgation and widespread acceptance of this approach, to date there are no published randomized, controlled trials (RCTs) that validate its superiority over any other management strategy or technology. There are no long-term outcome studies comparing neurologic, pulmonary, and other findings among infants treated in this manner with others who are managed differently. Additionally, clinicians should be concerned about the potentially deleterious effects of "permissive hypercapnia" on cerebral autoregulation and the developing brain.

Van Marter and colleagues[16] assessed the differences in outcomes between the Columbia NICU and two NICUs in Boston. Although CLD was less common at Columbia, this review has been criticized because of differences in patient populations, indications for mechanical ventilation, and other treatment strategies, as well as the definition of CLD that was used. Much of the apparent success of the Columbia approach has been attributed to the diligent management of sick neonates by a single senior clinician. A rigorously designed, randomized, controlled trial (RCT) is sorely needed to assess whether or not bubble CPAP will truly prevent or mitigate CLD. Nevertheless, knowledge of the Columbia experience has contributed to the flurry of research concerning CPAP over the past 20 years.

Methods of Generating Continuous Distending Pressure

Following Gregory's initial publication demonstrating success using CPAP in premature infants,[8] efforts were made to simplify the manner in which CDP was generated, as well as the mode of delivery. Kattwinkel et al.,[10] as well as Caliumi-Pellegrini and colleagues,[11] described devices in which binasal prongs were used for delivery. These methods were standard for a number of years. In the subsequent section, various methods of CPAP delivery (prongs, mask, and others) are described later in this chapter.

The gas mixture delivered via CPAP is derived from either a continuous flow or variable flow source. From the 1970s through the 1980s, only continuous flow was used. Continuous flow CPAP consisted of gas flow generated at a source and directed against the resistance of the expiratory limb of a circuit. In ventilator-derived CPAP, a variable resistance in a valve is adjusted to provide this resistance to flow.

A second method of continuous flow CPAP is the so-called "bubble" or water-seal CPAP (see Fig. 8-1, *B*), the method advocated at the Columbia University NICU.[15,17] With bubble CPAP, blended gas flows to the infant after being heated and humidified. Typically, nasal prong cannulae are secured in the infant's nares, such as with the Hudson® prongs (Hudson Respiratory Care, Inc., Temecah, Calif) (Fig. 8-2) or Inca® prongs (Ackrad Laboratories, Inc., Cranford, NJ). The distal end of the expiratory tubing is immersed under either 0.25% acetic acid or sterile water to a specific depth to provide the approximate level of CPAP desired. Clinicians must be cautious when using this method, however, because the level of CPAP is always higher than the submerged depth of the expiratory tubing and is flow dependent.[18,19]

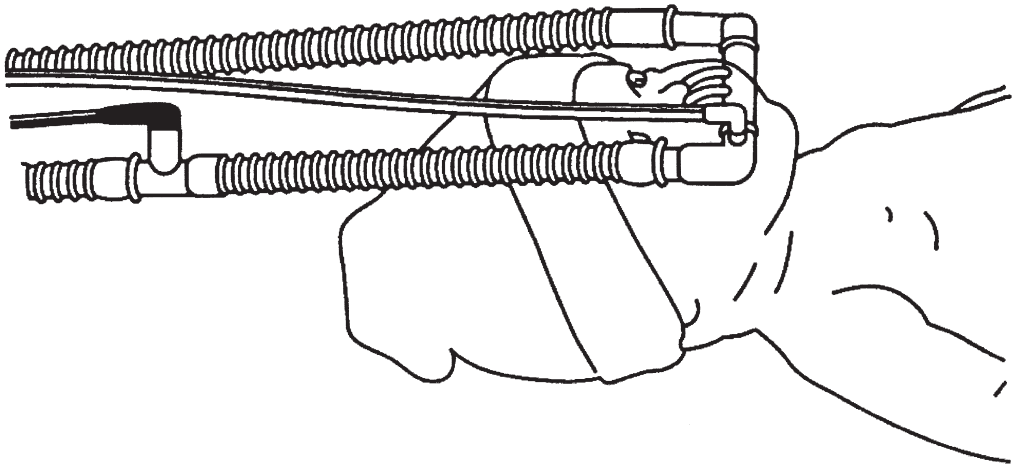


Figure 8-2 ■ A representation of the positioning and appearance of Hudson nasal prongs, which are commonly used for NCPAP. (From Arch Dis Child Fetal Neonatal Ed 85:F82-F85, 2001; used with permission.)

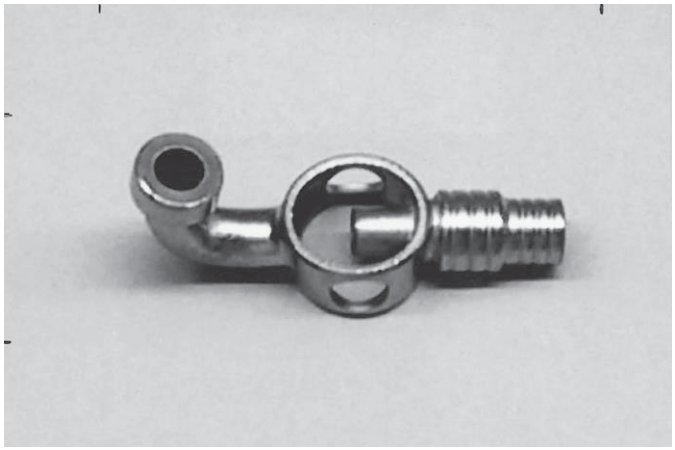


Figure 8-3 ■ A photograph of a Benveniste gas-jet valve. The device consists of two metal coaxially positioned tubes connected by a metal ring. (Photograph courtesy Dr. Jens Kamper).

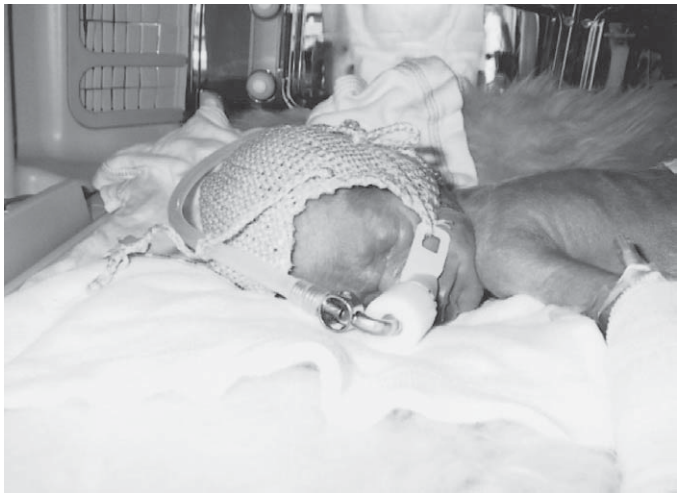


Figure 8-4 ■ Photograph of a baby being managed with the Benveniste gas-jet valve. The depicted infant is of 28 weeks' gestation with a birth weight of 1080 g and is being managed for RDS. No expiratory tubing is necessary because the exhaled gas leaves the system through the jet valve. (Photograph courtesy Dr. Jens Kamper.)

Lee and colleagues[20] observed vibrations of infants' chests during bubble CPAP at frequencies similar to those used with high-frequency ventilation When compared to ventilator-derived CPAP, Lee's group found bubble CPAP to result in decreased minute ventilation and respiratory rate. These authors speculated that the observed vibrations enhanced gas exchange. Pillow et al.[21] described similar findings in the lamb model. However, in both of these studies, bubble CPAP was delivered via an endotracheal tube, not nasal prongs. Data obtained using a NCPAP model suggest that these oscillations are quite minimal and unlikely to contribute in a significant way to ventilation.[18] Morley et al.[22] assessed bubble CPAP in a randomized, crossover trial. The bubbles were generated at various rates, from "slow" to "vigorous." These investigators found that bubbling rates had no effect on carbon dioxide, oxygenation, or respiratory rate. The gas-exchange mechanisms of the bubble CPAP set-up must be further explored to elucidate whether there is a to-and-fro oscillatory waveform that truly augments ventilation.

The Benveniste gas-jet valve (Dameca, Copenhagen, Denmark) has been used extensively in Scandinavia.[9,23-25] The device consists of two coaxially positioned tubes connected by a ring (Fig. 8-3). The device then is connected to a single nasal prong or to binasal prongs. The device works via the Venturi principle to generate pressure and is a continuous-flow CPAP system. The Benveniste gas-jet valve is typically connected to a blended gas source and then to the patient (Fig. 8-4).

Over the past 15 years, variable-flow CPAP has come into widespread use. The technique was developed by Moa et al.[26] to reduce the patient's work of breathing. CPAP is generated by varying the flow delivered to the infant's nares and a specially constructed nosepiece is employed. These devices use the Bernoulli effect and gas entrainment via dual injector jets directed toward each nasal prong to maintain a constant pressure (Figs. 8-5 to 8-10). With the variable-flow system, when the infant makes a spontaneous expiratory breathing effort, there is a so-called fluidic flip, which causes the flow of gas going toward the nares

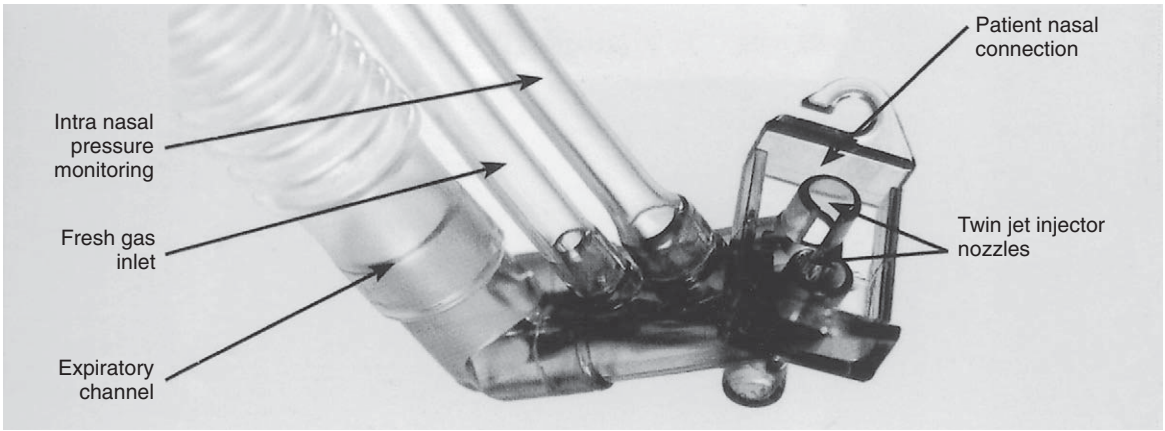


Figure 8-5 ■ A photograph of the Infant Flow Driver pressure generator without the nasal prongs being attached. This is a variable-flow CPAP device. Dual injector jets are directed toward the nasal prongs after they are attached. (Courtesy Electro Medical Equipment, Ltd., Brighton, England.)

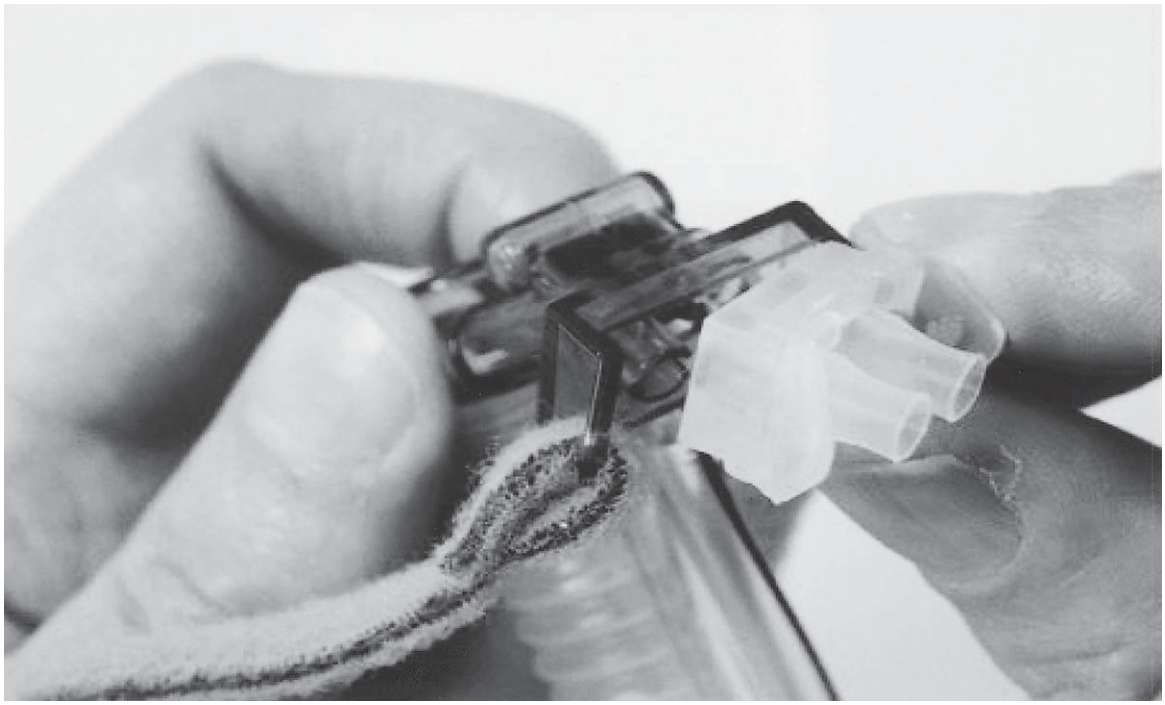


Figure 8-6 ■ Attachment of nasal prongs to the Infant Flow Driver prior to insertion in an infant's nares. (Courtesy Electro Medical Equipment, Ltd., Brighton, England.)

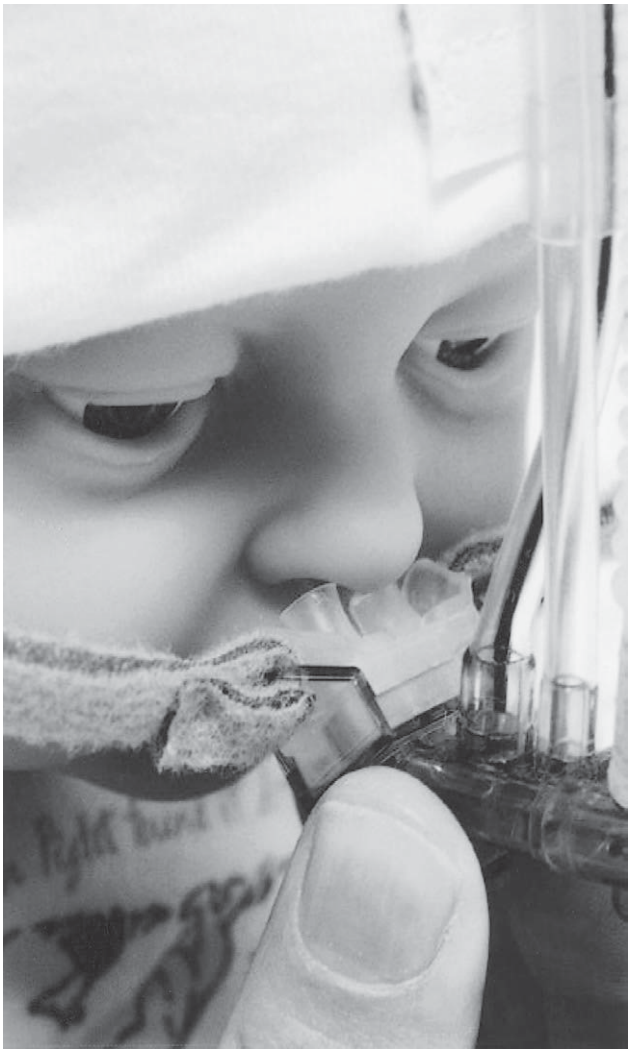


Figure 8-7 ■ Placement of the nasal prongs and Infant Flow Driver pressure generator in a mannequin's nares. (Courtesy Electro Medical Equipment, Ltd., Brighton, England.)

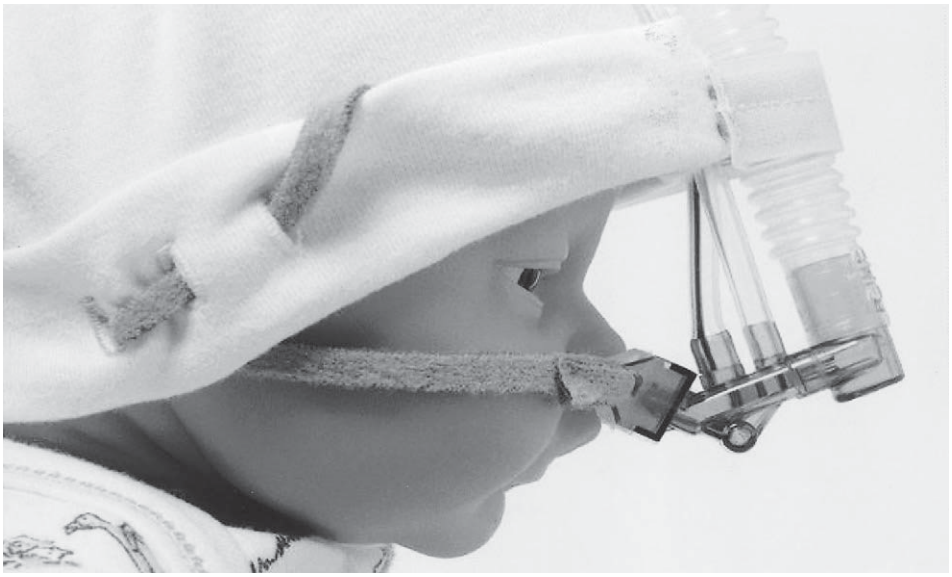


Figure 8-8 ■ Lateral view of a mannequin on which the Infant Flow Driver is attached. Note the proper fixation of the device. (Courtesy Electro Medical Equipment, Ltd., Brighton, England.)

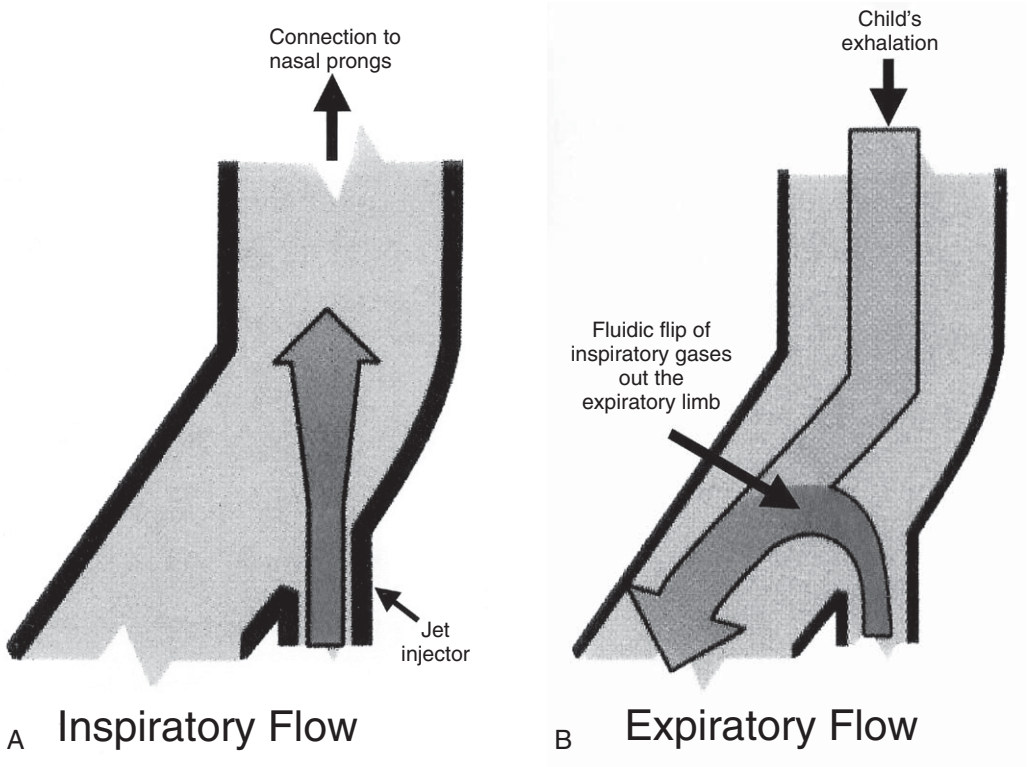


Figure 8-9 ■ Schematic representations of the "fluid flip" of the variable-flow CPAP device, the Infant Flow Driver. **A,** During the child's inspiration, the Bernoulli effect directs gas flow toward each nostril to maintain a constant pressure. **B,** During the child's exhalation, the Coanda effect causes inspiratory flow to "flip" and leave the generator chamber via the expiratory limb. As such, the child does not have to exhale against high inspiratory flow, and work of breathing is decreased compared to continuous-flow CPAP. The residual gas pressure enables stable levels of CPAP to be delivered to the child. (Courtesy Electro Medical Equipment, Ltd., Brighton, England.)

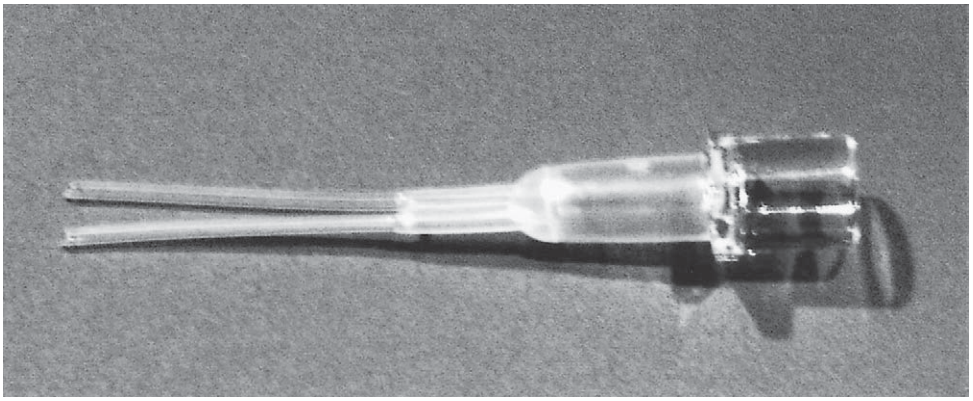


Figure 8-10 ■ An example of nasopharyngeal prongs used for CPAP. (This particular device is produced by NeoTech, Inc., Chatsworth, Calif.)

to "flip" around and to leave the generator chamber via the expiratory limb (Figs. 8-9, *A* and *B*), thus assisting exhalation. This phenomenon is due to the Coanda effect, which describes the tendency of a fluid or gas to follow a curved surface. A residual gas pressure is provided by the constant gas flow, enabling stable CPAP delivery at a particular pressure during the entire respiratory cycle.

A extensive description of the physiology of variable-flow CPAP can be found elsewhere.[27-29] Klausner et al.[28] used a simulated breathing apparatus and found the work of breathing via nasal prongs to be one-fourth that of continuous-flow CPAP. Pandit et al.[29] assessed work of breathing in premature infants treated with either continuous-flow or variable-flow NCPAP. They found the work of breathing to be significantly less with variable-flow NCPAP. Additionally, the variable-flow devices appear to be able to maintain a more uniform pressure level compared to continuous-flow CPAP.[26,28] This may be the reason for the improved lung recruitment seen with variable-flow CPAP of this type.[30]

Currently two variable-flow CPAP systems are commercially available. The Infant Flow has been the most extensively evaluated and is marketed by Cardinal Health (Dublin, Ohio). The Arabella® system (Hamilton Medical, Reno, Nev.) has a flow-generating chamber that varies slightly from the IFS, although the same principles (Venturi, Bernoulli, and Coanda) apply. These two systems appear to function similarly.[31]

Several investigators have assessed whether differences exist among the various methods of delivering NCPAP. Liptsen et al.[32] compared work of breathing in bubble vs. variable-flow CPAP in 18 premature infants. These investigators found more labored and asynchronous breathing with bubble NCPAP compared to variable-flow NCPAP. Boumecid and colleagues[33] compared variable-flow NCPAP with ventilator-driven, continuous-flow NCPAP. They described increased tidal volume and improved breathing synchrony with the variable-flow device compared to the ventilator-driven NCPAP.

Devices Through Which CPAP Is Provided

Multiple nasal devices are available through which continuous-flow CPAP may be delivered. The devices may be either short (6-15 mm) or long (40-90 mm). It is probably more accurate to refer to the former as nasal prongs and to the latter as nasopharyngeal prongs. The acronym for nasal CPAP (NCPAP) is often used in reference to both. A single nasopharyngeal prong is sometimes used to transmit CPAP, and typically consists of an endotracheal tube that has been cut and shortened and then inserted through one of the nares into the nasopharynx.

There are multiple types of binasal prongs. Two examples are noted in Figures 8-10 and 8-11. The nasal prongs used with the Infant Flow Driver are depicted in Figures 8-6 and 8-7. Unfortunately, little comparative data is available to guide clinicians in choosing one type of prong over another. Some prongs, such as those used with the IFS, are specific to the device (Fig. 8-12). Prongs may vary in the type of material, length, configuration, and diameters (both inner and outer). These aspects will affect the resistance to flow in a particular device and, as a result, the pressure entering the device may differ considerably from that entering the child's nares or nasopharynx. DePaoli et al.[34] compared the pressure drop for five different CPAP devices at various rates of gas flow. These authors found great variation between devices in the pressure drop. Although the least amount of drop-off occurred with the Infant Flow system, these authors cautioned that their findings do not establish clinical superiority of one mode of NCPAP or nasopharyngeal CPAP (NPCPAP) over any other. DePaoli and colleagues[35] have published a more in-depth appraisal in their Cochrane review characterizing NCPAP devices and pressure sources.

Multiple other methods of delivering CPAP to neonates have been described over the past four decades. The initial studies describing CPAP for treatment of premature infants with RDS most often used the endotracheal tube to deliver CDP.[8] This is one of the most effective methods with many advanatages[36]: (1) ease of use; (2) minimal to no leakage in the system; (3) ability to achieve high pressure with low flow; (4) ease of switching back and forth to mechanical ventilation; and (5) straightforward fixation of the tube. Unfortunately, the resistance of an endotracheal or nasotracheal tube makes it difficult for babies to spontaneously breathe through them for prolonged periods of time. The length of the tube contributes to the dead space of the respiratory system. Moreover, intubation is invasive and is

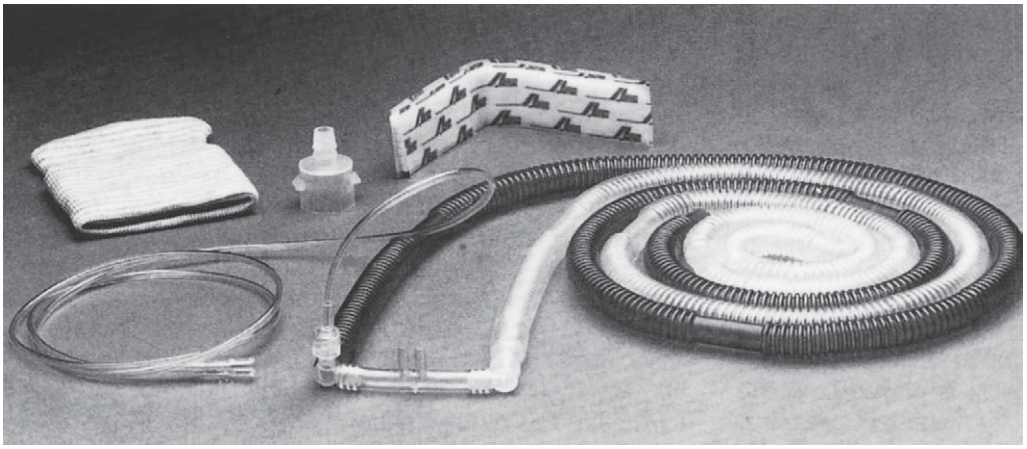


Figure 8-11 ■ The Hudson NCPAP equipment. Note the wide-bore short prongs. Depictions and actual photographs of children being managed with this device are shown in Figures 8-1, *B*, 8-2, 8-15, and 8-19, *B*. (Courtesy Hudson RCI, Temecula, Calif.)

associated with complications (e.g., trauma from the tube, vagal response, infection).

The head chamber (head box) and face chamber, although noninvasive, never gained wide acceptance because of technical difficulties and mechanical disadvantages. The head chamber is a closed system that permits use of low flows. The chamber seals around the infant's neck, thus limiting access to the child's face. It is difficult to administer in infants weighing less than 1500 g. The devices are very noisy and have been associated with complications such as hydrocephalus, nerve palsies, and local neck ulceration from mechanical compression by the neck seal.[8,37,38] The face chamber was originally described by Alhstrom et al.[39] and consists of the application of CPAP via a mask covering the entire face. The mask is held in place by negative pressure. This system is simple, effective, and there are no reported patient complications or mechanical problems such as loss of pressure during administration. There is reported success in using the face chamber for treating RDS[39,40] and in weaning infants.[41] The major limitations are lack of access to the infant's face and the cumbersome method of administration.

The face mask is another simple, effective mode for administering continuous distending pressure in the treatment of RDS in preterm infants[42,43] and is associated with relatively less work of breathing compared to nasal prong CPAP.[44] The mask must cover both nose and mouth and be securely placed with a good seal to prevent loss of pressure. However, severe gastric distension may be produced. An orogastric tube could relieve this distension, but loss of pressure may occur because the tube must pass under the edge of the face mask. Other reported pressure-induced effects include trauma to the facial skin and the eyes, as well as the occurrence of intracerebellar hemorrhage and gastric rupture.[42-45] Hypercapnia due to excessive CO_2 retention from increased dead space of the mask may result if the infant cannot compensate by increasing ventilation. For all of the reasons stated above, CPAP is seldom applied

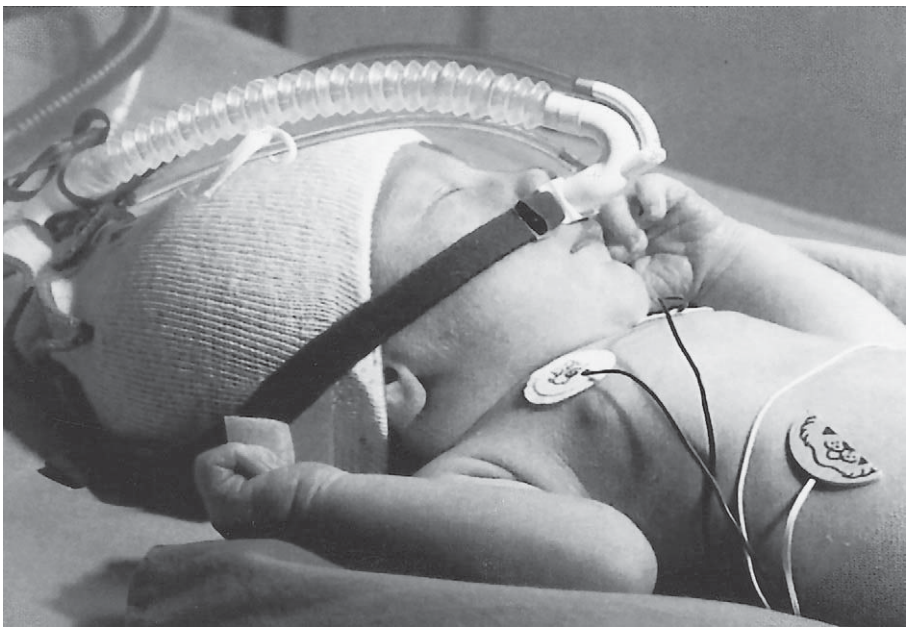


Figure 8-12 ■ Photograph of a baby being managed with the Arabella variable-flow CPAP system. This device has to be fixed properly to optimize function and to prevent injury. (Courtesy Hamilton Medical, Reno, Nev.)

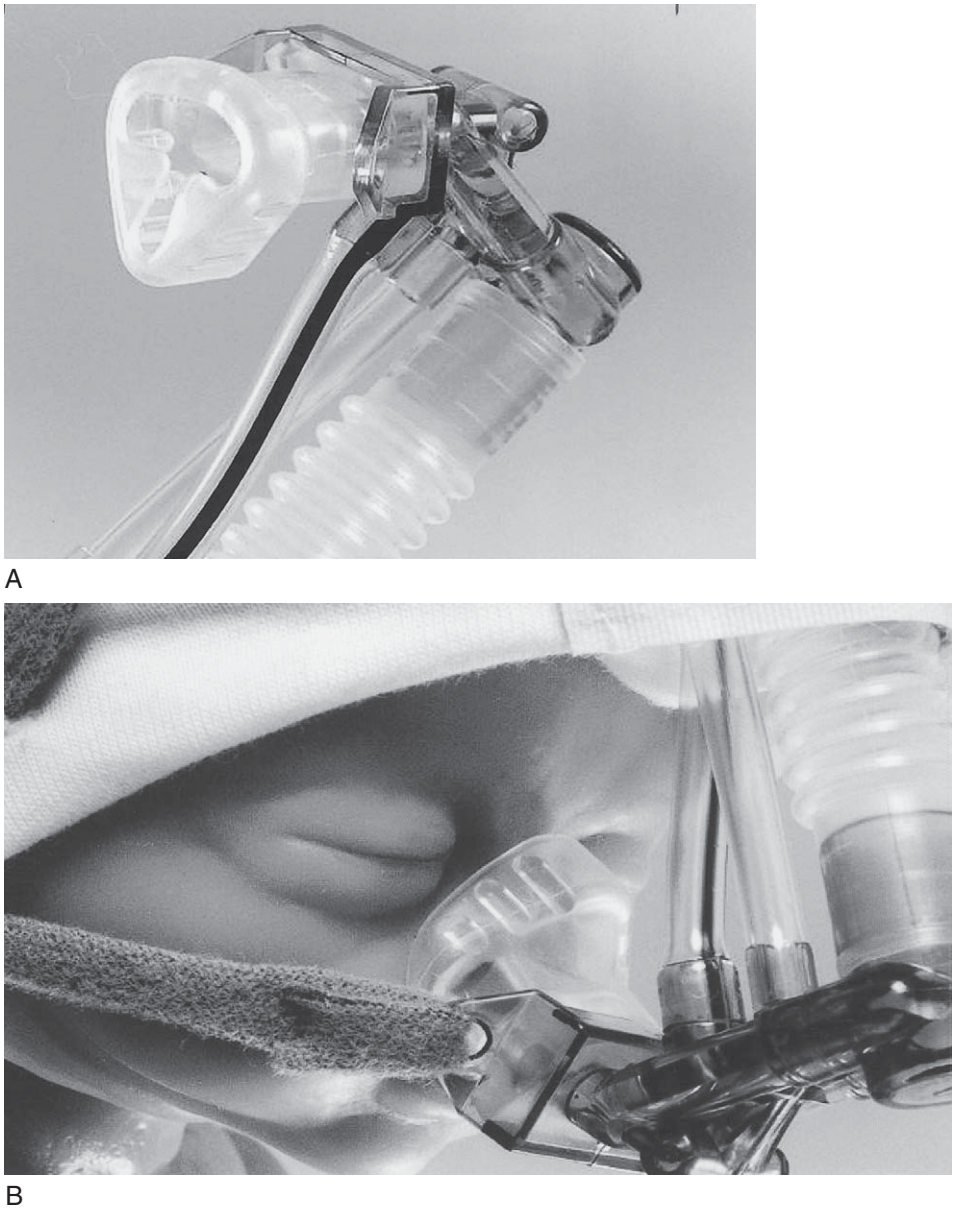


Figure 8-13 ■ A and B, The nasal mask used with the Infant Flow Driver continuous-flow NCPAP system. The mask is attached to the pressure chamber in the same location as nasal prongs. (Courtesy Electro Medical Equipment, Ltd., Brighton, England.)

today with a head chamber, face chamber, or face mask.

Nasal masks are a relatively recent innovation available with the variable-flow systems. A small, soft mask is attached to the pressure generator (Figs. 8-13, *A* and *B*). Such masks are markedly smaller than face masks; hence there is little additional dead space. Nasal masks may be useful when the infant's nares are too small to accept the nasal prongs. Some units also use them in conjunction with nasal prongs, alternating several hours on and off each device to minimize the pressure effects on the nares of the prongs. However, a good seal must be present to prevent pressure loss with the nasal mask. There are no published data concerning the safety and efficacy of nasal masks.

Nasal cannulae (NC) are typically used to provide supplemental oxygen (Fig. 8-14). However, depending on the flow rate, size of the NC, degree of leak, and size of the nares, these devices may also provide distending pressure.[46,47] As no pop-off valve is present on currently available NC, pressure generated is uncontrolled and may be substantial. Cannulae can also be easily dislodged; it is not unusual to pass by a child being treated with NC and to note that the cannulae are not in the nares but on the cheek or in the mouth or elsewhere. NC and humidified high-flow are discussed further later in this chapter.

Nasal and nasopharyngeal prongs remain the most common methods of administering CPAP in neonates. Because infants are generally obligate nose breathers, CPAP may be facilitated when delivered directly into the nose. The most common complications with these devices are obstruction by secretions and kinking of nasopharyngeal prongs in the pharynx. Infants may lose pressure through

Figure 8-14 ■ Nasal cannulae in place in a growing premature infant. This was a 4-week-old infant of 27 weeks' gestation and birth weight of 960 g. The nasal cannulae were being used in this case to generate NCPAP as therapy for apnea of prematurity.

their open mouths while undergoing NCPAP or NPCPAP. Thus many clinicians actively try to prevent pressure loss by means such as placing a pacifier in the child's mouth or by using a strap under the infant's chin to close the mouth (Fig. 8-15). Fortunately, when NCPAP and NPCPAP are applied, there is often enough downward pressure on the palate that it is frequently contiguous to the tongue, providing a natural seal with minimal to no pressure loss through the mouth.

Clinical Use of CPAP: Anecdotal Experiences

Much of the literature describing CPAP use in neonates consists of anecdotal experiences: case reports, case series, and cohort-comparison studies (concurrent or historical). Few randomized, controlled trials (RCTs) have been performed. The former carry considerably less strength than RCTs in validating the safety and effectiveness of a therapy. Nevertheless, to present a comprehensive review of CPAP, available literature, including anecdotal experiences, is summarized here.

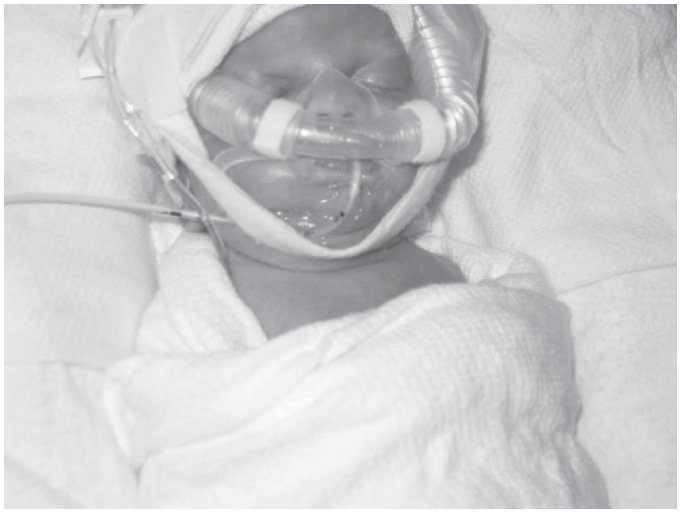


Figure 8-15 ■ A child on NCPAP whose mouth is being kept closed with the use of a strap under the chin. This is done to prevent pressure loss through an open mouth.

The Benveniste gas-jet valve's use in neonates was first described in 1968.[23] Jacobsen and colleagues[48] described the "minitouch" approach in which very-low-birth-weight (VLBW) infants (neonates less than 1500 g birth weight) were managed with minimal handling and early use of NCPAP via the Benveniste valve. They compared their experience over 1 year with that of a previous 2-year-long period in which most VLBW infants with respiratory failure were intubated and treated with mechanical ventilation. Gitterman et al.[49] compared outcomes of VLBW infants during two periods: (1) 1990: most infants were not treated with NCPAP and (2) 1993: generalized use of NCPAP was implemented. These authors used Hudson prongs. The method of pressure generation was not stated. They found that during the second epoch fewer infants required mechanical ventilation. There were no differences in CLD or mortality.

Lindner and colleagues[50] similarly addressed management of extremely low-birth-weight (ELBW) infants (birth weight less than 1000 g) during two different epochs. In 1994, ELBW infants were generally intubated and ventilated immediately after delivery once initial resuscitation was accomplished with a mask and bag. By 1996, however, management had changed. During the latter period, ELBW infants had a nasopharyngeal tube placed in the delivery room and initial continuous pressure of 20 to 25 cm H_2O was applied for 15 to 20 seconds. The infants were then managed with NPCPAP at 4 to 6 cm H_2O. This group occasionally received ventilator breaths via the NP tube until there was sufficient respiratory effort achieved by the child. The authors reported that during the latter period (1996), the percentage of babies never needing intubation and mechanical ventilation was 25%, compared with 7% during 1994. Moreover, the infants born in 1996 had lower frequencies of CLD and intracranial hemorrhages (ICHs), as well as shorter hospital stays. There were no differences in mortality.

DeKlerk and DeKlerk[51] also performed a historical comparison of two groups of infants, birth weight 1000 to

1499 g, over a 5-year period. During the first part of that period, early intubation and ventilation were frequently performed, whereas during the latter part of the period, infants were routinely placed on NCPAP when they demonstrated respiratory distress. The DeKlerks used bubble CPAP delivered via Hudson nasal prongs. These authors reported that during the second epoch, fewer infants required mechanical ventilation or exogenous surfactant. However, they did not find differences in mortality or CLD.

Kavvdia and colleagues[52] assessed a group of 36 infants managed postextubation with (1) NCPAP via the Infant Flow device (IFD); (2) NCPAP via a single nasal prong; or (3) no CPAP. There were no differences in lung function after 24 hours. The nasal prong group had a significant reduction in supplementary oxygen concentration after 24 hours. Kurz[53] assessed the effect of NPCPAP on breathing pattern and incidence of apneas in preterm infants. Thirteen preterm infants who were weaning from single-prong NPCPAP were evaluated for 2 hours on NCPAP and for 2 hours off any CPAP. During NPCPAP, the respiratory rate was significantly lower. Additionally, there were fewer obstructive apnea periods, less severe apnea-associated desaturation episodes, and more central apnea events. During NPCPAP, infants spent significantly more time in a state of quiet breathing.

Clinical Use of CPAP: Randomized, Controlled Trials

Several randomized, controlled trials (RCTs) have been performed assessing CPAP for resuscitation or early management in the delivery room, for early management of respiratory distress syndrome (RDS), as treatment for apnea of prematurity, and for postextubation management after mechanical ventilation. The trials essentially consist of comparisons of CPAP with a standard therapy or comparisons of different types of CPAP.

Effects of CPAP or PEEP

Finer et al.[54] conducted a feasibility trial addressing the effects of CPAP or PEEP in premature infants less than 28 weeks' gestation from initial resuscitation in the delivery room; 104 infants were randomized to either no CPAP and 100% oxygen or to CPAP/PEEP using a T-piece resuscitator (NeoPuff™ Infant Resuscitator, Fisher & Paykel, Auckland, New Zealand). Overall mean birth weight of subjects was approximately 775 g and mean gestational age was approximately 25 weeks. Delivery room intubation was needed for 49% of the CPAP/PEEP group vs. 41% of controls. Intubation at some point during hospitalization was required in 78% of the CPAP/PEEP group vs. 82% of controls (not symptomatic [NS]). Death was more likely in the CPAP/PEEP group (27% vs. 13%, $P = 0.07$), as was the incidence of pneumothoraces (13% vs. 9%, NS). The incidence of chronic lung disease was not assessed. Although this was a feasibility trial, the numbers enrolled were more than in the majority of CPAP studies. No positive benefits were noted from early delivery room management with CPAP/PEEP, and the complications of death and pneumothoraces were more common among infants receiving this therapy.

CPAP vs. Intubation and Ventilation

Morley and colleagues[55] randomized 610 premature infants (25-28 weeks' gestation) in the delivery room at 5 minutes after birth to CPAP or to intubation and ventilation. The CPAP infants were initially treated with either a short single nasal prong or binasal prongs at a pressure of 8 cm H_2O. The primary outcome was the combined endpoint of death or bronchopulmonary dysplasia (BPD), defined as the need for oxygen at 36 weeks' postmenstrual age. Although there was a trend for CPAP babies to have less death/BPD (34% vs. 39%), this difference was not statistically significant. There was a 50% decrease in the use of surfactant in CPAP-treated neonates ($P < 0.001$). Although there was a significant decrease in the number of ventilator days in the CPAP group, this difference was only 1 day. Of note, the CPAP-treated infants were significantly more likely to develop pneumothoraces (9% vs. 3%, $P < 0.001$).

Value of Nasal or Nasopharyngeal CPAP

A number of investigators have assessed the value of nasal or nasopharyngeal CPAP as primary therapy for premature infants with RDS. Verder and colleagues[24] randomized premature infants with moderate to severe RDS to either NCPAP alone ($n = 33$) or to NCPAP plus surfactant ($n = 35$). They used the Benveniste gas-jet valve to provide NCPAP in both groups. In the surfactant group, infants were transiently intubated and given Curosurf® (Chiesi Farmaceutici, Parma, Italy) followed by several minutes of mechanical ventilation. These infants were then extubated and placed on NCPAP. The NCPAP plus surfactant group was significantly less likely to subsequently require mechanical ventilation (15/35, 43%) compared to the NCPAP-only group (28/33 [85%], $P = 0.003$). Nevertheless, there were no differences at 28 days of life in mortality, grade 3 or 4 intracranial hemorrhage or periventricular leukomalacia (PVL), or need for oxygen. Verder et al.[25] subsequently performed a second small trial to assess whether "early" administration of Curosurf (median age 5.2 hours) was better than "late" administration of this surfactant when infant's respiratory status had worsened (median age 9.9 hours). This was not a prophylaxis versus rescue surfactant trial. The Benveniste gas-jet valve was the method of NCPAP. The neonates who received surfactant earlier were significantly less likely to require mechanical ventilation prior to discharge (8/33 [24%] vs. 17/27 [63%], $P = 0.005$).

In a group of 36 premature infants with RDS, Mazzella et al.[56] randomized subjects to either the IFS or to bubble NPCPAP delivered via a single nasal prong. Although IFS-managed infants had more rapid declines in oxygen requirement and respiratory rate, there were no differences between groups in the need for mechanical ventilation or the total duration of respiratory support.

Sandri and colleagues[57] randomized 230 premature infants (28-31 weeks' gestation) to either prophylactic use of NCPAP (started within 30 minutes of birth) or to "rescue" NCPAP (applied once the infants required an F_{IO_2} greater than 0.40 to maintain oxygen saturation levels

greater than 93%). NCPAP was administered with the IFS in all infants. There were no significant differences between groups in the need for exogenous surfactant (23.8% vs. 22%) or in the need for mechanical ventilation (12% in both groups).

Thompson et al.[58] randomized 237 neonates of 27 to 29 weeks' gestation to one of four groups: (1) early NCPAP with prophylactic surfactant; (2) early NCPAP with rescue surfactant if needed; (3) early mechanical ventilation with prophylactic surfactant; or (4) early mechanical ventilation with rescue surfactant if needed. NCPAP was given via the IFS, whereas Curosurf was the surfactant used in this trial. There was significantly less need for mechanical ventilation in the two NCPAP groups during the first 5 days of life. Nevertheless, there were no significant differences among the groups in either mortality or oxygen dependency (at either 28 days of life or at 36 weeks' postmenstrual age). Although this trial was fairly large and the results have been frequently quoted since 2001, we are disappointed that there has never been a published manuscript concerning the study in a peer-reviewed medical journal.

In an interesting variation, Goldstein et al.[59] randomized seven mature infants (35 or more weeks' gestational age) to either ventilator-generated NCPAP (n = 3) or to negative end-expiratory pressure (NEEP) (n = 4) via the Emerson negative pressure chamber (J.H. Emerson Co., Cambridge, Mass.). The NCPAP infants were placed at 4 cm H_2O, whereas the initial pressure in the NEEP group was −4 cm H_2O. Infants in the NEEP group were weaned to room air significantly faster than the NCPAP infants ($P < 0.05$).

INSURE Approach

The "INSURE" approach to VLBW infants has been described. Basically, this consists of Intubation, surfactant administration, and rapid extubation to NCPAP. The original Verder trial[24] used this approach. Dani and colleagues[60] randomized 27 total infants with RDS in a nonblinded fashion to either INSURE or to surfactant/mechanical ventilation. Their infants were approximately 29 weeks' gestation. These researchers found the INSURE approach resulted in a decreased need for mechanical ventilation, decreased duration of oxygen use and ventilation, and decreased surfactant use. They found no differences in BPD/CLD. The Texas Neonatal Research Group[61] enrolled 132 infants with RDS (mean gestational age 32.7 weeks) to INSURE vs. standard management (surfactant or ventilation, as needed). They found no differences in need for mechanical ventilation or in BPD. Reininger et al.[62] similarly randomized infants with RDS (mean gestational age 32.5 weeks) to either INSURE or to NCPAP alone. They did not find differences in the need for mechanical ventilation or BPD. Most recently, Sandri and colleagues[63] assessed very premature infants (25-28 weeks' gestational age) randomized to either INSURE or NCPAP alone soon after birth. They found no differences in the need for mechanical ventilation, mortality, or CLD. Alarmingly, the INSURE group had significantly more pneumothoraces.

Finally, several unpublished RCTs were performed in the years 2000 to 2002 that evaluated the INSURE approach.[58,64,65] Although there were trends in the latter trials for the INSURE approach to result in a decreased need for mechanical ventilation, no differences in mortality or chronic lung disease were found. It has been 7 to 8 years since the latter three trials were completed and no publications have resulted from any of them. The authors of this chapter are intrigued by the INSURE approach to surfactant use and NCPAP. We believe the published data indicate that fewer premature infants of 29 to 34 weeks' gestation treated in this manner will require mechanical ventilation. However, infants of 28 or fewer weeks' gestation are unlikely to benefit from this approach. Most importantly, we do not believe the data indicate that management with the INSURE protocol will decrease the key outcomes of mortality and chronic lung disease.

Apnea of Prematurity

Apnea of prematurity (AOP) is a common disorder in premature infants born before 34 weeks' gestation. These infants exhibit various combinations of apnea, bradycardia, and oxygen desaturation. Apnea may be classified as obstructive, central, or mixed. Methylxanthines are effective in treating AOP (see Chapter 3). The sole trial comparing CPAP with methylxanthine therapy was performed more than 25 years ago.[66] In that trial, face mask CPAP at levels of 2 to 3 cm H_2O was compared with theophylline in 32 infants of 25 to 32 weeks' gestation. The investigation found theophylline to be more effective than face mask CPAP in (1) reducing prolonged apnea episodes; (2) the need for intubation and ventilation because of worsening AOP; and (3) reducing the number of bradycardia spells. The Cochrane review regarding CPAP use for AOP concludes that this topic needs additional evaluation.[67] We are aware there is widespread use of NCPAP and NPCPAP for management of AOP despite the dearth of supportive evidence. Indeed, since the early 1990s caffeine has been used considerably more commonly than is theophylline. Yet, to date there have been no published trials comparing caffeine with NCPAP for treatment of AOP.

Premature infants being extubated after a period of mechanical ventilation via an endotracheal tube are at risk for developing respiratory failure that may manifest as increased frequency or severity of apnea, CO_2 retention, diffuse atelectasis, increased work of breathing, increased oxygen requirement, or need for reintubation and mechanical ventilation. All of these findings are typically included in "treatment failure" criteria in the various trials that have assessed whether CPAP may be a good therapy for infants postextubation. Davis and Henderson-Smart[68] reviewed the literature to assess whether direct extubation of mechanically ventilated preterm infants would be as successful as extubation after a short period of endotracheal tube CPAP (ETCPAP). After identifying three appropriate clinical trials addressing this question in their review, these authors concluded that a trial of ETCPAP prior to extubation did not provide any advantages. In fact, there was a trend toward an increased number of apnea episodes in ETCPAP-treated infants.

Oxyhood vs. NCPAP

Engleke and colleagues[69] randomized 18 premature neonates recovering from RDS to either oxygen delivered via an oxyhood or to NCPAP. During the 24 hours of the study, the NCPAP group of infants had lower respiratory

rates, better oxygenation, lower $PaCO_2$ values, higher pHs values, and less radiographic atelectasis. Higgins et al.[70] similarly randomized 58 infants of less than 1000 g birth weight to either NCPAP or oxyhood at the time of extubation. They found 22 of 29 (89%) of NCPAP babies remained successfully extubated compared to 6 of 29 (21%) of the oxyhood babies ($P < 0.0001$). Chan and Greenough[71] performed a trial in which ventilated infants with both relatively acute (less than 14 days of age) and chronic (14 days or more of age) disease were randomized to either NCPAP at 3 cm H_2O or to headbox oxygen. These authors did not find any differences in extubation failure rates in either group (NCPAP vs. headbox oxygen) or in acute versus chronic respiratory distress. One should note, however, that 3 cm H_2O is a relatively low amount of distending pressure. Annibale et al.[72] randomized 124 preterm infants meeting extubation criteria to either (1) a long course of NPCPAP (until lung disease was resolved); (2) a 6-hour course of NPCPAP; or (3) oxyhood. These investigators found no differences among groups in the extubation success rate. So and colleagues[73] randomized 50 VLBW infants in an extubation protocol to either NCPAP or oxyhood. Successful extubation was achieved in 21 of 25 (84%) of NCPAP subjects compared to 12 of 25 (48%) of the oxyhood group ($P = 0.01$). Tapia et al.[74] assigned 87 preterm neonates to either oxygen alone, endotracheal tube CPAP for 12 to 24 hours with subsequent extubation, or to NPCPAP. They found no differences in extubation failure rates among groups.

Davis and colleagues[75] randomized 92 ventilated preterm infants ready for extubation to either NCPAP or headbox oxygen. Thirty-one of 47 (66%) were successfully extubated in the NCPAP group compared to 18 of 45 (40%) in the headbox oxygen group ($P = 0.013$). Robertson and Hamilton[76] performed a variation of the preceding trials. They randomized 58 preterm infants after extubation to either immediate NCPAP for 72 hours or to headbox oxygen with "rescue" NCPAP as an option if necessary. These authors found no differences between groups in successful extubation up to 2 weeks after enrollment. Dimitriou et al.[77] performed a RCT in premature infants (24-34 weeks' gestation) that were thought to be ready for extubation. The infants were randomized to either headbox oxygen or to NCPAP via either single or binasal prongs. There were no differences between groups in extubation failure. Because there could have been outcome differences between the two types of NCPAP (unfortunately no subgroup analysis was presented), we do not think the Dimitriou study adequately assessed the use of either type of NCPAP for extubation. The Cochrane collaboration analysis[78] of NCPAP use immediately after extubation concludes that it is an effective therapy in preventing failure of extubation. Nevertheless, the latter evaluation stresses the need for further studies to determine the gestational age and birth weight groups that would benefit most. The Cochrane review also stresses the need for further trials to determine optimal levels of NCPAP and optimal methods of administering NCPAP.

Comparison of Different Types of NCPAP

Several investigators have compared different types of NCPAP to see if one method would be more effective than another after extubation of mechanically ventilated preterm infants. Davis et al.[79] compared ventilator-generated CPAP via either single or binasal prongs. Their population consisted of 87 premature infants of less than 1000 g birth weight. Single-prong NPCPAP was delivered via a shortened endotracheal tube inserted 2.5 cm into one nostril, whereas binasal NCPAP was given through Hudson prongs. Significantly more infants, 26 of 46 (57%), randomized to the single-prong NPCPAP met failure criteria compared to 10 of 41 (24%) of those managed with binasal NCPAP ($P = 0.005$). Stefanescu et al.[80] enrolled 162 ELBW (less than 1000 g birth weight) infants into a postextubation RCT. In this trial neonates were randomized to either the IFS or NCPAP administered with binasal prongs. These authors were unable to demonstrate any differences between groups in extubation success rates. Nevertheless, the IFS-managed group had significantly fewer days on supplemental oxygen (66 vs. 77 days, $P = 0.03$) and a significantly shorter duration of hospitalization (74 vs. 86 days, $P = 0.02$).

Sun and Tien[81] compared the Infant Flow system (IFS) to "conventional" binasal NCPAP that was ventilator generated. Their population consisted of 73 ventilated premature infants of 30 weeks' or less gestational age and 1250 g or less birth weight who met extubation criteria. Sun and Tien found 19 of 35 (54%) of the "conventional" group met failure criteria compared to 6 of 38 (16%) of the IFS-managed neonates (<0.001). Similarly, Roukema and colleagues[82] randomized 93 VLBW infants to either IFS or to NPCPAP. The NPCPAP group was significantly more likely to fail extubation compared with the IFD group (60% vs. 38%, $P = 0.0006$). Of note, these latter two trials were presented in abstract form only a decade ago.

Conclusions

Cochrane collaborative reviews have addressed diverse CPAP RCTs. To date the following conclusions have been made: (1) there is insufficient evidence to assess the benefits and risks of prophylactic NCPAP in the preterm infant[83]; (2) early use of CPAP may reduce the need for mechanical ventilation[84]; and (3) early therapy with surfactant and NCPAP may be of benefit.[85] Concerning overall CPAP use, there are no definitive conclusions in the Cochrane evaluations. All of the reviews stress the need for further large, prospective RCTs.

Nasal Ventilation

Nasal ventilation (NV) is an intriguing concept that has gained popularity with limited medical evidence. The concept is attractive: provision of positive pressure breaths noninvasively. Potentially, NV would avoid potential complications of prolonged ventilatory support via an endotracheal tube (volutrauma, subglottic stenosis, infections). Moreover, NV may have advantages over NCPAP or NPCPAP in stabilizing a borderline functional residual capacity, reducing dead space, preventing atelectasis, and improving lung mechanics.[86,87] The practice was performed in the United States during the mid-1970s (Steven M. Donn, personal communication), as well as in Canada during the mid-1980s, with more than half of the level III

NICUs in that country using the technique.[88,89] In general, NV has been studied to determine its potential usefulness in (1) preventing extubation failures[90-92]; (2) treating apnea of prematurity[88,92]; and (3) as a primary mode of treating respiratory disorders.

Friedlich et al.[90] randomized 41 premature infants to either nasopharyngeal CPAP (NPCPAP) or nasopharyngeal synchronized intermittent mandatory ventilation (NPSIMV) to be used after extubation. These authors used the Infant Star® ventilator (Infrasonics, Inc., San Diego, Calif.) with the "StarSync" abdominal capsule-triggering device (Graesby capsule, Infrasonics, Inc., San Diego, Calif.) for synchronization. Binasal nasopharyngeal prongs were used in both groups. Treatment failure was defined as one of multiple parameters: (1) pH of 7.25 or less; (2) increased $Paco_2$; (3) increased Fio_2 requirement; (4) need for a NPSIMV rate greater than 20/min; (5) need for a peak inspiratory pressure (PIP) on NPSIMV of 20 cm H_2O or more; (6) need for PEEP on NPSIMV of 8 cm H_2O or more; or (7) severe apnea. Friedlich and colleagues reported significantly fewer extubation "failures" with NPSIMV (1/22, 5%) compared to NPCPAP (7/19, 37%) ($P = 0.016$). Barrington et al.[89] randomized 54 VLBW infants to NCPAP or NSIMV after extubation. They used binasal Hudson prongs with the Infant Star ventilator as the generating source for both groups, as well as the StarSync triggering device. Extubation failure criteria were similar to those of Friedlich. Barrington and colleagues found the NSIMV group to have a lower incidence of failed extubation (4/27, 15%) compared with the NCPAP group (12/27, 44%) ($P < 0.05$). Khalaf et al.[91] randomized 64 premature infants to either NSIMV or NCPAP applied after extubation using either the Bear Cub Model BP 2001 (Bear Medical Systems, Inc., Riverside, Calif. or the Infant Star ventilator with the StarSync triggering device, and Argyle nasal prongs. Failure criteria were similar to the two previous trials. Treatment failure occurred in 2 of 34 (6%) NSIMV infants compared to 12 of 30 (40%) NCPAP infants ($P < 0.01$).

Management of apnea of prematurity (AOP) using NV has been evaluated in two randomized, controlled trials (RCTs).[88,92] Ryan et al.[88] used nasal intermittent positive-pressure ventilation (NIPPV) in a crossover study in which 20 premature infants less than 32 weeks' gestation were being treated for apnea with NCPAP and aminophylline. Infants were randomized to either continue on this regimen or to be treated with NIPPV, using either binasal prongs or nasopharyngeal tubes for a period of 6 hours. The subjects then crossed over to the alternative therapy for an additional 6 hours. There were no differences in the rate of apnea between groups. Lin and colleagues[92] subsequently performed an RCT in which 34 premature infants (gestational age 25-32 weeks) were treated with aminophylline and enrolled to be treated with either NCPAP or NIPPV. In both groups Hudson nasal prongs were used. In Lin's study, all infants had previously been treated with aminophylline, but were not on any type of positive-pressure support (NCPAP or other support) at the time of enrollment. The infants were treated for a 4-hour period. Those treated with NIPPV had significantly fewer apnea spells ($P = 0.02$), as well as a trend toward fewer bradycardia spells ($P = 0.09$) compared to neonates managed with NCPAP.

Bhandari and colleagues[93] performed an RCT comparing synchronized NV after an initial dose of surfactant with mechanical ventilation after surfactant administration. They found significantly less BPD in the NSIMV group. This was a small trial with 41 total babies enrolled. Kugelman and colleagues[94] randomized 84 premature infants to NIPPV or to NCPAP. These authors reported a decreased need for mechanical ventilation in the NIPPV group, as well as significantly less BPD.

In a novel application, van der Hoeven et al.[95] reported use of nasal high-frequency ventilation (NHFV) in which high-frequency breaths were delivered via a single nasopharyngeal tube in 21 neonates of both preterm and term gestation. NHFV was provided by the Infant Star high-frequency flow interrupter. Six of the 21 neonates had previously received mechanical ventilation, whereas in the other 15 infants, NHFV was used early in the course of their respiratory disease. The authors reported a decline in $Paco_2$ levels after initiation of NHFV.

In 1985 Garland and colleagues[96] reported an increased risk of gastrointestinal perforation among infants ventilated noninvasively with either nasal prongs or a face mask. Of note, however, subsequent publications concerning NV have not confirmed higher rates of this complication As with standard NCPAP, we think an orogastric tube should be placed in all infants undergoing NV to vent the stomach of swallowed air.

Recently one company has marketed bilevel NCPAP as an alternative to constant NCPAP (SiPAP, Viasys, Inc., Conshohocken, Pa.). Using the technology of the Infant Flow driver, these devices can alternate between a lower and higher CPAP pressure. Synchronization using the Graesby capsule is available in Europe and Canada. Whether this device offers any advantage over standard single-pressure NCPAP is not known at this time, though several RCTs are underway.

Much of the preceding NV data have come from trials assessing efficacy of synchronized NV using the StarSync triggering device and Graesby capsule. Neither of these are currently available for use in the United States. The conclusion of the Cochrane collaboration review[97]is that NV may be useful in augmenting NCPAP in preterm infants with apnea that is frequent or severe. However, additional safety and efficacy data are required before recommending NV as standard therapy for apnea. The Cochrane collaboration review[98] assessing NV postextubation concluded that NV may augment the beneficial effects of NCPAP in preterm infants.

Other Applications of CPAP in Neonates

We have mainly concentrated on describing the three primary uses of CPAP, particularly NCPAP, in newborn infants: (1) postextubation management; (2) treatment of apnea of prematurity; and (3) primary therapy for respiratory distress syndrome. Nonetheless, CPAP has been applied in a variety of other conditions (Box 8-1).[99] There are, however, even less data supporting CPAP use in these other conditions. With use in infants with congenital heart disease postoperatively, CPAP improved pulmonary mechanics and oxygenation.[100-102] Additionally, CPAP may

Box 8-1 CONDITIONS FOR WHICH CONTINUOUS DISTENDING PRESSURE HAS BEEN USED CLINICALLY

- Respiratory distress syndrome (RDS) in premature newborn infants
- Apnea of prematurity (AOP)
- Postextubation management of premature infants
- Postoperative respiratory management:
  - Congenital heart disease
  - Abdominal wall defects (gastroschisis, omphalocele)
  - Other abdominal or thoracic surgical conditions
- Differentiating congenital cyanotic heart disease from pulmonary disorders
- Meconium aspiration syndrome (MAS)
- Other aspiration syndromes (e.g., blood or gastric aspiration)
- Transient tachypnea of the newborn ("wet lungs")
- Pulmonary edema
- Congestive heart failure
- Patent ductus arteriosus (PDA)
- Pneumonia
- Laryngo-, broncho-, and/or tracheomalacia
- Resuscitation of infants in the delivery room
- Increased work of breathing
- "Other" disorders with radiographic findings of atelectasis, poor lung expansion, or pulmonary infiltrates
- Persistent pulmonary hypertension of the newborn (PPHN)
- Pulmonary hemorrhage
- Provision of high PEEP during extracorporeal membrane oxygenation (ECMO)

PEEP, Positive end-expiratory pressure.

assist in the differentiation of congenital cyanotic heart disease from cyanotic pulmonary disorders.[103] After surgical repair of abdominal wall defects (gastroschisis and omphalocele), increased abdominal pressure may adversely affect pulmonary function. CPAP has been found to improve oxygenation in these disorders.[104] Fox and colleagues[105] described improved oxygenation with the application of CPAP (at 4-7 mm Hg [0.6-1 kPa]) among infants with meconium aspiration syndrome.

CPAP is often used for the management of laryngo-, broncho-, and/or tracheomalacia.[106,107] The positive pressure will distend these large airways and mitigate their tendency to collapse, particularly during expiration. Conceptually, CPAP should help neonatal pulmonary disorders in which there is excessive lung fluid: transient tachypnea of the newborn, patent ductus arteriosus, pulmonary edema, congestive heart failure, and hydrops fetalis. Data, however, are lacking. We would note that Keszler et al.[108] assessed the use of different levels of background PEEP applied during extracorporeal membrane oxygenation. These investigators randomized 74 neonates requiring extracorporeal membrane oxygenation (ECMO) to either low PEEP (3-5 cm H_2O) or high PEEP (12-14 cm H_2O). Infants in the high PEEP group had significantly improved lung compliance and the duration of ECMO therapy was significantly shorter.

Complications of CPAP

Malpositioned Nasal Cannulae

A major difficulty with the use of nasal cannulae (NC) or nasal prongs is keeping them in proper position. One may walk through most neonatal intensive care units (NICUs) at any given time and note infants with malpositioned or displaced cannulae and prongs. It should be noted that with the variable-flow CPAP systems (the Infant Flow Driver, SiPAP™, and Arabella devices), meticulous attention has to be paid to ensure proper fixation of the nasal prongs. Airway obstruction by secretions, particularly mucus, is a common finding in babies managed with CPAP. Optimal gas humidification, as well as frequent irrigation with saline followed by suctioning, should mitigate airway obstruction. Although nasopharyngeal prongs (single or binasal) may be less likely to be displaced, they are more easily blocked by secretions or can kink and may not be as effective as the shorter prongs. Local irritation to the nares and oral cavity may also occur with CPAP. Some clinicians use steroid and antibiotic ointments on the outer surfaces of the CPAP devices to minimize the effects of this irritation. We have found success in using an inert product, Ayr Gel™. Good oral hygiene (e.g., with lemon glycerin swabs or saline) should be considered to prevent drying and cracking.

Inadvertent PEEP

A number of adverse side effects and complications of CPAP, PEEP, and nasal ventilation have been described. One is the development of inadvertent PEEP—a problem that may occur in ventilated babies, primarily those ventilated via endotracheal tubes. Conceivably, inadvertent PEEP could occur with nasal ventilation. The mechanism is related to fast ventilatory rates and inadequate (too short) expiratory times. Inadvertent PEEP may occur in babies with minimal to no lung disease (such as postoperative patients) or in those with sick lungs. Healthy lungs have longer time constants. Hence passive exhalation requires a greater amount of time. Inadvertent PEEP results in air trapping. Clinically, this may appear as hyperexpanded lungs on chest roentgenograms. Air trapping may clinically manifest as hypoxemia and hypercapnia. Clinicians should be suspicious of this entity when oxygenation deteriorates as inspiratory pressure is increased. Air trapping contributes to the development of air leaks. Additionally, air leaks (pneumothorax, pneumomediastinum, and pulmonary interstitial emphysema [PIE]) may be a direct complication of CPAP/PEEP.[109-111] The mechanism may be related to overdistension of the more compliant areas of the lung. The recent COIN trial[55] highlights this potential complication. As a generalization, pneumothoraces appear to be a problem with babies in whom CPAP was the primary ventilatory therapy for RDS. We are unaware of any reported increased risk for air leaks when CPAP is used for postextubation respiratory management or as therapy for apnea of prematurity. Moreover, there is no apparent increased risk among infants that are nasally ventilated. In any future trials in which CPAP is compared to mechanical ventilation or to other therapies, air leaks remain an important outcome parameter that should be followed and reported.

Carbon Dioxide Retention

Retention of carbon dioxide (CO_2) has been noted with higher levels of CPAP, particularly at levels above 8 cm H_2O. Alveolar overdistension, as well as inadequate expiratory times, may lead to reduced tidal volumes and cause the CO_2 retention. Other manifestations of lung overdistension[112] include increased work of breathing, impaired systemic venous return, decreased cardiac output, and increased pulmonary vascular resistance. In addition, mechanical ventilation with PEEP may produce a decrease in glomerular filtration rate and a decrease in urine output.[113] Renal effects of CPAP in preterm infants are notable at higher levels of pressure.[114] These effects on the kidney may be due to decreased cardiac output and thus decreased perfusion to the organs. In addition, CPAP and PEEP are known to increase intracranial pressure.[99] Nevertheless, with the widespread use of screening ultrasonography over the past two decades, we are unaware of any direct links between CPAP/PEEP and adverse brain injury in premature or term-gestation neonates.

Decreased Gastrointestinal Blood Flow

Gastrointestinal blood flow may decrease with the application of CPAP.[115] Additionally, marked bowel distension ("CPAP belly") is frequently recognized in infants treated with this therapy.[116] With NCPAP, administered gas can easily pass into the esophagus. Infants may swallow a considerable volume of gas and present with bulging flanks, increased abdominal girth, and visibly dilated intestinal loops. There may be upward pressure placed on the diaphragm and compromise of the child's respiratory status. Unquestionably, routine placement of an orogastric tube should take place whenever CPAP is used. The orogastric tube should prevent or alleviate "CPAP belly." We are unaware of any direct linkage between CPAP and necrotizing enterocolitis (NEC). Although Garland et al.[96] have reported an increased risk of gastric perforation with nasally ventilated neonates, virtually all recent investigations of nasal ventilation have not confirmed this association.[97,98] Moreover, NCPAP alone has not been reported to cause gastric perforation.

Skin Trauma

Nasal prongs may cause trauma to the nose that can be mild (edema or erythema) or severe. Robertson and colleagues[117] have reported a series of cases of severe trauma, including nasal snubbing (Fig. 8-16), flaring of the nostrils (Fig. 8-17) and columella necrosis (Fig. 8-18, *A* and *B*). Nasal deformities may occur with different types of nasal prongs and NCPAP devices.[117,118] Lubrication of the nares with various substances has been used in an attempt to mitigate the contact trauma between the prongs and the internal surfaces of the nose, including antibiotic ointments, steroids ointments and creams, and Ayr gel™. We are unaware, however, of any clinical trials assessing such therapy. It is of paramount importance that meticulous attention be paid to appropriate positioning of the nasal prongs, with frequent examinations to assess the possibility of developing injury. With variable-flow devices, some clinicians alternate use of nasal prongs with nasal masks in an attempt to obviate trauma. No trials to date have assessed such management. Lastly, attempts have been made to use barrier material to protect the nares. One such material is the Cannulaide™ (Beevers Manufacturing Incorporated, McMinnville, Ore.). It comes in multiple sizes (Fig. 8-19, *A*) that can be used for varying sizes of preterm infants. Figure 8-19, *B*, shows a baby with the Cannulaide in place. Other clinicians have used alternative material such as DuoDerm® (hydrocolloid gel) or Mepilex® (soft silicone) to similarly cushion the nares. There are limited clinical data that assess the effect of any of the aforementioned materials in preventing nasal trauma.

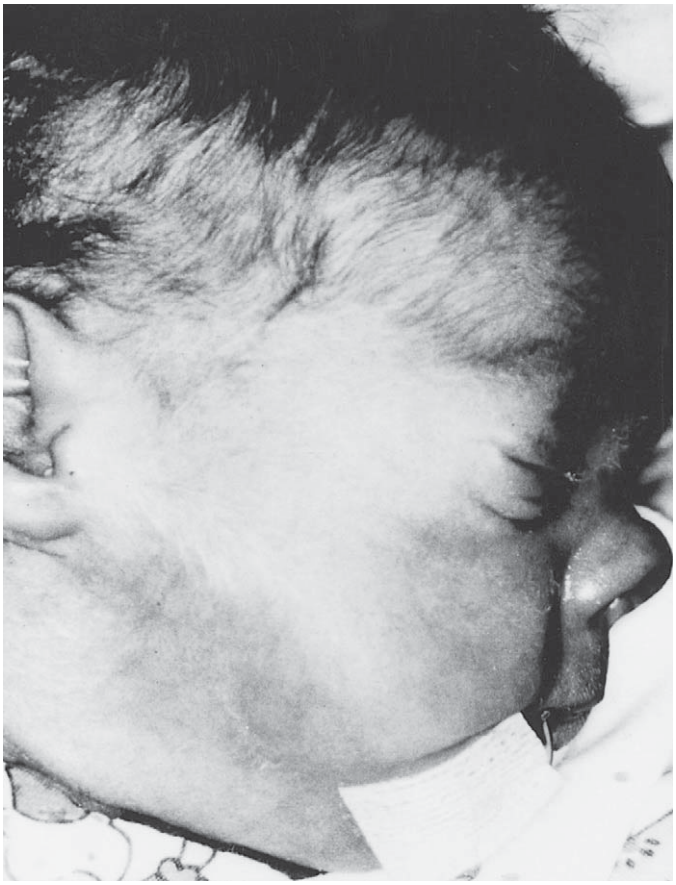


Figure 8-16 ■ Severe nasal "snubbing" noted after prolonged nasal CPAP use in a 3-month-old (24-week gestational age) premature infant. (From Arch Dis Child Fetal Neonatal Ed 75:F209-F212;108:759-761, 1996; used with permission. Courtesy Dr. Nicola Robertson.)

Other rare complications have been described in single case reports. Peck et al.[119] described the dislodgement of a single nasal prong that slipped into the child's stomach and ultimately needed endoscopic retrieval. Additionally, a preterm infant developed a pneumatocele approximately 24 hours after CPAP was instituted.[120] Wong and colleagues[121] described an infant being managed on NCPAP who developed bilateral tension pneumothoraces and extensive vascular air embolism.

Contraindications to CPAP

There are several contraindications to CPAP.[112,122] These include the following:

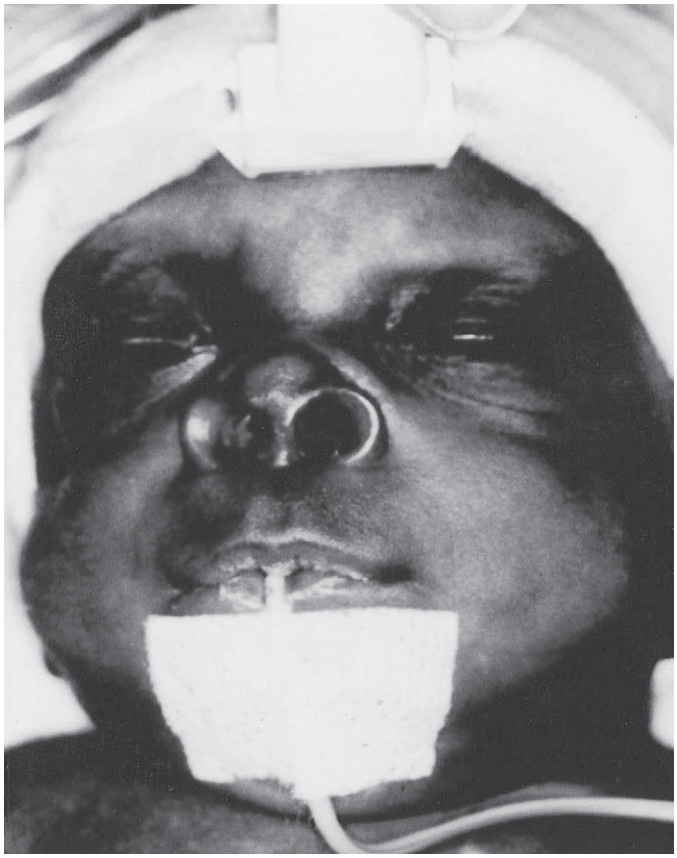
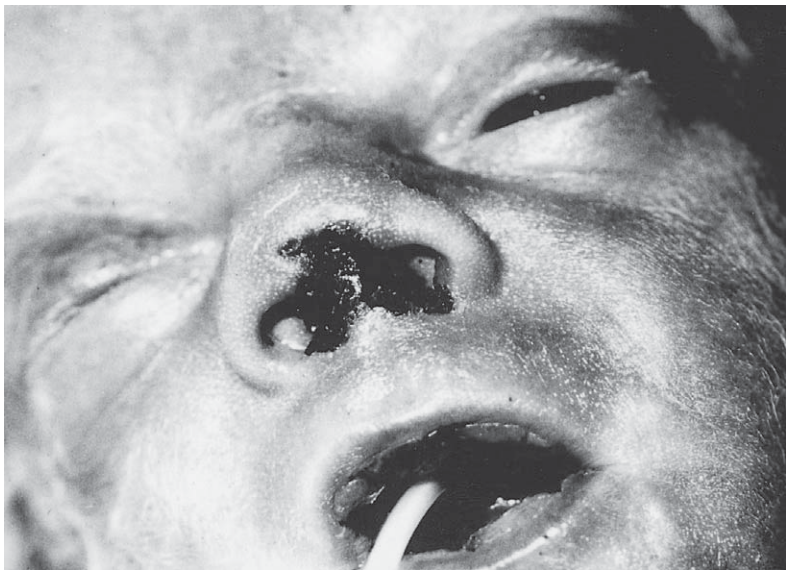


Figure 8-17 ■ A 3-month-old infant with a circumferential distortion noted after prolonged (6 weeks) NCPAP therapy. (From Arch Dis Child Fetal Neonatal Ed 75:F209-F212;108:759-761, 1996; used with permission. Courtesy Dr. Nicola Robertson.)

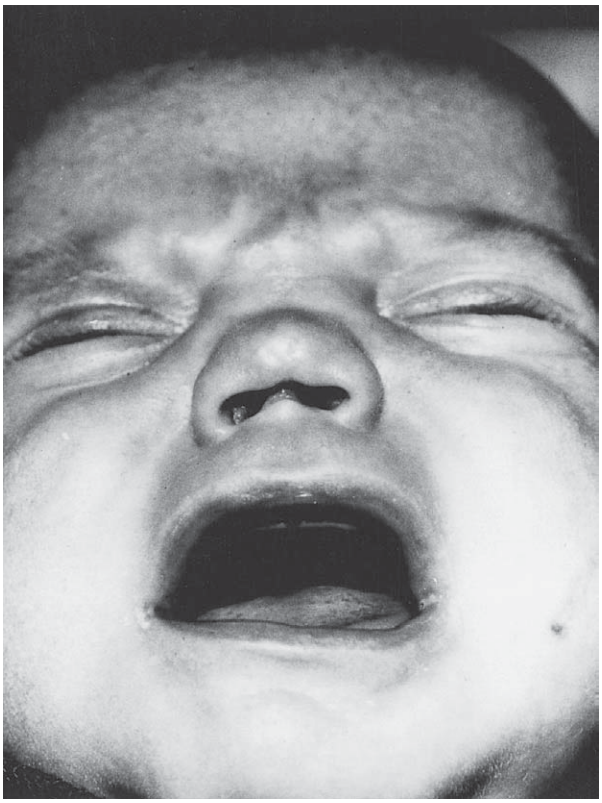
- Infants who have progressive respiratory failure and are unable to maintain oxygenation, $PaCO_2$ levels greater than 60 mm Hg (8 kPa), and/or pH levels of 7.25 or less
- Certain congenital malformations: congenital diaphragmatic hernia, tracheoesophageal fistula, choanal atresia, cleft palate, gastroschisis
- Infants with severe cardiovascular instability (hypotension, poor ventricular function)
- Neonates with poor or unstable respiratory drive (frequent apnea, bradycardia, and/or oxygenation desaturation) that is not improved by CPAP

Determining Optimal Levels of CPAP and PEEP

What is the best level of CPAP or PEEP? We believe it is the level at which oxygenation and ventilation occur in acceptable ranges without evidence of atelectasis or overdistension and no adverse side effects. Unfortunately, no simple and reliable methods exist to find the most advantageous pressure.[99,112,122] Clearly, each baby's support needs at any given moment cannot be extrapolated to all neonates with similar problems. Some investigators have used esophageal pressures or changes in the inspiratory limbs of pressure-volume curves to guide their efforts to find the elusive pressure level. However, these techniques are not generally available at the bedsides of most clinicians.

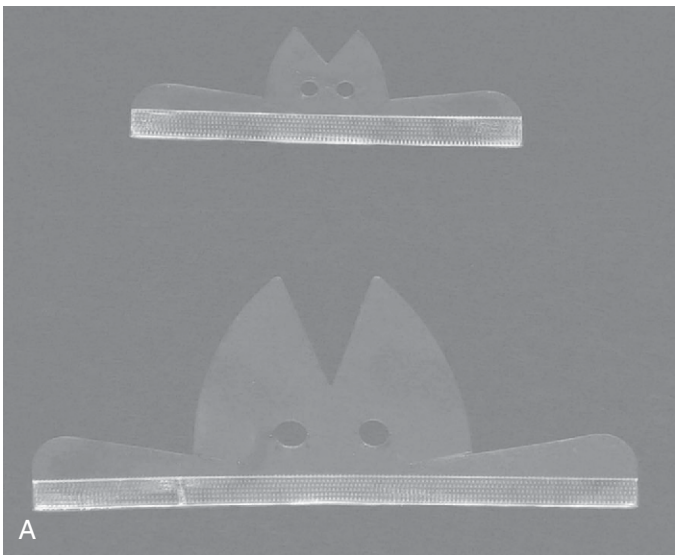


A



B

Figure 8-18 ■ **A,** Columella necrosis noted after 3 days of NCPAP. **B,** Progression of the columella necrosis in the same infant to absent columella at 4 months of age. (From Arch Dis Child Fetal Neonatal Ed 75:F209-F212;108:759-761, 1996; used with permission. Courtesy Dr. Nicola Robertson.)



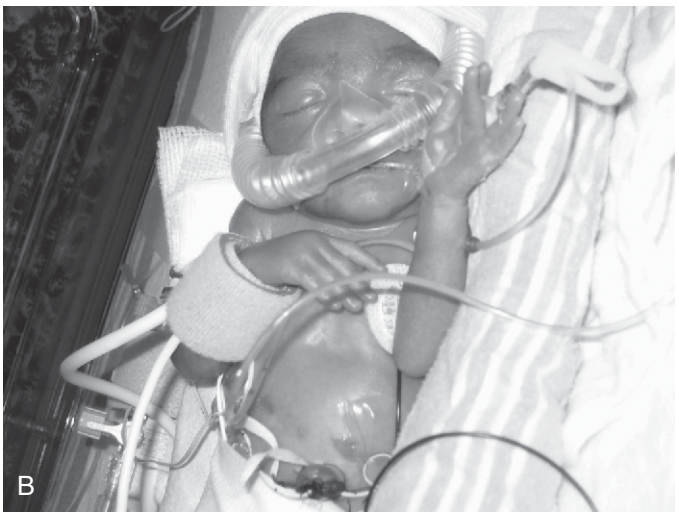


Figure 8-19 ■ **A,** Two of several different sizes of the Cannulaide material that is used to protect the nares during NCPAP therapy. The triangular shaped upper portions are placed on the external portion of the nose and the NCPAP prongs are inserted through the holes in the lower portion. **B,** A child undergoing therapy with NCPAP with the Cannulaide in place to help protect the delicate tissue of the nose.

In general, to determine whether a particular level of pressure is appropriate, clinicians should assess the chest radiograph. The appearance should be assessed for the type of disorder the baby has and the degree of lung expansion. Diseases with atelectasis (volume loss) and increased fluid (e.g., pulmonary edema) should be treated with increasing pressures. Overdistension should be avoided. Most often we start with pressure levels of 5 to 6 cm H_2O and increase as necessary to improve oxygenation. We have used levels as high as 8 to 10 cm H_2O. Occasionally, babies with particularly poor compliance have needed even higher levels.

Serial chest radiographs will help one assess the degree of lung expansion. If the lungs are overinflated, air trapping may occur and the CPAP/PEEP levels should generally be decreased. Additionally, following the child's oxygenation and carbon dioxide levels with appropriate use of arterial or capillary blood gases, as well as oxygen saturation monitoring, will further assist in the assessment of appropriate CPAP level.

As a general rule, we perform blood gas analysis within 30 to 60 minutes after any changes in pressure. If oxygenation worsens or CO_2 levels increase after increases in the pressure, the lungs may be overdistended. Many of the current mechanical ventilators have graphic monitors available on which pulmonary mechanics are displayed. If one uses ventilator-generated CPAP or PEEP via an endotracheal tube with such a device, these monitors may be useful in determining the optimal pressures.

Weaning from CPAP

Once a child is being treated with NCPAP, there are no magic guidelines as to when the child can be weaned off. As we are decreasing the pressures, we assess the baby's oxygen saturation levels, occurrence of apnea and/or bradycardia, and work of breathing. Hopefully, we have been able to lower the F_{IO_2} to a relatively low amount. In general, infants who require an F_{IO_2} greater than 0.40 or are clinically unstable are unlikely to be successfully weaned off NCPAP. Generally, we prefer to decrease pressures down to a relatively low level (≈5 cm H_2O). Once the CPAP is at this level without increasing work of breathing and the baby does not have substantial apnea, bradycardia, or oxygen desaturation levels, we attempt to discontinue NCPAP. Infants without oxygen requirement may be trialed off NCPAP with no additional support. Infants still requiring oxygen may require a nasal cannula. The baby's subsequent clinical findings and oxygen requirement will guide the clinician as to whether NCPAP needs to be reinstituted.

Nasal Cannula, Including Humidified High-Flow Nasal Cannula

Nasal cannulae (NC) are mainly used to deliver supplemental oxygen. Locke et al.[46] demonstrated that NC could deliver continuous distending pressure to infants and alter breathing patterns. However, they advised against its use. Subsequently, Sreenan et al.[47] compared the use of nasal cannulae at flows of up to 2.5 L/min with NCPAP generated by a ventilator using Argyle prongs (Argyle-Sherwood Medical Company, St. Louis, Mo.) in premature infants already being treated with NCPAP for apnea of prematurity. This was a crossover design study in which all infants initially started on NCPAP. After 6 hours, the infants were changed to NC for another 6-hour period. The authors assessed delivered airway pressure by measuring esophageal pressures. Sreenan's group found that comparable continuous distending pressure could be generated by the NC. The amount of flow required to generate comparable pressures depended upon the infant's weight. There were no differences between the two systems in the frequency and duration of apnea, bradycardia, or desaturation episodes. Typical flow rates that are used for nonhumidified NC are 0.5 to 2 L/min. Because the gases used are nonhumidified, low-flow NC may have a drying effect on nasal

secretions that could lead to obstruction or to localized bleeding.

Widespread use of humidified, high-flow nasal cannula (HHFNC) (Fig. 8-20) has become common in NICUs over the past decade. These devices represent one of the least-tested major therapies currently in vogue. The premise is that gases at flow rates greater than 2 L/min are humidified to prevent the adverse effects of dry gas. The higher flow rates are used clinically to provide respiratory support in neonates in lieu of NCPAP or oxygen hoods. Although not specifically approved as devices for generating positive pressure, clinicians generally use HHFNC in the hope that it will be a less invasive form of continuous distending pressure that will prevent some of the complications of NCPAP (nares injury) and low-flow, unhumidified NC (thickened secretions, nasal bleeding). The two major commercial devices that are available are produced by Vapotherm, Inc. (Stevensville, Md.) and by Fisher & Paykel Healthcare (Auckland, New Zealand).

The limited literature concerning HHFNC is mainly in abstract form. Clinicians are unable to continuously measure the pressures generated by HHFNC. Widely variable, extremely high pressures have been noted among infants treated with this therapy.[46,123] The pressure that is generated is unregulated and unpredictable. Moreover, the Vapotherm® was temporarily removed from the market for approximately 1 year because of the recovery of a bacterium (*Ralstonia* sp.) in infants who were treated with the device. It has since been marketed again with new guidelines on cleaning. There have also been isolated reports of facial burns, a perforated ear drum, and subcutaneous scalp emphysema/pneumocephalus.[124] Woodhead and colleagues[125] found an improved appearance in the nasal mucosa of children treated with HHFNC compared to those managed with nonhumidified NC. Saslow et al.[126] found similar work of breathing using HHFNC at 3 to 6 L/min compared to NCPAP of 6 cm H_2O. Two groups[123,127] have reported pressure to be dependent on the flow rate that is used, as well as the infant's weight.

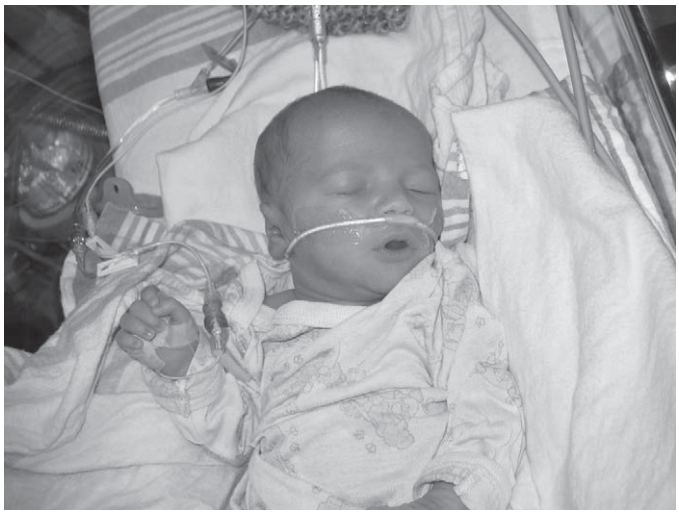


Figure 8-20 ■ Humidified, high-flow nasal cannula being used in a 36-week gestational age infant who had a pneumothorax.

With so little data, potential for adverse effects and comparability to NCPAP, the question is why are clinicians using HHFNC so frequently? The major reasons appear to be its ease of use with noncumbersome tubing that seems to be better tolerated by the patient. The indications for its use are nonspecific. However, clinicians have used HHFNC as a primary therapy for RDS, as a substitute for NCPAP after extubation, and for treatment of apnea. We and others[128] are concerned about the widespread use of what we consider to be a minimally studied therapy that has potential safety concerns.

Summary

The use of noninvasive respiratory support (NRS), such as CPAP, is not a new concept. Apparent benefits were first noted more than three decades ago. For a 20-year-long period, however, treatment with NRS, as well as research concerning the technology, waned. Renewed interest in these therapies came about in the mid-1990s. With advances in obstetric and neonatal care, survival of increasingly smaller and less mature neonates has become possible. The hope is that CPAP and other forms of noninvasive respiratory support could lessen iatrogenic injury to newborn infants, particularly those of very low birth weight. However, the history of neonatology is replete with widespread enthusiastic acceptance of diverse therapies with a modicum of supportive evidence.

We must carefully evaluate use of CPAP and other forms of NRS so that we may understand the potential benefits and potential disadvantages. The major areas in which these therapies are being used are for postextubation management, for apnea of prematurity, and for primary treatment of RDS. There is some supportive data for NCPAP use postextubation. However, NCPAP use for apnea of prematurity is currently unfounded. There is some evidence that early NCPAP use, often after exogenous surfactant therapy, may reduce the need for mechanical ventilation in premature babies with RDS. There is minimal evidence at this time that early NCPAP will prevent chronic lung disease or mortality. Air leaks may increase with CPAP use. Although CPAP use in the delivery room makes good physiologic sense for infants prone to atelectasis, clinical trials demonstrating benefit are lacking. A similar lack of evidence does not permit us to definitively define a role for nasal ventilation in infants at this time. Simple questions have yet to be answered:

- Does CPAP use increase (or decrease) caloric expenditure?
- What are the long-term pulmonary and neurodevelopmental outcomes among infants that are primarily managed with CPAP or other types of NRS?
- What are acceptable ranges of pH, Pa_{O_2}, and Pa_{CO_2} among infants receiving NRS?
- Does early use of NCPAP delay timely administration of exogenous surfactant or does it obviate the need for surfactant therapy?
- Is humidified, high-flow nasal cannulae (HHFNC) therapy a safe and effective form of NRS?
- What forms of NRS are most effective? Safest?

- Should synchronization of nasal ventilation breaths to the infant's breaths be performed, and if so, how?

There are many additional questions concerning these therapies that have not yet been answered. Although we believe NRS, particularly NCPAP, may play a major role in our management of neonates, that role has yet to be clearly defined by evidence-based medicine.

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9 Positive-Pressure Ventilation in the Treatment of Neonatal Lung Disease

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Although a variety of new modalities for the ventilatory support of neonates have been introduced in recent years, positive-pressure mechanical ventilation remains the most common approach to the treatment of respiratory failure in neonatal intensive care units (NICUs) in the United States. In the Pediatrix Medical Group Clinical Data Warehouse, between 1996 and 2007 there were 246, 359 reports of infants requiring respiratory support beyond room air. Of this population, 78,922 (32.0%) received some form of conventional mechanical ventilation; 52,587 required nasal continuous positive airway pressure (NCPAP) (21.3%), and 15,805 (6.4%) were treated with high-frequency ventilation, either high-frequency oscillatory ventilation (HFOV) or high-frequency jet ventilation (HFJV). A solid understanding of the principles of positive-pressure mechanical ventilation is therefore mandatory in modern neonatology practice.

Since the last edition of this text (2003), mechanical ventilators have been increasingly modified with a variety of new technologies. Many of these changes have been introduced with two primary goals in mind: (1) to ease the work of breathing in the critically ill neonate and (2) to reduce the incidence of neonatal lung injury, or bronchopulmonary dysplasia (BPD).[1] As will be noted in this chapter, many of these modifications have been added to the positive-pressure ventilator with limited studies to support their effectiveness, and research in most instances is ongoing.[2] In all instances, however, application of the fundamental principles and physiology of positive-pressure ventilation remains critical to the treatment of the neonate with pulmonary problems.

Many of the newer ventilator alterations have been designed especially for the care of the extremely low-birth-weight neonate (ELBW; 1000 g or less birth weight).[3] These infants remain a primary focus of attention, although they comprise only a small part of overall NICU admissions (5%-8%).They remain hospitalized for long periods of time, suffer the most acute and long-term complications of neonatal intensive care, and consume a disproportionate number of hospital days. For these fragile neonates, continuous positive airway pressure (CPAP) and noninvasive ventilation,[4] synchronized intermittent mandatory ventilation (SIMV),[5] assist-control ventilation,[6] volume-controlled ventilation,[7] high-frequency jet ventilation (HFJV),[8] high-frequency oscillatory ventilation (HFOV),[9] and inhalational nitric oxide therapy[10,11] are now used in a variety of problematic clinical situations.

Because of the substantial difficulties encountered in the management of the neonate with respiratory failure, the basic approaches to positive-pressure respiratory support remain a focal point, not only from a pulmonary perspective but also from a neurodevelopmental viewpoint. As clinicians have become increasingly adept and facile with pulmonary therapy, the consequences of these forms of ventilation upon neurodevelopment have also emerged as issues of paramount importance.[12] The goal of intact neurologic outcome must therefore always be considered a priority in the care of the neonate with lung disease, and neonatal positive-pressure ventilators have been increasingly designed with this goal in mind (see Chapter 28).

Although the ELBW infant is typically seen as the most difficult pulmonary patient in the NICU, the larger infant with pulmonary problems often can be just as challenging to treat.[13,14] Many of the approaches to care noted above are also used in these larger infants, as well as extracorporeal membrane oxygenation (ECMO).[15] Since the introduction of inhaled nitric oxide, ECMO use has declined, but it has not vanished as a therapeutic modality and is reviewed elsewhere in this book (see Chapter 16). The purpose of this chapter, therefore, is to review the uses of pressure-limited, time-cycled, positive-pressure ventilation in the management of neonatal respiratory failure in both the premature and term neonate.

Design Principles

Classification

Positive-pressure mechanical ventilators are referred to by most clinicians as either "volume" or "pressure" types. *Volume-preset* ventilators deliver the same tidal volume of gas with each breath, regardless of the inflating pressure that is needed. *Pressure-preset* ventilators, in contrast, are designed to deliver a volume of gas with each breath until a preset limiting pressure designated by the physician is reached. The remainder of volume in the unit is then released into the atmosphere. As a result, the tidal volume that is delivered to the patient by pressure-preset ventilators with each breath may be variable, but the peak pressure delivered to the airway remains constant. The flow generation necessary to drive pressure-preset ventilators may occur in the following ways: constant-flow generator (high-pressure gas source or compressor),

nonconstant-flow generator (cam-operated piston), or a constant-pressure generator (weighted bellows).

Ventilators have been introduced that have the capability of serving as either volume- or pressure-controlled, time-cycled ventilators, depending on the operator's preference (e.g., Babylog 8000 plus, Drager Medical USA, Telford, Pa.). These units have significant advantages for some patients and represent an important advance in the technology of ventilator development. In addition, new modifications of ventilator circuits allow a variety of pressure- and volume-assisted modes designed to reduce the effort required (especially in the ELBW infant) to generate, sustain, and terminate a ventilator breath.

Termination of inspiration is now recognized to be an important component of ventilator control, because prolongation and plateau formation during inspiration, especially with pressure-limited modes, may lead to air trapping, air leak, and chronic lung injury. In this respect, newer ventilator approaches such as volume guarantee ventilation (VGV) have been introduced to more tightly regulate the volume delivery to the lung (Babylog 8000). In VGV, the operator chooses a target tidal volume and selects a pressure limit up to which the inspiratory pressure may be adjusted. The microprocessor of the unit then compares exhaled tidal volume of the prior breath to the desired target and readjusts the inspiratory pressure up or down to deliver the targeted tidal volume. Exhaled tidal volume is used in this mode for the regulation of the inspiratory pressure because it more closely approximates the tidal volume in the neonate who has a leak around an uncuffed endotracheal tube.

The newer modalities of ventilatory support are byproducts of the modern computer era and have been made possible by the use of microprocessors that permit very small, but theoretically beneficial modifications to pressure, flow, and volume throughout the ventilatory cycle. The primary rationale behind these novel approaches is that the volume delivered to the lung, or volutrauma, may be of greater importance in lung injury than pressure injury, or barotrauma.[16,17] This concept represents a significant change in thinking in recent years, because it has always been assumed that pressure, especially peak pressure, was likely to be most directly related to ventilator-induced lung injury (VILI) in the neonate.[18]

In addition to volutrauma and barotrauma, especially at lower lung volumes that may vary from breath to breath, the phenomenon of atelectotrauma may also be important in the etiology of lung injury.[19] Atelectotrauma is thought to occur from the shearing forces that appear during a variable volume delivery of gas to the lung, which results in opening and closing of smaller airways, especially in a surfactant-deficient lung. This changing volume delivery produces a type of injury to the small airways that further contributes to chronic lung disease in the neonate. Volume support ventilators, such as the Avea (Viasys Healthcare, Palm Springs, Calif.) attempt to overcome this problem by providing a preset, consistent tidal volume (usually 4-6 mL/kg) with each breath.

Microprocessor technology also permits approaches such as proportional assist ventilation (PAV) and respiratory muscle unloading (RMU) during the ventilatory cycle, modes which would have been impossible just a few years ago.[20,21] With these techniques, pressure at the airway is increased during inspiration proportionate to the inspired tidal volume (with restrictive lung disease) or to flow (with resistive or obstructive airway disease) to diminish the elastic work of breathing. Many of these approaches are described in greater detail elsewhere in this chapter.

Volume Versus Pressure Ventilators

For many years, an ongoing debate has persisted in neonatal respiratory care as to the relative merits of volume-controlled versus pressure-controlled mechanical ventilation for the neonate. This debate has centered on the question of whether it is barotrauma (pressure injury) or volutrauma (volume injury) that primarily damages the lung during mechanical ventilation in the treatment of neonatal respiratory disease.[22] As noted earlier, the most recent evidence would seem to suggest that volutrauma is the primary culprit in the development of BPD.[17] As a result, some neonatologists have begun to move toward the use of ventilators in which the delivery and regulation of tidal volume or minute ventilation is the primary control variable. The lack of large-scale, rigorously controlled trials that clearly demonstrate superiority of a single approach, however, has impeded any rapid change in care practices and many clinicians still select a ventilator on the basis of their familiarity with individual units (most commonly, the ventilator used in the nursery in which they trained!), personal bias, or anecdotal information. It is apparent that most current neonatal ventilators, however, whether used in pressure or volume modes, are capable of providing appropriate respiratory support. Understanding the basic principles of physiology that support mechanical ventilation and the ventilator in use should help minimize the incidence of lung and neurologic injury.

As mentioned previously, volume-preset ventilators deliver a consistent tidal volume with each breath. Areas of the lung that are atelectatic from collapsed or obstructed airways require a higher opening pressure, which can often be achieved with a volume-preset ventilator. Most of the tidal volume, nonetheless, will be preferentially delivered into segments of the lung that remain partially inflated and more compliant (LaPlace's law). Consequently, the volume-preset ventilator, although delivering a more consistent tidal volume, may occasionally overdistend the "healthier" areas of the lung and promote air leaks. This concept is particularly true in neonatal lung disease states, in which areas of lung inflation and atelectasis commonly coexist. Furthermore, these ventilators, although delivering a selected preset volume, may lose some of that volume around the endotracheal (ET) tube because, unlike endotracheal tubes for older children and adults, the neonatal tube is uncuffed.

Ventilator monitors can now measure the amount of the volume loss secondary to the ET tube leak by comparing inspiratory flow and expiratory return through the ET tube adapter. Recent modifications allow some ventilators to adjust for this volume loss, and continue to deliver a more consistent tidal volume up to a peak preset pressure. In diseases in which shifting or migratory atelectasis is commonplace (e.g., acute stages of respiratory distress syndrome [RDS] or BPD) with frequent compliance changes, the delivery of a consistent tidal volume may prevent the

frequent episodes of oxygen (O_2) desaturation that often occur.

With pressure-controlled ventilation, the volume of gas delivered to the distal air spaces depends on the compliance of the lungs and, to a lesser degree, that of the airway and the thoracic wall. With a decrease in lung compliance (increased lung stiffness), the preset pressure is reached more rapidly during gas compression and delivery, and residual volume is released to the atmosphere. As a result, tidal volume decreases, and if ventilation is inadequate, the physician must compensate for this loss of volume by increasing the peak inspiratory pressure (PIP). An obvious shortcoming, therefore, with pressure-controlled ventilation is that in disease states in which compliance is frequently changing, the inability of the operator to vary the peak preset pressure with each breath may be problematic. With volume-controlled ventilation, changing compliance is compensated for by terminating the delivery of a breath only when the desired volume has been delivered to the patient. A beneficial adjunct to volume ventilation, therefore, is that during weaning phases of ventilatory support, as the lung compliance improves, the required pressure needed to ventilate the patient will automatically decrease.

Comparisons of Pressure-Preset and Volume-Regulated Ventilators

Simplicity of Design

Pure pressure-preset ventilators use simple flow meters or pressure meters to monitor ventilator gas delivery. These ventilators therefore have greater simplicity of design (fewer working parts), compact design, operate by means of a pressure source alone in some models (no electricity needed), and therefore have decreased cost. Volume-preset ventilators, in comparison, require a piston or volume meter to regulate breath size, in addition to the pressure metering. Volume-preset ventilators therefore usually have more working parts, more complex metering requirements, and in general, greater cost. In the more modern ventilator units with SIMV, assist/control capability, pressure-assist modes, or both pressure and volume preset capability, the devices increase in complexity, and the cost typically exceeds that of the volume-preset ventilator alone. The disadvantages in cost and complexity of such units, however, are usually compensated for by their enhanced flexibility in clinical use.

Ease of Operation

Pressure-preset ventilators are, in general, relatively simple to operate. As a result, neonatal fellows, house staff, and nurse practitioners can be taught the basic principles of therapy more easily. The pressure delivered to the infant can be immediately read from the pressure meter, and adjustments to therapy can be made once appropriate monitoring has been performed or an arterial blood gas is obtained. With volume-preset ventilators, either compliance of the ventilator and tubing must be estimated or calculated to assess volume, or an approximation must be made as to the volume required and delivered to the infant. The calculations involved are often complex and more difficult for physicians in training to grasp readily, although the newer volume-regulated ventilators, capable of measuring and compensating for leakage around the uncuffed ET tube, have begun to overcome these obstacles. The differences between pressure-preset and volume-preset monitors have decreased in recent years with the addition of the various other modalities used in mechanical ventilation. These additions to ventilator controls, however, have made some of the decisions regarding the approach to ventilation more complex than was true in earlier eras of neonatal positive-pressure ventilation.

Possibility of Lung Injury

Peak inspiratory pressure (PIP) has traditionally been thought to be the factor most directly related to the risk of developing air leaks and chronic lung disease in the newborn infant.[18] Judicious use of PIP, with constant monitoring of that variable or the use of patient-controlled modes of ventilation, was believed to aid in reducing these complications. More recently, however, as noted previously, the evidence has shifted in support of volutrauma being the most important factor in lung injury in the neonate (and in adults as well). Studies that varied pressure and volume while examining markers of lung injury have demonstrated that high volume and high pressure produce lung injury, as did the combination of high volume and low pressure. Similar levels of lung injury, however, did not appear to occur with the combination of high pressure and low volume.[23,24] In addition, it appears that end-inspiratory volume may be most directly causative of lung injury.[25]

With this evidence in mind, if volume injury is the primary reason for the development of either air leaks or chronic lung disease in neonates, cautious monitoring of volume delivery to the lung may be preferable. In actual practice, however, it is somewhat difficult to divorce pressure- and volume-related injury, and this controversy may be more theoretical than practical. Even with devices that more precisely control volume delivery to the lung, the critical consideration is that a volume of gas is being forced into the lung under pressure. This very abnormal circumstance, which is the opposite of that seen in spontaneous negative-pressure breathing, prevents one from entirely divorcing the roles of volume and pressure in lung injury. Cautious assessment of pressure delivery, therefore, would still seem to be of value in avoiding lung injury.

Delivery of Excessive Volume

With a pressure-controlled approach, pressure is provided to the infant with each ventilator breath, and one does not have to constantly review the peak pressure delivery and the risk it poses to the lung. Volume delivery, however, in these circumstances can be exceedingly variable, especially in acute stages of lung disease or in diseases with changing compliance. Because volutrauma may be the most critical factor in lung injury, and changing low volumes may promote atelectotrauma,[26] our earlier thinking about the role of peak inspiratory pressure may need to be revised. With older volume ventilators, as compliance improved (e.g., during recovery from RDS), volume delivery could become excessive in a short period and then injury would occur. In the newer volume-limited modes, and more importantly, in ventilators that use volume guarantee approaches, the desired volume is constantly assessed and

pressure will be reduced as compliance improves, even calculating for air leaks around the uncuffed ET tube. Consequently, the previous concerns about excessive volume and pressure delivery to the recovering airway and lung are no longer quite so threatening. Because excessive volume is always dumped from the ventilator circuit once the preset pressure is reached during pressure preset ventilation, the delivery of excessive volume is limited. Overdistension of the lung is therefore less likely with both forms of ventilatory support than was previously the case, although air leaks and BPD can and will occur with any form of mechanical ventilation, even in the best of hands.

Volume Guarantee Ventilation

The distinction between pressure- and volume-support ventilation has continued to blur even further with the introduction of volume guarantee ventilation (Drager Babylog 8000 Ventilator), perhaps achieving simultaneously the best of both approaches to neonatal ventilation. With volume guarantee, a targeted mean tidal volume or minute ventilation for an infant can be assured, while still maintaining operator control of peak airway pressure (PIP). A predetermined tidal volume is thereby assured even in the face of an elevated PIP, which would normally result in tidal volume loss to the atmosphere. In a recent study, a modest reduction in peak inspiratory pressure for very-low-birth-weight infants was achieved with this form of mechanical ventilation, while gas exchange was well maintained.[27] Further evaluation of this form of ventilation will no doubt occur in the near future.

Basic Ventilator Design

Commonly used infant positive-pressure ventilators operate on similar principles, as illustrated in Figure 9-1. Some other technologies, such as the dual microprocessor units that open and close a series of solenoid valves during flow that were used in the Infant Star ventilator (Infrasonics, Inc., San Diego, Calif.—no longer for sale), vary this approach to some extent. The underlying concept, however, is the same: a certain volume of gas is delivered to the patient until a specific pressure is reached. The provision of additional ventilator capabilities, such as volume guarantee, assist-control, or SIMV ventilation, requires sophisticated microprocessor assistance during mechanical ventilation. The microprocessor must be able to assess ventilator cycle timing, the changeover from inspiration to expiration and expiration to inspiration, and the relative pressure, flow rate, and tidal volume levels during ventilatory cycling. Without this capability, many of the newer ventilatory modalities would not be possible. To assist in this regard, especially if one is also using ventilator graphics monitoring, flow sensor capability is also needed. Many ventilators therefore have a low-volume pressure transducer within, or added to, the ventilator circuit (usually at the proximal airway) to measure gas flow (and flow per unit time, or volume) into and from the patient. In their basic design, however, ventilators basically remain pistons that deliver a volume of gas under pressure to the lung.

In the system illustrated in Figure 9-1, a pressure source of either compressed air, oxygen (O_2), or both from a wall source is introduced into chamber A. The wall pressure is approximately 50 to 150 cm H_2O. This pressure is never applied directly to the infant but acts as a driving force for the ventilator. Mixing of compressed air and O_2 occurs in a blender before the gases reach the chamber, so that a known concentration of O_2 is delivered to the infant. A second chamber, chamber B, is added, and a flowmeter or resistor is inserted between the two to regulate the amount of air flow delivered into chamber B, which is smaller in the diagram and operates at a much lower pressure.

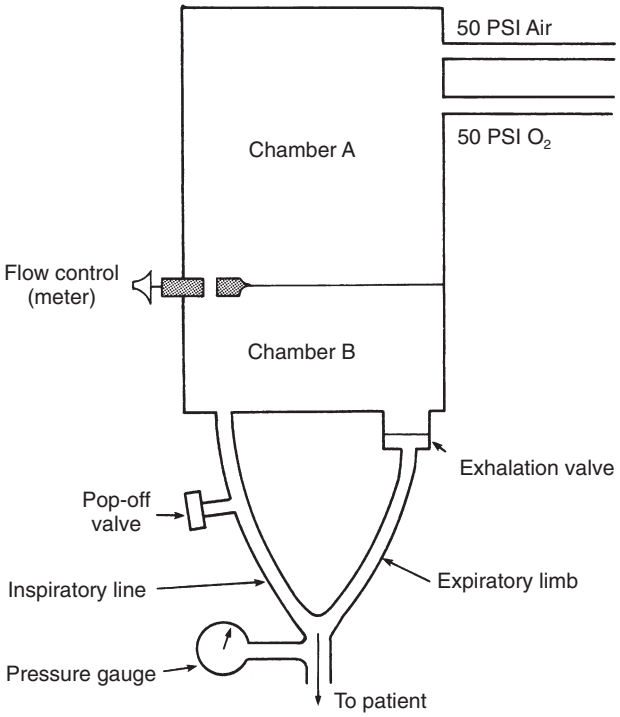

Figure 9-1 ■ Diagram of the basic system used in infant positive-pressure ventilators. The pressure source is compressed air or O_2, or both, from a wall source to *Chamber A*. A flowmeter between Chambers A and B regulates air flow to *Chamber B*, which operates at a much lower pressure. The pressure gauge and pop-off valve prevent the pressure from exceeding 50 to 70 cm H_2O. The ventilator is cycled by the opening and closing of the expiratory valve, which prevents CO_2 accumulation in the tubing. *PSI,* Pounds per square inch.

From the diagram, one can see that if the flow rate between the two chambers is high and the system were closed, the smaller chamber (B) could eventually reach driving pressure levels. Because chamber B interfaces with the infant, a maximum of 70 cm H_2O should rarely, if ever, be exceeded. For this reason, a pressure gauge and a "pop-off" regulating valve are added to the system to prevent excessive pressures from developing in chamber B (and in the infant's airway) when pressure preset ventilation is used. In volume guarantee ventilation, the pressure limit may be overridden or regulated to allow consistency of volume delivery to the lung.

In addition, an exhalation valve is added to the system. When open, a continuous flow occurs through the system, preventing accumulation of excessive carbon dioxide (CO_2) in the tubing. On closure of this valve, pressure increases in chamber B, the ventilator tubing, and the infant's airway until the preset pressure level is reached. The ventilator is cycled by the opening and closing of the expiratory valve or by the solenoid system in the Infant Star. In the Infant Star and the Bird V.I.P. ventilators, there

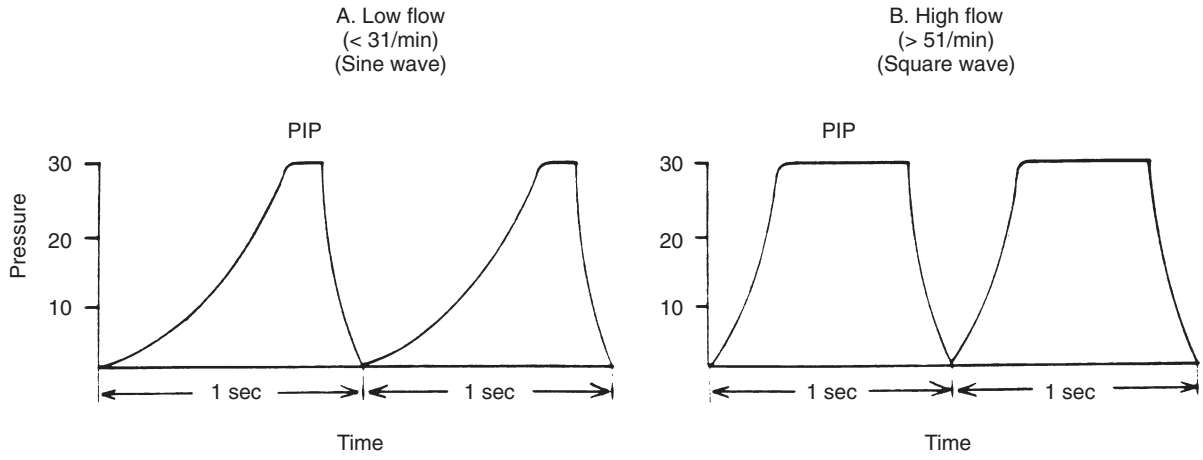

Figure 9-2 ■ Comparison of ventilator wave forms. **A,** Relative sine wave. **B,** Relative square wave.

is an additional "demand flow" modification in which the negative pressure created in the circuit during a patient's spontaneous breath is augmented by an additional fast response demand valve that increases flow through the circuit, easing work of breathing. In the Newport Wave ventilator (Newport Medical Instruments Inc., Newport Beach, Calif.), there is a separation of the spontaneous flow system from the mechanical breath system, called the *Duoflow system*. This system acts as a separate-standing continuous positive airway pressure (CPAP) unit during spontaneous respiration in the exhalation phase of respiration.

Lastly, the design of the system is such that the "upstroke" of the ventilator during inhalation can be modified by flow rate between chambers A and B. If flow is high, inspiratory pressure is reached quickly, and the respiratory waveform is "squared" (Fig. 9-2). If flow rate is reduced, the rate of rise of the inspiratory pressure is lessened, and the waveform appears more sinusoidal. In pressure-controlled ventilation, the rise time of the pressure slope may also be regulated. Because sudden distension of the airways is thought by some neonatologists to contribute to tracheobronchomalacia and BPD, many current ventilators are designed to produce a more sinusoidal waveform. Volume delivery modes of ventilation will almost always produce a sinusoidal wave pattern, because once the desired volume is delivered to the patient, inspiration ceases and expiration starts. Ventilator design during the past decade overall has moved toward more sinusoidal gas delivery, even though evidence for the effect of waveform on development of chronic respiratory complications is more theoretical than evidence-based.

Cycling

In conventional positive-pressure ventilators, the cycling process determines the method by which the inspiratory phase is initiated and terminated. Volume-preset ventilators are cycled when a preset volume is attained. Most standard pressure-preset ventilators are regulated by either an electrical timer (time-cycled) or by a pneumatic timer (pressure-cycled). The pneumatic-cycled ventilators have a small chamber in which pressure increases to a preset level and subsequently closes the inspiratory valve.

Although these ventilators are called *pressure-preset ventilators* because one sets the machines according to desired inspiratory pressure, they are technically *flow generators*. The power source produces such high pressure that even if the infant's lung compliance or airway resistance changes, the inspiratory flow rate is not affected. Examples of the most common time-cycled and pressure-cycled ventilators in current use are listed in Box 9-1. Some ventilators have two or more cycling modes and are called *mixed-cycle* ventilators. These are generally volume-cycled ventilators with an additional time-cycle control. The control capabilities of each ventilator, and the differences between the methods in which pressures and volumes are delivered, sustained, and terminated, are important to understand but are very detailed and technically beyond the scope of this discussion. Clinicians are strongly urged to carefully review the operator's manual for each specific ventilator to avoid any error in management.

If one operates pressure-preset ventilators at a high respiratory rate, the flow rate must be sufficiently high if one wishes to deliver a full tidal breath or reach the desired pressure within a brief period of time. In addition, if inspiratory time is short, a higher flow rate may be necessary to deliver the required volume and pressure in the limited time period. Consequently, one should avoid excessive ventilator rates (more than 70 breaths per minute) in most neonatal lung diseases. Given the reduced compliance that is often present in these restrictive lung diseases, the

Box 9-1 COMMONLY USED NEONATAL POSITIVE-PRESSURE VENTILATORS

Bird V.I.P. Infant/Pediatric Ventilator
Bird V.I.P. Gold Infant/Pediatric Ventilator (see Figure 9-3)
Bear Cub 750 PSV Infant Ventilator
Infant Star Ventilator
Sechrist IV-200 SAVI Ventilator
Newport Wave Ventilator
Draeger Babylog 8000 Plus Infant Care Ventilator
Siemens Servo 300 Ventilator

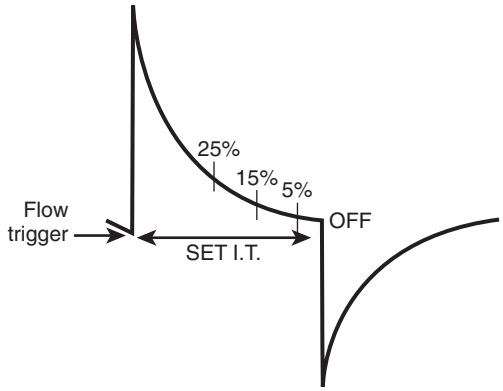

Figure 9-3 ■ Termination sensitivity or expiratory trigger. Inspiration is initiated by a change of flow at the airway. When the lungs have inflated, flow decreases at the proximal airway, resulting in breath termination. The point of termination can be adjusted by the clinician, and represents a percentage of peak inspiratory flow. For example, a 10% termination sensitivity will end the breath when flow is 10% of peak flow. (From Becker MA, Donn SM, Bird VIP Gold Ventilator. In Donn SM and Sinha SK (eds.). Manual of Neonatal Respiratory Care, 2nd ed. Mosby, Elsevier, 2006 p. 251)

combination of short inspiration and reduced compliance may result in inadequate tidal volumes and little more than dead space ventilation and gas trapping.

An addition to some neonatal ventilators is the concept of *termination sensitivity*. Termination sensitivity is a ventilator control that the clinician can set to terminate a ventilator breath at a specific percentage of peak flow during expiration (see Fig. 9-3). Termination sensitivity is an effective way to limit prolongation of the inspiratory phase of the ventilatory cycle. By setting a termination sensitivity of 5% to 10%, inspiration will cease when inspiratory flow decreases to 5% to 10% of peak flow. A termination sensitivity of 5% to 10% will usually limit inspiration to 0.2 to 0.3 second during neonatal mechanical ventilation. In practice, however, we have often found it preferable to simply set the desired inspiratory time directly on the ventilator and turn off the termination sensitivity control.

Suggested Procedure for Initiating Mechanical Ventilation

Mechanical ventilation of the newborn, especially in the ELBW infant (less than 1000 g), is associated with numerous complications. Before using this therapy, all clinical personnel must be thoroughly familiar with the operation of ventilators and the physiologic principles that govern their use. The authors believe that successful mechanical ventilation is 5% device-related and 95% understanding of physiologic principles in delivering optimal patient care. Unfortunately, too many clinicians become overly concerned with the "hardware" of mechanical ventilation and forget that the "software" (the decisions governing use of the devices) is far more important. With the increasing complexity of modern neonatal mechanical ventilators, however, it is becoming more difficult to avoid becoming enmeshed in hardware issues, even when it is unclear to what extent the newer modifications provide any substantial long-term clinical benefit. It is therefore essential to have a comprehensive understanding of both the equipment being used and the controls on that equipment that function in treating the critically ill neonate. However, the methods offered throughout the remainder of this chapter focus primarily on the basic physiologic principles of neonatal respiratory care rather than the innumerable technologic manipulations that one can achieve with modern neonatal ventilators. Additional information about the many different approaches to neonatal mechanical ventilation is discussed in Chapter 13.

First Steps

Although the procedures in this section may appear routine and simple, they are crucial to care because errors made at this point may be life threatening (e.g., if one does not correctly connect the gas sources to the ventilator). In addition, although this discussion will focus primarily on the pulmonary physiology and ventilator management of the infant, one should never overlook many of the important peripheral issues for successful respiratory care, such as infection surveillance and control, nutritional support, fluid and electrolyte management, comfort and pain relief of the infant, and emotional support for the family. The authors have frequently observed that a discussion with the family early in the child's hospitalization about the benefits and perils of ventilatory assistance can be extremely important in reducing the understandable concern of the family.

When not in use, the ventilator should be carefully cleaned, the circuits should be sterilized, and the unit should be stored in a clean, dry area. A plastic cover should be placed over the ventilator. Periodic infection control surveillance and culturing of ventilator equipment is a valuable practice. When the ventilator is removed from storage, the following steps should be taken to prepare it for use:

1. Check the electrical connections. Only grounded sources (three pronged) should be used. Any unit that undertakes the care of neonates on ventilators must have access to back-up generators in case of power failure in the nursery.
2. Check wall connections. The O_2 and room air gas sources should be connected to the wall, and the required pressure must be adequate to drive most conventional ventilators (approximately 50 psi). Wall gauges should monitor this pressure.
3. Check tubing connections. All connections must fit securely, and the correct ventilator tubing and circuitry should be placed for the specific ventilator. The ET must fit tightly into the ventilator connector, otherwise serious leaks may result. Circuits should never be "jury-rigged" if appropriate connectors are unavailable. Such modifications can be lethal to an infant if a circuit comes undone at a critical point in care.
4. Check and properly fill humidification systems. Newer units that use hydrophobic humidification techniques, especially those with heated filaments in the tubing, may not show droplet formation, which indicates saturation of the gas. Alternative methods

of periodically checking the humidifiers for adequate humidification are therefore essential. Inadequately humidified gas can injure the airway and has been associated with necrotizing tracheobronchitis in a variety of mechanical ventilation forms and is not limited to high-frequency ventilation, as was previously believed.[28]

5. Check temperature devices. Temperature devices should be examined periodically to ensure appropriate and accurate temperature of the gas entering the lungs. Inspired gas should be approximately at body temperature—35° to 36° C (+2° C). Inadequately warmed gas can produce bronchospasm, especially in the chronically ventilated infant,[29] whereas excessively heated gas can inflame the immature airway.

Ventilator Controls

The ventilator controls that are found on most pressure-controlled ventilators include the following (as seen on a Drager Babylog 8000 ventilator). Some are dialed in and some are computer generated. Some ventilators are entirely touch-screen and have no actual "dials" to set (Avea, Viasys Healthcare, Palm Springs, Calif.):

1. Inspired O_2 concentration (FIO_2)
2. Inspiratory time (T_I) (Some ventilators may also have expiratory time [T_E], as does the Drager Babylog 8000, or inspiratory-expiratory ratio [I:E].)
3. Inspiratory flow rate
4. Peak inspiratory pressure (PIP)
5. Positive end-expiratory pressure/continuous positive airway pressure (PEEP/CPAP)
6. Rate or frequency (f)
7. Assist or trigger sensitivity
8. Termination sensitivity
9. Selection of SIMV/CPAP mode, assist/control mode, pressure support, or volume guarantee mode
10. Variable inspiratory and variable expiratory flow
11. Graphics monitoring settings
12. Ventilator alarm settings

From these controls, waveform and mean airway pressure may be indirectly selected. Newer ventilators also digitally display controls. The external waveform monitor on the Drager has unusually extensive capabilities, including demonstration of flow-volume and pressure-volume loops. Some ventilators may have the following additional control capability:

1. Demand flow (Bird V.I.P.)
2. Exhalation assist
3. Manual breath
4. Pressure support modes
5. High-frequency modes (e.g., Drager Babylog 8000)

Although sales representatives often stress the utility of these additional capabilities, the scientific evidence that underscores the value of these modifications is not extensive. A number of investigations are emerging, however, that appear to show some benefit from these modifications. The use of SIMV, assist/control, and pressure support has become very widespread and does appear to offer demonstrable advantages in neonatal respiratory care. Volume guarantee ventilation similarly appears to effectively ventilate babies while reducing the potential for lung injury. One of the great difficulties in any study of ventilatory management is that so many confounding variables (fluid therapy, infection, nutritional factors, environment, lighting, sound, etc.) are always present in neonates that attempting to control for everything except the ventilator is essentially impossible. As a result, it is profoundly difficult to demonstrate that the use of a physiologically useful adjunct such as pressure support can affect upon such critical issues as length of stay and incidence of BPD, which are often the endpoints of neonatal investigations.

High-frequency ventilators have additional controls, such as peak-to-peak pressure, jet valve on-time, amplitude, and sigh frequency and duration. The reader is referred to Chapter 11 for more detailed discussion of these ventilators.

Fraction of Inspired Oxygen

Oxygen is probably the most commonly used drug in neonatal intensive care, yet it is rarely thought of as such by physicians. Appropriate use of O_2 is highly therapeutic in most cases of neonatal cardiopulmonary disease. In addition to relieving hypoxemia, its action as a pulmonary vasodilator in cases of persistent pulmonary hypertension of the neonate has long been established.[30] In fact, pulmonary hypertension may be an important component of many neonatal lung diseases, such as RDS, in which relief of pulmonary vasoconstriction with O_2 has great value for the patient.[31] Inadequate O_2 administration with resultant hypoxemia, however, may result in severe neurologic injury.[32] Excessive O_2 administration has been implicated as one of the most important provocative factors in retinopathy of prematurity,[33] with subsequent retinal scarring and loss of vision, and in BPD,[34] leading to further O_2 or ventilator dependency. Accurate measurement of O_2 administration and arterial O_2 tension (PaO_2) or oxygen saturation is therefore mandatory in any neonate requiring O_2 therapy.

Regulation of ambient O_2 concentration during mechanical ventilation is performed by blenders. Commercial blenders precisely mix O_2 and compressed air into desired concentrations of O_2 as determined by the patient's O_2 requirements. Many ventilators have blenders incorporated into their design, particularly the newer units. Older ventilators have separate blenders that can be attached to the O_2 inflow source on the ventilator. Blenders are usually easy to operate and work by simply dialing in the desired O_2 concentration. Although blenders are generally very accurate, the clinician must usually employ an additional device periodically to check that the blender is actually delivering the desired O_2 concentration to the patient. Portable O_2 analyzers or continuous in-line sensing devices may be used to check the inspired O_2 concentration at the connector of the patient to the ventilator.

Administration of poorly humidified oxygen may result in bronchospasm and airway injury in neonates. It is important that oxygen be warmed to 35° to 36° C to reduce the risk of airway problems. When warming and humidifying any gases administered to patients, excessive humidification may get into the circuit and produce "rain-out," or the formation of droplets that can drip into the airway. A heating wire within the ventilator circuitry can reduce the severity of this problem.

Peak Inspiratory Pressure

With pressure-limited ventilators, peak inspiratory pressure (PIP) is the primary control used to deliver tidal volume. The difference in pressures between PIP and positive end-expiratory pressure (PEEP) is the primary determinant of tidal volume when used in pressure control modes. In most ventilators, PIP can be directly selected by the physician, but the operator should be aware that PIP may change if either flow rate or the I:E ratio is changed.

When starting levels of PIP are selected, several physiologic factors must be considered: the infant's weight, gestational age and postnatal age, type and severity of the disease process, lung compliance, airway resistance, and time constant of the lung. A time constant, which is the product of compliance and resistance, refers to the unit of time necessary for the alveolar pressure to reach 63% of the total change in airway pressure during positive-pressure ventilation. Time constants can be measured during inspiration and expiration. If, for example, inspiration lasts for a period of time equal to one time constant, then 63% of the difference in pressure between airway opening and alveoli equilibrates, and a proportional volume of gas enters the airways of the lung. With additional time during inspiration for further pressure equilibration, an additional 63% of the remaining pressure equilibrates (total = 86% now [or 63% + 63% × the remaining 37%]), and an additional equivalent volume of gas follows. After three to five time constants, little additional pressure change occurs, so that gas volume delivery is essentially complete (Fig. 9-4).

With reduced compliance, as seen in respiratory distress syndrome (RDS), the time constant decreases, so that pressure equilibration occurs during a shortened inspiration and expiration. Inspiration and expiration, with volume movement of gas in and out of the lungs, therefore occur in a shorter time period than is seen in normal lungs. When the time constant of the lung becomes so short during either inspiration or expiration that pressure equilibration cannot occur, then either inadequate delivery of volume during inspiration may result or air trapping and incremental overdistension of the lung during expiration may ensue. This latter phenomenon appears to be very important in the development of air leak syndromes during neonatal ventilation.

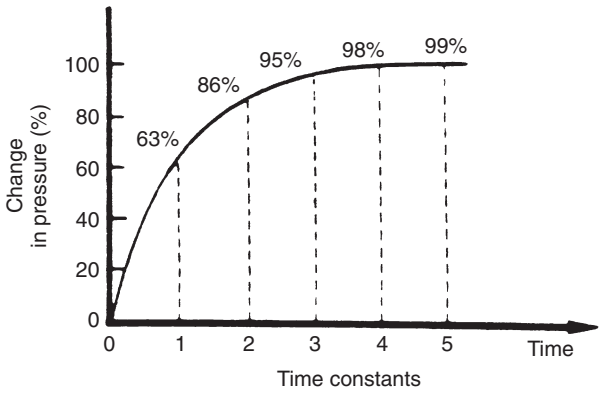

Figure 9-4 ■ Percentage change in pressure in relation to the time (in time constants) allowed for equilibration. As a longer time is allowed for equilibration, a higher percentage change in pressure occurs. The same rule governs the equilibration for step changes in volume. (From Carlo WA, Martin RJ: Principles of assisted ventilation. Pediatr Clin North Am 33:221, 1986.)

Before attachment of any patient to the ventilator, inspiratory pressure should be carefully checked to be certain that it is neither excessive nor inadequate. The adapter that connects to the ET tube should be occluded, and the pressure gauge on the ventilator should be checked, with adjustments made as necessary. Once the patient is attached to the ventilator, the PIP should be rechecked to be certain it has not changed significantly from what was observed with the adapter occluded. If it has changed more than 2 to 3 cm H_2O, one must consider the possibility of air leak or an obstructed ET tube.

Considerable controversy exists regarding the level of PIP that should be used for infants with respiratory disease. This issue is considered in greater detail later in this chapter in the section on ventilator management, as well as in the chapter on ventilatory techniques and lung-protective strategies (Chapter 13). It appears that as a basic principle, the lowest PIP that adequately ventilates the patient is usually the most appropriate. Clearly, with volume regulated modes of ventilation, volume delivery takes precedence over PIP, though the PIP should be carefully followed, along with pulmonary graphics. Another important consideration in this regard is the overall approach to mechanical ventilation that is used. In general, the use of assist/control ventilation will result in a more reduced PIP than may be seen with either conventional mechanical ventilation (with pressure that is entirely operator selected) or SIMV, especially when combined with volume guarantee ventilation.[35] With assist/control alone, infants will usually tend to increase their own spontaneous respiratory rate somewhat to compensate for a lower PIP that is selected by the clinician. This strategy is usually effective unless one selects a PIP that is inadequate to provide sufficient gas exchange and only dead space ventilation occurs. Simply increasing the PIP slightly may be sufficient to achieve success if the $PaCO_2$ remains excessively elevated (more than 55 mm Hg). In some clinical circumstances, such as acute RDS, this style of ventilatory support may be beneficial and may reduce exposure to higher PIP. It appears that the incidence of pulmonary complications (air leaks and BPD) may also be reduced with this technique.[5] The use of pressure support may also help ease the spontaneous breaths during spontaneous or SIMV ventilation and maintain a more consistent degree of airway and lung inflation.

In contrast, some neonatologists, fearful of lung injury and therefore attempting to avoid it at all costs, may persist in using an inadequate PIP for excessively long periods. Based on the infant's size, some physicians arbitrarily set a certain PIP level (even during volume-controlled ventilation) above which they will not venture, even when ventilation remains grossly insufficient, as seen in arterial blood gases. In contrast to the excellent and well-conceived "gentle ventilation" approach developed by Jen-Tien Wung at the Children's Hospital of New York (formerly Babies Hospital),[36] protracted hypercarbia and respiratory acidosis can result in serious systemic and neurologic injury. A

study by Vannucci and colleagues[37] indicates that in an animal model, extreme hypercapnia ($PaCO_2$ greater than 100 mm Hg) may result in cardiac depression and reduced cerebral blood flow, with subsequent hypoxic-ischemic brain injury. The necessity of adequate gas exchange under all circumstances, therefore, cannot be overemphasized. It does no good to avoid barotrauma while the patient dies or suffers significant injury from insufficient gas exchange that results in long-term morbidity. Appropriate PIP can usually be judged on clinical examination (chest movement and breath sounds) and on the basis of blood gas analysis.

Table 9-1 summarizes advantages and side effects of different pressure ranges. Barotrauma can be reduced with the use of lower PIP, and the incidence of air leaks and chronic lung disease may be decreased. There remain, however, surprisingly few data, especially follow-up, to suggest a definite value to extreme pressure reduction with permissive hypercapnia.[38,39] Normal lung development may be enhanced by a lower PIP, although even distribution of gas throughout the lung may be more important than low pressure. High-frequency ventilation appears to decrease barotrauma to some extent by providing such gas distribution. Again, one must provide adequate PIP to deliver an appropriate tidal volume (V_T) to the patient. Low V_T from low PIP may reduce minute ventilation (V_E = rate × V_T), resulting in elevated arterial carbon dioxide tension ($PaCO_2$) and hypoxemia. Long-term follow-up on children treated with this approach has not been extensive to date; thus the degree of morbidity is not known.

High PIP should usually be avoided because of the risk of air leaks, such as pneumothorax, interstitial emphysema, and pneumomediastinum. Furthermore, high intrathoracic pressure, when transmitted to the myocardium, may impede venous return to the heart and decrease cardiac output. There appears to be a neutral range of $PaCO_2$. Although a high or low $PaCO_2$ by itself may not be harmful, it may be related to alterations in cardiac output that can produce injury to the central nervous system. Certain clinical conditions, however, may warrant the use of high PIP. In patients with markedly decreased compliance or in those with decreased lung volume from atelectasis, a high PIP may be needed to maintain adequate gas exchange or to reexpand collapsed sections of the lung. Also, some physicians treat persistent pulmonary hypertension of the newborn (PPHN) with high PIP to hyperventilate patients intentionally to a lower $PaCO_2$ in an effort to decrease pulmonary artery pressure.[30] As a general rule, however, hyperventilation has been shown to induce a variety of neurologic injuries in infants and is no longer a recommended therapy in PPHN except as a potentially short-term life-saving measure.

TABLE 9-1 Peak Inspiratory Pressure (PIP)

LOW (≤20 cm H_2O)		HIGH (≥20 cm H_2O)	
Advantages	**Adverse Effects**	**Advantages**	**Adverse Effects**
1. Fewer side effects, especially BPD, PAL 2. Normal lung development may proceed more rapidly	1. Insufficient ventilation; may not control $PaCO_2$ 2. ↓ PaO_2, if too low 3. Generalized atelectasis may occur (may be desirable in some cases of air leaks)	1. May help reexpand atelectasis 2. ↓ $PaCO_2$ 3. ↑ PaO_2 4. Decrease pulmonary vascular resistance	1. Associated with ↑ PAL, BPD 2. May impede venous return 3. May decrease cardiac output

BPD, Bronchopulmonary dysplasia; *PAL,* pulmonary air leaks.

Positive End-Expiratory Pressure

Although it has been used since Gregory's original work in 1971,[40] continuous positive airway pressure (CPAP) has reemerged as a highly effective way to initiate ventilatory assistance in the delivery room for the lowest birth weight babies, with the least risk of airway and neurologic injury.[41] Furthermore, extubation to CPAP after mechanical ventilation appears to decrease the likelihood of reintubation and reduces the frequency of apnea. In current practice, most infants receive a trial of CPAP prior to initiation of mechanical ventilation. There is some information suggesting that there are outcome differences in the methods by which CPAP is delivered.[42] In addition, some groups suggesting that "bubble" or underwater CPAP may be more effective than ventilator-delivered CPAP.[43] Although it is difficult to reconcile how relatively small pressure differences could be reflected in an infant's outcome, given the normal attenuation of pressures down the airway, there is some recent evidence that there are measurable differences between underwater, or "bubble," CPAP and the CPAP that is delivered by current mechanical ventilators. In this animal trial,[43] it appeared that bubble CPAP promoted enhanced airway patency during treatment of acute postnatal respiratory disease in preterm lambs and offered some protection against lung injury compared with constant pressure technique. Further studies in neonates should be undertaken in this regard (see Chapter 8).

While on the ventilator, the use of PEEP, or continuous distending pressure, has become a standard technique in the ventilatory management of the neonate. The approach to treatment is similar to that recommended for CPAP in the spontaneously breathing patient. Selection of the appropriate PEEP depends on the size of the patient, the pathophysiology of the disease process, and the goals of treatment. In most clinical situations, there appears to be an "optimal PEEP" below which lung volumes are not well maintained and above which the lung becomes overdistended. On most ventilators, PEEP is selected directly by setting the desired pressure. One must be aware, however, that the chosen PEEP may be altered by other ventilator variables. For example, if expiratory time is too short or if airway resistance is increased, a degree of inadvertent PEEP may be generated that is additive to the selected level.[44] This inadvertent PEEP in such situations may contribute to gas trapping and increase the potential for pulmonary air leaks.

The major benefits of PEEP are similar to those seen with CPAP in the spontaneously breathing infant. PEEP stabilizes and recruits lung volume, improves compliance (to a certain point, after which compliance may actually decrease), and improves ventilation-perfusion matching in the lung.

Table 9-2 summarizes the effects of PEEP at various levels. PEEP of less than 2 cm H_2O is not recommended, except in rare instances, because the presence of an ET tube bypasses the normal airway mechanics that typically provide a low level of end-distending pressure during spontaneous breathing. Furthermore, the resistance of the ET tube requires a certain PEEP level if the atelectasis that is produced by an inspiratory load in the face of inadequate PEEP is to be avoided.

Low PEEP levels (2 to 3 cm H_2O) are most often used during weaning phases of ventilatory management, and some ELBW babies on assist/control support may be adequately treated at these levels. When such levels are provided early in the course of disease in larger infants, however, atelectasis may result with CO_2 retention. In most clinical circumstances, medium levels of PEEP (4 to 7 cm H_2O) are most often appropriate. Such levels allow appropriate maintenance of lung volumes yet minimize the potential side effects associated with higher PEEP and pulmonary overdistension. PEEP levels above 8 cm H_2O are rarely used in conventional mechanical ventilation because of the risk of pulmonary air leaks and reduction of cardiac output. With high-frequency jet ventilation (HFJV), however, higher PEEP may sometimes be needed to ensure adequacy and maintenance of lung volume, because HFJV tidal volumes are relatively low. Severe respiratory failure in the larger infant may also occasionally require a higher PEEP level (8 to 10 cm H_2O and above) for a period, until an alternative therapy (HFJV or ECMO) can be initiated. Extreme vigilance for pneumothoraces, pneumomediastinum, increased pulmonary vascular resistance, and inadequate cardiac output is essential at any level of CPAP or PEEP, but it should always be considered at the higher levels of support.

Rate or Frequency of Ventilation

Respiratory rate or frequency (f) is one of the primary determinants of minute ventilation in mechanical ventilation (minute ventilation = $f \times V_T$) (Table 9-3). No conclusive studies demonstrate the optimal ventilatory rate for the treatment of neonatal respiratory disease. Some studies have indicated improved oxygenation at higher rates (60 or more breaths per minute).[45] Other studies have historically suggested more success with slower rates (40 or fewer breaths per minute).[46] As with other previously mentioned ventilator controls, the best rate in a given situation depends on several variables, including the size of the infant, type and stage of the disease, presence of complications, and clinical response. Furthermore, the successful introduction of high-frequency ventilators suggests that frequency may be important only in reference to other controls being used at that time. For example, very high rates can be successfully used if PIP (and consequently V_T) and T_I can be reduced simultaneously. Without such a reduction, high frequencies might result in severe complications.

In conventional ventilation, especially during assist/control, high frequencies may be spontaneously generated by an infant with PIP kept at a minimum level. Many babies will subsequently "auto-wean" their rate as lung compliance improves. This circumstance, however, is very much different than the patient intentionally treated with hyperventilation to deliberately lower $PaCO_2$.

In most instances, whether the clinician selects a high or low respiratory rate, the goal of therapy is the reduction of potential volutrauma or barotrauma with an associated decrease in air leaks and chronic lung disease. Again, neurologic effects from whatever ventilatory technique is used must always be taken into consideration. Both high and low ventilatory rates can achieve these objectives if the

TABLE 9-2 Continuous Positive Airway Pressure or Positive End-Expiratory Pressure (CPAP or PEEP)

LOW (2-3 cm H_2O)		MEDIUM (4-7 cm H_2O)		HIGH (>8 cm H_2O)	
Advantages	**Adverse Effects**	**Advantages**	**Adverse Effects**	**Advantages**	**Adverse Effects**
1. Used during late phases of weaning 2. Maintenance of lung volume in very premature infants with low FRC 3. Useful in some extremely LBW infants on A/C ventilation	1. May be too low to maintain adequate lung volume 2. CO_2 retention from $\dot{V}/\dot{Q}$ mismatch, as alveolar volume is inadequate	1. Recruit lung volume with surfactant deficiency states (e.g., RDS) 2. Stabilizes lung volume once recruited 3. Improve $\dot{V}/\dot{Q}$ matching	1. May overdistend lungs with normal compliance	1. Prevents alveolar collapse in surfactant deficiency states with severely decreased C_L 2. Improves distribution of ventilation	1. PAL 2. Decreases compliance if lung overdistends 3. May impede venous return to the heart 4. May increase PVR 5. CO_2 retention

A/C, Assist/control; C_L, lung compliance; *FRC*, functional residual capacity; *LBW*, low birth weight; *PAL*, pulmonary air leaks; *PVR*, pulmonary vascular resistance; *RDS*, respiratory distress syndrome; $\dot{V}/\dot{Q}$, ventilation-perfusion.

TABLE 9-3 Neonatal Mechanical Ventilatory Rates (f)

SLOW (≤40 breaths/min)		MEDIUM (40-60 breaths/min)		RAPID (≥60 breaths/min)	
Advantages	**Adverse Effects**	**Advantages**	**Adverse Effects**	**Advantages**	**Adverse Effects**
1. ↑ PaO_2 with increased MAP 2. Useful in weaning 3. Used with square wave ventilation 4. Needed when I:E ratio is inverted	1. Must ↑ PIP to maintain minute ventilation 2. ↑ PIP may cause barotrauma 3. Patient may require paralysis	1. Mimics normal ventilatory rate 2. Will effectively treat most neonatal lung diseases 3. Usually does not exceed time constant of lung, so air trapping is unlikely	1. May not provide adequate ventilation in some cases 2. ↑ PIP may still be needed to maintain minute ventilation	1. Higher PaO_2 (may be the result of air trapping) 2. May allow ↑ PIP and VT 3. Hyperventilation may be useful in PPHN 4. May reduce atelectasis (air trapping)	1. May exceed time constant and produce air trapping 2. May cause inadvertent PEEP 3. May result in change in compliance (frequency dependence of compliance) 4. Inadequate VT and minute ventilation if only dead space is ventilated

I:E, Inspiratory to expiratory; *MAP*, mean airway pressure; *PEEP*, positive end-expiratory pressure; *PIP*, peak inspiratory pressure; *PPHN*, persistent pulmonary hypertension of the neonate; *VT*, tidal volume.

physician has an overall strategy for ventilator management such as that outlined later in this chapter. Most complications involving ventilator rates occur because the clinician fails to recognize the impact of rate change on other aspects of ventilatory care. For example, if higher rates are selected, a prolonged T_I and an inadequate T_E may result in decreased compliance and air trapping, if the time constant of the lung does not adequately allow for gas exit. Thus ventilatory changes cannot be entertained without evaluating the overall effects of that decision.

In addition to the considerations already noted, it is essential that the capabilities of the ventilator in use be examined to be certain that what is selected for the patient is actually delivered by the machine. Boros et al.[47] and Simbruner and Gregory[48] have shown that there is significant variability among ventilators to deliver pressures and VT, especially at higher frequencies. Some ventilators have exhalation-assist modes to help in alleviating gas trapping in the tubing at higher rates, but this provision does not ensure consistent VT delivery.

Physicians who prefer slower-rate ventilation often cite the work of Reynolds and Tagizadeh[46] and Boros,[49] who demonstrated that lower rates, when delivered with higher mean airway pressures, produced better oxygenation. Again, lower rates can be used successfully, with a minimum of complications, if one is aware of the potential sources of problems. Slower-rate ventilation could not have been developed without modification of ventilator circuitry to provide continuous gas flow, rather than intermittent flow. This modification, introduced by Kirby and colleagues during the early 1970s,[50] has now been extended in some ventilators to include a separate circuit entirely for spontaneous breathing. Before the introduction of continuous flow, an infant who attempted to breathe against a closed valve would rebreathe exhaled gas, with a potential increase in $PaCO_2$. With constant flow in a time-cycled device, the physician could now choose to provide a predetermined amount of mechanical ventilation in combination with spontaneous breathing. This technique is referred to as intermittent mandatory ventilation (IMV), and it has been a useful adjunct to ventilator weaning. With the addition of a provision to synchronize the ventilator to the infant breath (SIMV), the technique has become increasingly important as a weaning approach. As the pulmonary disease improves, the infant receives fewer machine breaths, and spontaneous breathing is allowed to increase.

Ventilator rate is usually controlled by directly selecting the rate in time-cycled machines, which comprise the majority of neonatal ventilators today. In pressure-cycled machines, the rate is changed by altering T_I, T_E, or the I:E ratio.

Inspiratory-Expiratory Ratio

Possible variations in I:E ratios are summarized in Table 9-4. The ability to select an I:E ratio varies from ventilator to ventilator. In some pressure-cycled units, both T_I and T_E can be directly selected to produce the desired I:E ratio. On most units, however, the T_I is selected, and in combination with the desired frequency, the I:E ratio is then automatically set. In patient-triggered ventilation, however, with the termination sensitivity set at 5% to 10%, the I:E ratio may become variable, because the flow characteristics of the inspiratory phase of ventilation will alter the duration of inspiration from breath to breath. If a specific I:E ratio is desired, the termination sensitivity must be shut off.

I:E ratio has been considered an important variable in ventilator management strategies, beginning with Reynolds and Tagizadeh's work that emphasized its role in controlling oxygenation.[46] Normal inspiratory to expiratory ratio in a spontaneously breathing neonate is about 1:3 to 1:4. In the Reynolds studies, the I:E ratio was reversed (greater than 1:1), with inspiration longer than expiration. More recently, however, the I:E ratio has been regarded as less critical than controlling the T_I. There is still a great deal of debate among neonatologists regarding the

TABLE 9-4 Inspiratory: Expiratory (I:E) Ratio Control in Neonatal Mechanical Ventilation

INVERSE (>1:1)		NORMAL (1:1 to 1:3)		PROLONGED EXPIRATORY (<1:3)	
Advantages	**Adverse Effects**	**Advantages**	**Adverse Effects**	**Advantages**	**Adverse Effects**
1. ↑ MAP 2. ↑ PaO_2 in RDS 3. May enhance alveolar recruitment when atelectasis is present	1. May have insufficient emptying time and air trapping may result 2. May impede venous return to the heart 3. ↑ Pulmonary vascular resistance and worsens diseases such as PPHN and CHD 4. Worsens PAL	1. Mimics natural breathing pattern 2. May give best ratio at higher rates	1. Insufficient emptying at highest rates	1. Useful during weaning, when oxygenation is less of a problem 2. May be more useful in diseases such as MAS, when air trapping is a part of the disease process	1. Low TI may decrease tidal volume 2. May have to use higher flow rates, which may not be optimal for distribution of ventilation 3. May ventilate more dead space

CHD, Congenital heart disease; *I:E*, inspiratory to expiratory; *MAP*, mean airway pressure; *MAS*, meconium aspiration syndrome; *PAL*, pulmonary air leaks; *PPHN*, persistent pulmonary hypertension of the neonate; *RDS*, respiratory distress syndrome; *TI*, inspiratory time.

optimal T_I for neonatal mechanical ventilation. Increasingly, emphasis has been placed on using shorter inspiratory times to avoid excessive tidal volumes, with the belief that airway and lung injury will be reduced. It is evident, however, that if one reduces T_I too much, opening pressure within the lung will not be reached and only dead space ventilation will occur. As a result, we have tried to achieve a balance between shorter inspiratory times and adequate gas entry into the lung. In general, a starting T_I of 0.3 to 0.4 seconds is employed for most neonatal ventilation, shorter than was previously described in earlier editions of this book.

Selecting any two of the four variables (T_I, T_E, I:E, and rate) automatically determines the other two. Choosing a T_I of 0.5 second with an I:E of 1:1 automatically provides a T_E of 0.5 second and a rate of 60 breaths per minute. Furthermore, if rate is decreased to 30 breaths per minute and the I:E is left at 1:1, then the T_I increases to 1 second, possibly increasing the risk of airway overdistension and air leak. Consequently, many physicians prefer to set a T_I that they believe is adequate and are not as concerned about the I:E ratio directly. It is the authors' preference, in general, to select a T_I of 0.3 to 0.4 second during the acute phases of most neonatal lung diseases to avoid air trapping. Further recommendations about appropriate I:E ratios, however, depend on the type, severity, and stage of the disease being treated. One should not lock oneself into a specific T_I, but instead use an appropriate duration for the infant and disease being treated. It is evident, however, that the I:E ratio decreases as ventilatory rates are slowed, assuming that the T_I remains constant. This approach provides a higher mean airway pressure (MAP) and better oxygenation during the early phases of disease. As the infant's status improves, the slowing of the ventilator rate extends expiration and automatically decreases I:E and MAP, when it is often appropriate to do so.

An additional caution about prolonged I:E ratios involves cardiac output considerations. Increasing the duration of inspiration will enhance the amount of intrathoracic pressure that is transmitted to the heart. Venous return may be compromised, and cardiac output may be decreased. In addition, if an air leak develops, it may further impair venous return. As a result, prolonged I:E has been associated with an increased risk of intraventricular hemorrhage. The authors therefore use a reversed I:E only as a last resort to try to improve oxygenation, most often in cases in which another way of increasing oxygenation more effectively cannot be found. Since the introduction and widespread use of modern conventional ventilator modalities, high-frequency ventilators, inhalational nitric oxide therapy, and extracorporeal membrane oxygenation, prolonged I:E has not been used in our nurseries.

Flow Rate

Flow rates used for neonatal mechanical ventilation are summarized in Table 9-5. Flow rate is an important determinant of the ability of the ventilator to deliver desired levels of PIP, waveform, I:E ratios, and in some cases, respiratory rate. A minimum flow at least two times an infant's minute ventilation is usually required in mechanical ventilator support (neonatal minute ventilation typically ranges from approximately 0.2 to 1 L/min), but the usual operating range during mechanical ventilation is usually 4 to 10 L/min.

When low flow rates are used, the time it takes to reach peak inspiratory pressure is longer, and the pressure curve has a lower plateau and appears similar to a sine waveform (see Fig. 9-2). Normal neonatal spontaneous breaths are shaped like a sine waveform. Because maldistribution of ventilation occurs in many neonatal respiratory diseases, theoretically a reduction of barotrauma may result with this pattern of waveform. With sine wave ventilation,

TABLE 9-5 Flow Rate Adjustment in Neonatal Ventilation

LOW RATE (0.5-3 L/min)		HIGH (4-10 L/min or more)	
Advantages	**Adverse Effects**	**Advantages**	**Adverse Effects**
1. Slower inspiratory time, more sine wave 2. Less barotrauma to airways	1. Hypercapnia, if flow rate is not adequate to remove CO_2 from the system 2. At high ventilator rate, low flow may not enable the machine to reach PIP 3. ↓ PaO_2 in some cases	1. Produces more square wave ventilatory pattern 2. ↑ PO_2 3. Needed to deliver high PIP with rapid ventilator rates 4. Prevents CO_2 retention	1. Increased lung injury 2. In moderate-to-severe RDS, may produce more airway injury 3. ↑ Turbulence, ↓ VT in small ET tubes

ET, Endotracheal; *PIP*, peak inspiratory pressure; *RDS*, respiratory distress syndrome; *VT*, tidal volume.

however, if the flow rate is too low relative to minute ventilation, dead space ventilation may increase because effective opening pressure for the airways is not reached within an appropriate time. As a result, hypercapnia may result. In addition, if higher ventilator rates are used on sine waveform ventilators, inadequate flows may result in dead space ventilation because the ventilator does not reach PIP in the allocated time. Opening pressure of the lung is not reached and gas exchange is reduced.

Higher flow rates are needed if square wave ventilation (see Fig. 9-2) is desired. Also, at higher rates, a high flow may be necessary to attain a high or adequate PIP (and adequate VT) because T_I inspiratory time is short. Carbon dioxide rebreathing is also prevented in the ventilator tubing at higher flow rates. The most common complication of high flow rates is an increased incidence of air leaks because maldistribution of ventilation results in a rapid pressure increase in nonobstructed or nonatelectatic airways and alveoli.

In pressure support ventilation (PSV), flow is increased during the initial phases of the inspiratory cycle of spontaneous breaths (assuming that an infant is on SIMV ventilation). This added flow assists in overcoming the various sources of resistance that the infant may encounter (e.g., ET tube, ventilator tubing, etc.), which may add to increased work of breathing and also result in atelectasis. Pressure support ventilation with enhanced flow may also be used separately from SIMV, but it is crucial that an infant have sufficient respiratory drive during spontaneous breathing for this approach to succeed.

Waveforms

The waveforms commonly used in neonatal ventilation are described and summarized in Table 9-6. Waveforms are typically not selected by the physician in prescribing mechanical ventilation but are often the result of other factors, including ventilator design and several of the other variables listed above. Many of the considerations regarding waveform were discussed in the section on flow rate. Sine wave breathing approximates normal spontaneous respiration more closely than does a square waveform. The smoother increase in inspiratory pressure may be advantageous for infants with maldistribution of ventilation, which is commonly seen in many neonatal lung diseases.

Square waveforms have been shown to improve oxygenation, however, when used with slower rates and longer T_I. Square waves, in general, also provide a higher MAP than do sine waveforms if identical PIP is used because the PIP is reached more rapidly with square waves. The longer time at PIP with square waves may assist in opening atelectatic areas of the lung in some instances, although overdistension of inflated areas and air leaks may occur. With square waves and reversed I:E ratios, venous return to the heart and cardiac output may decrease.

The use of graphics monitoring is helpful in examining pressure-limited and volume-limited breaths, to obtain a better understanding of how these differ. Figure 9-5 shows the differences between the wave forms in these approaches to positive-pressure ventilation.

Mean Airway Pressure

Although no mechanical ventilator presently allows the operator to select MAP (the Sensormedics 3100 high-

TABLE 9-6 Wave Forms in Neonatal Mechanical Ventilation

SINE WAVE		SQUARE WAVE	
Advantages	**Adverse Effects**	**Advantages**	**Adverse Effects**
1. Smoother increase of pressure 2. More like normal respiratory pattern	1. Lower mean airway pressure	1. Higher MAP for equivalent PIP 2. Longer time at PIP may open atelectatic areas of lung and improve distribution of ventilation	1. With high flow, the ventilation may be applying higher pressure to normal airways and alveoli 2. Impede venous return if longer TI is used or I:E ratio is reversed

I:E, Inspiratory to expiratory; *MAP*, mean airway pressure; *PIP*, peak inspiratory pressure; *TI*, inspiratory time.

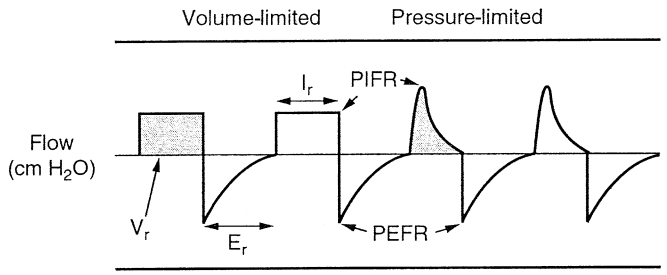

Figure 9-5 ■ Flow waveforms for both volume- and pressure-limited breath types. Inspiratory flow is above baseline,whereas expiratory flow is below. Peak inspiratory flow rate (PIFR) and peak expiratory flow rate (PEFR) are shown. (From Nicks JJ: Neonatal Graphic Monitoring, In Donn SM, Sinha SK (eds): Manual of Neonatal Respiratory Care, ed 2, St. Louis, Mosby, 2006, p. 137.)

frequency ventilator is an exception), this ventilator variable is considered to be important because of its relationship to oxygenation.[49] The clinician typically measures MAP by determining the mean of instantaneous readings of pressure within the airway during a single respiratory cycle. In waveform terminology, the MAP is equal to the area under the pressure curve for a single respiratory cycle divided by the duration of the cycle, or the integral of the pressure during a respiratory cycle. MAP is higher in square-waveform ventilation than in sine-wave ventilatory patterns when PIP and duration of PIP are equal. No studies to date have specifically implicated MAP as the primary determinant of air leaks or chronic lung disease. Increases in oxygenation, however, are directly related to increases in MAP. It is evident, however, that some changes in MAP, particularly with a short T_I, may not be reflected in increased oxygenation. The ventilator control variables that influence MAP are (1) PIP, (2) PEEP, (3) I:E ratio, and (4) waveform.

Because pulmonary barotrauma may be partly correlated with high PIP that is unevenly distributed throughout the lung, efforts have been made to ventilate patients with lower PIP and slower ventilatory frequency, while MAP is maintained. To accomplish this pattern of ventilator support, T_I must be increased, which also changes the I:E ratio. As MAP increases, alveolar recruitment occurs, reducing alveolar-arterial D_O (oxygen difference) gradient, and increasing arterial oxygenation. Techniques to recruit alveolar volume using sustained inflation and higher MAP during HFOV appear to be effective, although less so during conventional positive-pressure ventilation. The delivery of high MAP may be required during acute phases of neonatal lung disease, especially RDS, when compliance is low. In less severely affected infants and during recovery, high MAP may interfere with venous return in a manner similar to that seen with elevated PEEP. One must be particularly cautious after surfactant administration in the low-birth-weight baby because compliance and functional residual capacity changes may occur very rapidly. If efforts to reduce PIP and MAP are not made quickly, lung overdistension with the potential risk for air leaks may occur. It is also thought that sudden changes in compliance may predispose some infants to pulmonary edema and pulmonary hemorrhage.

An alternative approach to ventilation, first developed by Wung and colleagues[36] at Babies Hospital in New York, downplays the importance of close management of higher PIP and MAP. In that approach, lower PIP and MAP are commonly selected even during acute phases of illness, and goals for arterial blood gas measurements of pH and P_{CO_2} may fall outside the usual range. Dr. Wung has been very successful with what has often been described as "gentle ventilation," but the clinician should *always* attempt to ventilate infants as "gently" as possible. The goal of any strategy of ventilatory management is to provide adequate gas exchange with the lowest settings possible. Dr. Wung's approach to ventilation is discussed further in the section on ventilatory management of infants, as are a number of other management approaches, in Chapter 13.

The Management of Respiratory Failure with Positive-Pressure Ventilators

Definition of Respiratory Failure

Presently no single definition of what constitutes respiratory failure in the neonatal period has been agreed upon by clinicians. Because of the complexity of interplay between clinical and laboratory relationships in determining respiratory failure, management of this problem during the neonatal period is rarely simple and straightforward. Respiratory failure usually includes two or more criteria from the following clinical and laboratory categories:

Clinical criteria
- Retractions (intercostal, supraclavicular, suprasternal)
- Grunting
- Respiratory rate greater than 60 breaths per minute
- Central cyanosis
- Intractable apnea (perhaps the only clinical sign that *always* requires ventilatory support)
- Decreased activity and movement

Laboratory criteria
- Pa_{CO_2} greater than 60 mm Hg
- Pa_{O_2} less than 50 mm Hg or O_2 saturation less than 80%, with an F_{IO_2} of 1.0
- pH less than 7.20

In the current era, opinions among clinicians vary greatly in regard to what values constitute blood gas abnormalities that mandate mechanical ventilation. The values listed above are suggested as guidelines—values at which one must seriously consider initiating support.

The clinical presentation of respiratory failure can be widely variable in the neonatal period. Some infants exhibit severe distress immediately, whereas others may have marked abnormalities in arterial blood gas levels and yet appear to be far less compromised. Close observation of infants is critical in this setting. Retractions typically indicate a significant loss of lung volume. The infant then attempts to recruit alveolar volume by increasing respiratory effort, but the excessively compliant neonatal chest wall makes this endeavor futile in most cases. Rather than acting as a rigid strut, the neonatal thorax collapses, and the negative intrapleural pressure that is generated fails to reopen alveoli that are atelectatic.

Grunting often accompanies retractions, particularly in the neonate with RDS. Grunting is an expiratory effort

against a partially closed glottis that elevates the end expiratory pressure in an attempt to increase residual lung volume and oxygenation. It is also usually indicative of volume loss in the lung. Retractions and grunting should be considered ominous signs of impending respiratory failure during the neonatal period, particularly in the infant who weighs less than1500 g. Both retractions and grunting may occasionally be seen, however, in the neonate with cold stress, in which case these signs should last for no longer than 2 to 4 hours, and disappear once the child has been warmed appropriately. The clinician should therefore always maintain appropriate thermal stability for any infant; otherwise the medical care may become far more complicated than should be necessary. Grunting is a nonspecific sign of many neonatal disorders including hypoglycemia and sepsis.

If significant grunting and retractions are observed in an infant, early ventilatory assistance should be offered. One should quickly place infants on nasal continuous positive airway pressure (NCPAP) in an attempt to halt progressive volume loss in the lung. Nasal CPAP is often initiated in the delivery room, especially in the very smallest infants, until the need for surfactant administration can be determined. We will intubate some infants temporarily to give surfactant, then return a baby to CPAP (INSURE protocol, see Chapter 13). If such measures are ineffective, however, intubation and mechanical ventilation may be required, because metabolic derangement in these infants may proceed rapidly once the child can no longer support gas exchange. Late institution of mechanical support is often less effective, and the complications and associated morbidity are far greater than for those who receive early intervention. Although the larger, more mature infant may have greater reserve and tolerate respiratory insufficiency for a longer period than the premature infant, one should keep in mind that recovery from respiratory failure rarely occurs in any infant during the neonatal period without some form of respiratory assistance. The authors therefore believe that an aggressive (but gentle) early approach is often preferable in neonates, regardless of their disease.

Connecting the Patient to the Ventilator

The positive-pressure ventilator should be selected on the basis of the size of the child, the disease to be treated, and the severity of the disease. It is important to try to visualize the potential changes in the disease that may await an infant in the days ahead and select a ventilator that has the capability of meeting the requirements for therapy in that child. Few events are more frustrating than having to change a ventilator in mid-therapy because the current ventilator does not have the needed capability. Fortunately, most neonatal ventilators introduced during the past decade have quite exceptional capabilities compared to earlier models that were far more limited.

Before treating a child with a ventilator, the following considerations should be kept in mind:

1. The ET tube should be well secured and appropriately positioned. The accidental extubation of an infant caused by a tube being improperly taped and positioned can be devastating in the course of care. The tip of the ET tube should be located about 1 to 2 cm above the carina. Breath sounds should be equal after insertion, and a chest radiograph should be obtained before mechanical ventilation is initiated to ensure correct placement of the tube and to permit the physician to follow changes in the disease with treatment.
2. Once the patient is connected to the ventilator, the clinical observations and mechanical factors listed in Table 9-7 should be followed. Vascular access is an important part of management and should occur shortly after initiation of ventilatory support, if not prior to that time. Most nursing staffs are extremely adept at IV placement and often have a catheter placed peripherally as rapidly as intubation can occur.

Ventilator Management

Since the last edition of this book, many ventilator options have been added to units that markedly increase their capabilities. SIMV and assist/control mode ventilation have already become standard approaches in combination with pressure support; modalities such as nasal synchronized intermittent mandatory ventilation (nSIMV), volume guarantee ventilation, and proportional assist ventilation represent more recent modifications. The long-term benefits for these newer strategies of treatment are still somewhat uncertain, and their usefulness and effects upon long-term outcomes remain to be determined. Although these technologies do appear to provide distinct physiologic advantages, when using these various modes, the goals of ventilation should be clearly understood.

Because many of these strategies are discussed extensively elsewhere in this book (Chapter 13), this section concentrates specifically on some of the more commonly employed approaches to initial ventilatory management of the uncomplicated patient. It is, however, difficult to describe the use of positive-pressure ventilation without describing an overall management strategy for the particular circumstance of ventilator use under consideration. When appropriate, some brief discussion about the various new ventilator capabilities is provided, as well as how these capabilities might affect the patient's management.

Arterial blood gas analysis remains the "gold standard" for the assessment of effective gas exchange (see Chapter 17). It is essential for the clinician to understand which ventilator controls are most likely to correct or change specific blood gas abnormalities. Table 9-8 summarizes these adjustments. In general, it is sound practice to adjust only one ventilator control at a time. Multiple changes

TABLE 9-7 Preliminary Review for Initiating Ventilatory Support

Clinical Observations	Mechanical Factors
Color	Oxygen supply
Respiratory rate	Endotracheal tube placement
Breathing pattern	Ventilator circuit humidification
Retractions and grunting	Humidifier and heater function
Chest and abdominal synchrony	Chest radiograph
Synchrony with the ventilator (consider assist/control or SIMV)	Intravascular access

SIMV, Synchronized intermittent mandatory ventilation.

TABLE 9-8 Mechanical Ventilator Settings Used to Adjust Arterial Blood Gases

$Paco_2$	Pao_2	Respiratory Acidosis (low pH)	Metabolic Acidosis (low pH)
1. Rate and PIP (determine minute ventilation; ↑ rate or ↑ PIP will ↓ CO_2) 2. I:E ratio (determines duration of inspiration and expiration; longer expiration will ↓ $PaCO_2$) 3. PEEP (if too high or too low, may ↑ $PaCO_2$)	1. FIO_2 (↑ O_2 will ↑ PaO_2) 2. PEEP (↑ PEEP will ↑ PaO_2) 3. TI or I:E ratio (↑ TI will ↑ PaO_2; ↓ TI will ↓ PaO_2 in general) 4. PIP (↑ PIP will usually ↑ PaO_2; effect is less than others listed above)	1. Same controls as $PaCO_2$	1. Volume expansion or sodium bicarbonate 2. May correct with improved oxygenation and ventilation, as perfusion improves 3. Caution: High PEEP may result in metabolic acidosis due to impaired venous return

FIO_2, Fraction of inspired oxygen; *I:E*, inspiratory-to-expiratory; *PEEP*, positive end-expiratory pressure; *PIP*, peak inspiratory pressure; *TI*, inspiratory time.

made simultaneously are difficult to interpret, and the clinical care of the patient may be made more difficult to assess as a result. Oxygen saturation management appears to reduce the number of arterial samples that are needed.

One cannot overemphasize the importance of an overall strategy of management for ventilatory care of a neonate. Regardless of the approach to ventilation that is used, one should not respond only to individual blood gas measurements, but rather have a specific set of strategic goals in mind that are progressively approached throughout care. Furthermore, it is essential that the physician of record articulate this approach to everyone involved in the care of the infant. Nothing is more frustrating than coming to a child's bedside and finding that changes made on the ventilator (especially during the night), while not incorrect on a blood gas by blood gas basis, have nevertheless resulted in a child making little overall progress, or worse, evolved to an odd constellation of ventilator settings because the specific goals of treatment were not clearly explained.

The initiation of mechanical ventilation is often unnecessarily complicated. A scheme for the initiation of ventilation is shown in Figure 9-6. If one has a clear understanding of the goals of ventilatory support, steady progress toward those goals should be readily attainable. Once the clinician has decided that intervention is needed, the steps outlined

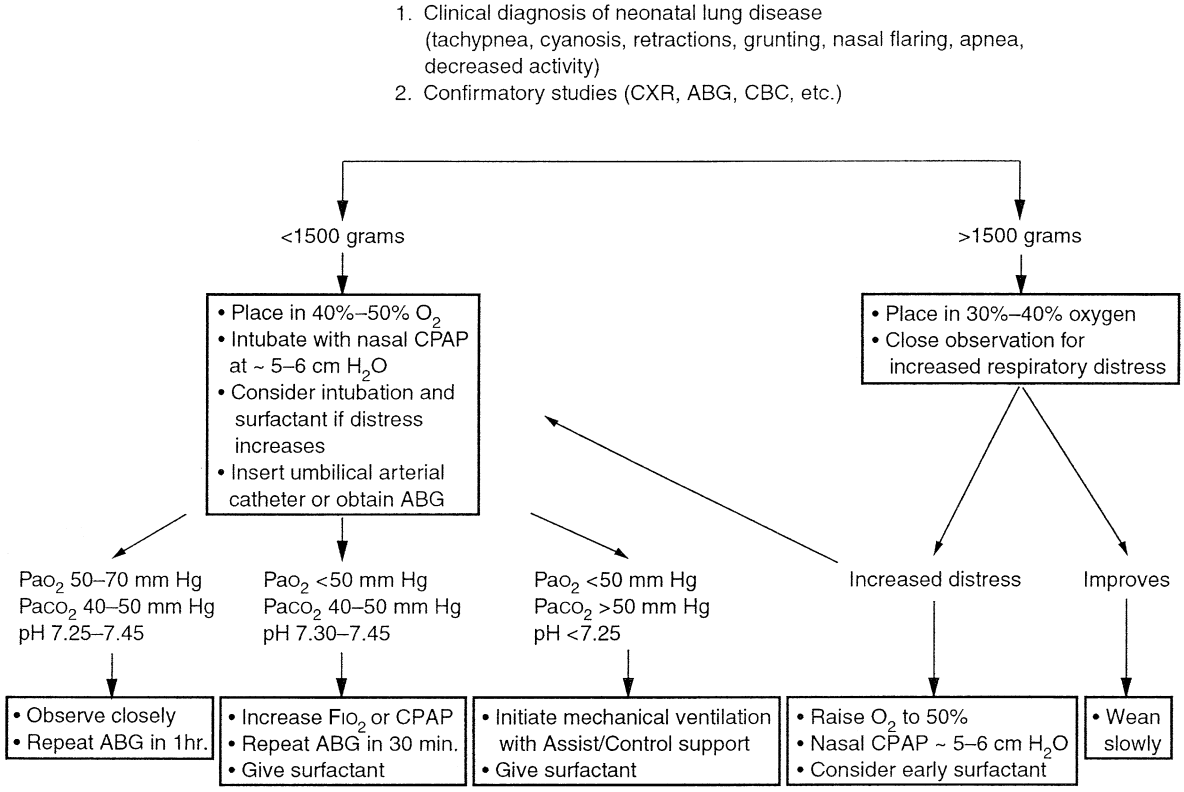

Figure 9-6 ■ Initial management plan for the neonate with pulmonary disease. *ABG*, Arterial blood gas analysis; *CBC*, complete blood count; *FIO_2*, fraction of inspired oxygen.

in Box 9-2 should be followed. Adjustment of ventilation after stabilization of the infant is detailed in Figure 9-7.

Some additional comments are appropriate here relative to this approach to management. The use of surfactant has become a standard adjunct to ventilatory management of the neonate. A more detailed discussion of surfactant therapy is presented in Chapter 22. Although optimal surfactant treatment is still not established at the present time, the practice at most level III neonatal intensive care units has been to use surfactant early in the infant diagnosed with RDS (surfactant deficiency disease), as well as for other diseases in which surfactant inactivation may be part of the pathophysiology (e.g., meconium aspiration syndrome). There are data to suggest that early use of surfactant, as soon as the diagnosis of RDS is made, produces better results than later rescue use after the disease is well established.

Several surfactants are now FDA approved for use in the United States. Beractant (Survanta, Ross Laboratories, Columbus, Ohio), calfactant (Infasurf, Forest Laboratories, Inc., New York, NY) and poractant (Curosurf, Dey L.P., Napa, Calif.) are all available and have their various advocates among neonatologists. Lucinactant (Surfaxin, Discovery Laboratories, Warrington, Penn.) should receive approval in the not too distant future. Discovery is also working on an aerosolized version of its surfactant, called Aerosurf. Aerosolized surfactants, if they can be made biologically available to the infant, may enhance the ability

Box 9-2 INITIATION OF MECHANICAL VENTILATION IN NEONATAL LUNG DISEASE

1. Intubate infant; secure endotracheal tube adequately
2. Place pressure manometer in gas flow line and begin manual ventilation to determine appropriate pressures for ventilation
3. Begin manual inflation with the following:
   F_{IO_2} at 0.5 or greater
   Rate at 40 to 50 breaths/min
   Initial PIP at 12 to 15 cm H_2O
   Initial PEEP at 4 to 5 cm H_2O
   I:E ratio at 1:1 to 1:2
4. Observe infant for
   Cyanosis
   Chest wall excursion
   Capillary perfusion
   Breath sounds
5. If ventilation is inadequate, increase PIP by 1 cm H_2O every few breaths until air entry seems adequate
6. If oxygenation is poor, and cyanosis remains, increase F_{IO_2} by 5% every minute until cyanosis is abolished
7. Draw ABG
8. Adjust ventilation as indicated by ABG results (see Fig. 9-7)

ABG, Arterial blood gas; *F_{IO_2}*, fraction of inspired oxygen; *I:E*, inspiratory to expiratory; *PEEP*, positive end-expiratory pressure; *PIP*, peak inspiratory pressure.

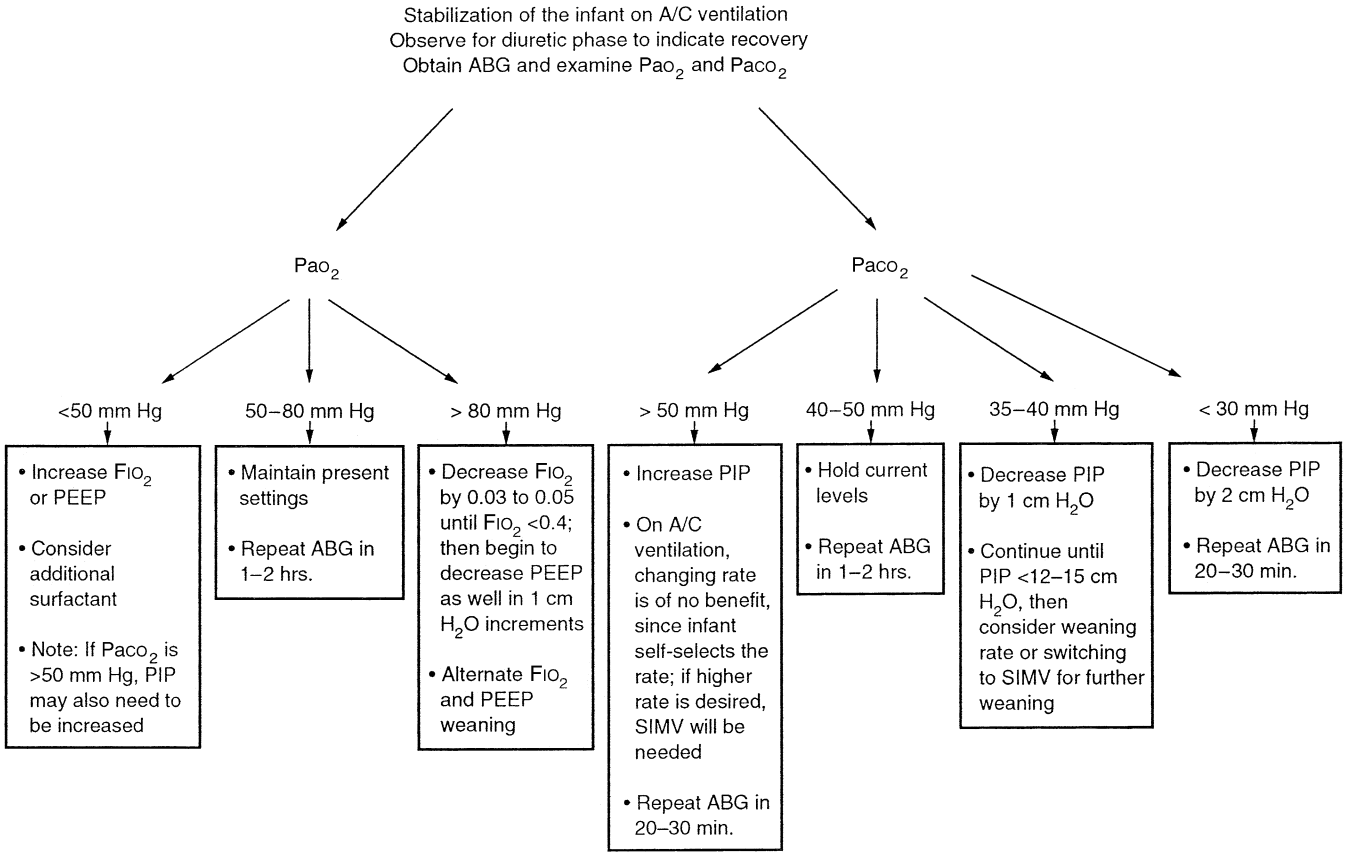

Figure 9-7 ■ An approach to ventilator management during neonatal lung disease.

of the clinician to give surfactant and consider noninvasive CPAP or ventilatory support, prior to introducing an endotracheal tube on a longer-term basis.

Depending on the specific surfactant used and the infant's response, one to four doses of the drug are given. It is important that the clinician observe the baby closely during the surfactant administration process. Although most infants tolerate the procedure well, some children do experience oxygen desaturation. Other infants may improve rapidly, and overventilation can occur with the possibility of air leaks. Pulmonary hemorrhage also appears to be slightly more common in some infants, although this complication is rarely a serious issue to contend with. Furthermore, excessively low $PaCO_2$ during the first days of life has been associated with an increased risk of cerebral palsy in some children.[51]

The use of pulmonary function testing may also guide ventilator management. In recent years, pulmonary graphics monitoring, either as an intrinsic part of the ventilator or as an adjunct, have become increasingly widespread in their use. Although not as precise as pulmonary functions performed independently, these units are extremely helpful in guiding ventilator management. Tidal volumes, minute ventilation, ventilator leak, chest wall distortion, flow-volume loops, pressure-volume loops, and several other functions can be readily evaluated. Overall lung volumes cannot be determined, however, except through the use of measurements of functional residual capacity (FRC) by either nitrogen washout or helium dilution. Recently, some interpolation methods have been studied that are less difficult to perform, but also somewhat less precise.

Improved FRC is probably the most important effect of surfactant administration in many disease conditions. The authors' practice has traditionally been to assess pulmonary mechanics frequently to guide ventilator management and weaning. With newer graphics monitors, much of the necessary information can be evaluated several times daily in managing neonates on ventilatory support. Pulmonary function testing and graphics assessment are described in greater detail in Chapter 18.

The management strategy outlined in Figure 9-7 is applicable to nearly all types of neonatal lung disease. The basic principles that guide this approach are discussed below.

Leading Causes of Lung Injury

It is generally accepted that the most damaging aspects of neonatal ventilation, or the leading causes of lung injury, are FIO_2 and PIP. Although it is not always possible to limit the use of FIO_2 and PIP during the most critical phases of illness, any approach to ventilatory support should try to reduce the levels of these variables as soon as the infant shows signs of improvement. The approach to ventilator assistance in Figure 9-7 is designed to achieve this goal.

In recent years, there has been no agreement on the optimal initial approach. Some common practices have been to initiate positive-pressure ventilation in one of a few different modes:

1. SIMV with pressure support
2. Assist/control or SIMV with volume guarantee
3. Volume guarantee ventilation
4. Early high-frequency ventilation

Each form of support has its advocates. Again, if there is a clear articulation of the ultimate goals of ventilatory assistance, any of these modes of support are likely to succeed.

SIMV with pressure support (SIMV/PS) has the value of synchronizing breaths for the infant and avoiding distortion of the airway, which can occur when the infant is attempting to breathe at the same time that the ventilator is delivering a positive-pressure breath. The use of pressure support eases spontaneous breaths initiated by the infant. Weaning should focus, as previously indicated, on reducing PIP and FIO_2 because they are the predominant agents that will injure airways and lungs.

Because of the nature of its design, assist/control (A/C) weaning will primarily occur by decreasing FIO_2 and PIP, not the rate or PEEP. When A/C or SIMV are used in conjunction with volume guarantee, or if volume guarantee is used alone as with the Drager Babylog, there will automatically be a weaning of PIP as lung compliance improves. These approaches therefore also reduce PIP and FIO_2 as primary initiatives, while later decreasing rate and PEEP. We have therefore found that the basic principles outlined in the previous editions of this book remain not only applicable but also are actually facilitated by the introduction of these newer ventilator modifications.

High-frequency ventilation as an initial support has not found support in studies as a valuable initial approach when compared to the modalities noted immediately above.[52] Comparative studies, however, are limited at best, again because of the continuing presence of confounding variables. In the hands of an experienced high frequency user, however, it can be a very useful approach to care, especially during periods when ventilator support reaches high and potentially toxic levels.

Timing of Ventilator Adjustments

It is preferable to make frequent small changes in ventilator support rather than infrequent larger changes in degree of support. Commonly, ventilator management is approached with no overall strategy in mind. In many nurseries, an arterial blood gas level is obtained at a random time (often right after an infant has had care performed and has not yet fully recovered!), and the neonatologist makes a change based on that single blood gas analysis.

Although the changes may seem reasonable at first, they can be inappropriate because they do not take place within a defined strategy for weaning. Ultimately, the combination of ventilator settings ordered for the child may appear incongruous, and yet the ventilator changes are not necessarily incorrect when viewed on a blood-gas by blood-gas basis. The clinician simply did not have a coherent plan for ventilator management.

For example, a child's treatment may progress to a setting of a PIP of 25 cm H_2O and a rate of 5 to 10 breaths per minute as weaning progresses because of low $PaCO_2$ levels. Each decision along the way might have been correct, but the overall "balance" of ventilatory support is not optimal (although occasionally, as in a child with chronic BPD, such support levels may be necessary). It is therefore important to develop a feel for overall balance of ventilator support, such as that listed in Table 9-9. If the

TABLE 9-9 Guidelines for Ventilator Care*

Inspired O_2 (%)	PEEP (cm H_2O)	PIP (cm H_2O) <1500 g	PIP (cm H_2O) >1500 g	Rate (breaths/min)
100%	6-8	25	25-30	40-60
90%	5-7	25	25-30	40-60
80%				
70%	5	20-25	22-30	35-50
60%				
50%	4	20-25	22-30	30-45
40%	3-4	15-20	18-25	20-35
30%	2-3	10-18	15-22	<30 (wean)

*NOTE: These values are only guidelines and may not be appropriate in all clinical situations. In general, they should be viewed as the maximum necessary levels of support. At the highest support levels, standard positive-pressure ventilation may no longer be appropriate and alternatives (high-frequency ventilation, inhalational nitric oxide, extracorporeal membrane oxygenation) should be considered on an individual basis. The reader also should note that we have lowered the acceptable levels of PIP from prior iterations of this chart because we no longer believe infants should receive peak pressures greater than 25 cm H_2O for infants <1.5 kg or 30 cm H_2O for infants >1.5 kg except in unique cases.

PEEP, Positive end-expiratory pressure; *PIP*, peak inspiratory pressure.

ventilator settings vary much from the overall patterns across any row in this table, the physician should consider a ventilator strategy that brings the patient's support back into a more appropriate combination of settings. Table 9-9 assumes an approximate I:E ratio of 1:1 to 1:3 and an initial back-up ventilator rate of 40 to 50 breaths per minute. Acceptable arterial blood gas values for this table are as follows:

PaO_2 = 60 to 80 mm Hg
$PaCO_2$ = 40 to 55 mm Hg
pH = 7.25 to 7.45

Ventilator Weaning

As previously indicated, the authors' suggested approach to ventilator weaning is shown in Figure 9-7. Once an infant has remained stable for at least 24 hours, one should begin to reduce the two factors that appear to have the greatest toxicity for the lung, namely FIO_2 and PIP. In volume guarantee modes, this will occur automatically, whereas SIMV or A/C modes (unless accompanied by volume guarantee) will require a conscious decision to decrease these variables. The weaning approach should be very gradual, and as stated above, frequent small changes are preferred to infrequent, larger decreases in support. The goal is to allow the infant to progressively assume greater responsibility for gas exchange while ventilator support is decreased. As FIO_2 and PIP are decreased, we usually switch an infant back to SIMV/PS when the FIO_2 is below 0.4 and the PIP is less than 12 cm H_2O. The child should be moved to nasal CPAP as early as possible once stability is achieved.

The general approach to SIMV weaning is to steadily decrease the number of ventilator breaths while the infant steadily increases spontaneous respiratory effort. No prospective controlled studies clearly demonstrate the benefit of this approach in the sick neonate as yet. However, theoretically this system does afford several advantages:

1. Allows a gradual transition from mechanical ventilation to spontaneous breathing.
2. Eliminates the need for special bedside equipment to provide PEEP during weaning (some data, however, suggest that there is a difference between ventilator-delivered and underwater-delivered or "bubble" CPAP.[42] This issue still needs to be clarified further. There appears to be substantive differences among CPAP devices).
3. Avoids the need for expensive and complicated sigh mechanisms seen in some ventilators.
4. Has been shown to increase lung volume in infants.
5. Decreases need to use muscle relaxants or sedation to prevent patients from fighting the ventilator during weaning.
6. May assist in coordinating respiratory muscular efforts during weaning. Pressure support can be reduced gradually to parallel this process, allowing the respiratory muscles to assume a greater level of work of breathing.

In practice, simply weaning the ventilator rate, especially in the ELBW infant, does not work well, and it may expose the infant to excessive PIP during weaning. As a result, our approach, as shown in Figure 9-7, emphasizes decreasing pressure first to a low level (less than 15 cm H_2O) before SIMV weaning. In this way, the risk of barotrauma and late air leak development is reduced.

Weaning should usually be initiated as soon as possible after the infant has demonstrated stability for at least 4 to 8 hours and when arterial blood gas values suggest that ventilatory needs are decreasing. Before initiation of weaning, a chest radiograph should be obtained as a baseline against which one can compare if problems arise during the weaning process. Examination of graphics monitoring is also very helpful in gauging the capacity for weaning. Increases in compliance and FRC typically herald recovery from pulmonary disease in the neonate. Our practice has been to follow pulmonary graphics on a daily basis in critically ill neonates to help define weaning possibilities. Improvement in the compliance slope on the graphics and increasing flow rates often will herald weaning and extubation potential. One should cautiously monitor flow-volume loops to be certain these do not deteriorate during weaning. It has also been demonstrated that, in infants with RDS, a diuretic phase occurs immediately before the improvement in pulmonary mechanics. Thus an increase in urine output (greater than 3 mL/kg per hour) may be a helpful observation during treatment.

Even the smallest infants may be weaned from positive-pressure ventilation to nasal CPAP very effectively. The authors have adopted nasal CPAP as a useful adjunct to therapy in the very-low-birth-weight (VLBW) infants (less than 1500 g). Without nasal CPAP, progressive atelectasis often occurs because the very compliant chest wall does not maintain lung volume well in these infants. Nasal CPAP often helps avoid the need for reintubation. Some recent work has suggested that nasal SIMV may be even more advantageous, but studies thus far are limited. Once extubation is planned, we usually place a baby on nasal CPAP for a minimum of 2 to 3 days or longer in some cases. This therapy is usually well tolerated, but

one must be attentive to stomach distension and nasal erosion.

During weaning, it is also important to follow the infant's complete blood count; electrolyte, calcium, glucose, and blood urea nitrogen levels; fluid balance; and urine specific gravity. Metabolic disturbances that manifest as abnormalities in these studies may affect weaning rate and prolong duration of support and length of stay. Appropriate caloric balance is also essential for successful weaning. The infant who is nutritionally depleted does not wean or extubate as well as the child who is in positive caloric balance. Calories may be given enterally or parenterally. The authors have not found intubation to be a contraindication to feeding in low-birth-weight babies. Feeding should always be stopped, however, at least 4 hours before an extubation attempt, or a nasogastric tube should be inserted and the stomach emptied. Following extubation, feeding should be held for a minimum of 4 to 6 hours.

Extubation

Some clinicians have difficulty managing the patient at the time of extubation. The authors have observed that, although ventilator care is often meticulous and thoughtful, extubation often seems to be chaotic and haphazard. The child who is to be extubated should be prepared for the procedure, as with any medical intervention. Extubation is reasonable when the child is receiving less than 40% O_2 and when the ventilator support has decreased to a rate of 10 breaths per minute and a PIP of 10 to 12 cm H_2O. For the past several years, the authors have rarely allowed a child to wean to endotracheal tube CPAP alone and prefer to extubate from a rate of 5 to 10 breaths per minute. In the authors' experience, the child who is intubated but only on CPAP of 2 to 4 cm H_2O expends increased effort in work of breathing that wastes calories and energy unnecessarily. The use of pressure support, however, makes caloric expenditure more optimal, and eases breathing for the infant with an adequate respiratory drive. In these instances, pressure support and CPAP alone may be more than adequate. Our success rate has improved with extubation from this low-level approach to ventilatory support.

The decision to extubate should be made well in advance of the procedure. A chest radiograph should be obtained before extubation to be certain that a baseline study is available should problems arise after extubation. Radiographs are repeated at 2 and 24 hours after extubation to evaluate for progressive atelectasis. Respiratory therapists are notified, and the equipment that is desired after extubation is immediately available. For VLBW infants, the authors usually extubate to a nasal CPAP of 5 to 6 cm H_2O; the child who weighs more than 1000 g is placed in a humidified oxygen hood or provided nasal cannula O_2 at the desired concentration. The child is typically treated at first with an O_2 concentration that is 5% above that received while he or she was still mechanically ventilated, until stable.

The child to be extubated should have all facial tape carefully removed so that skin injury to the face can be avoided. The ET tube is connected to a bag with a Mapleson valve, and the child is given a prolonged sigh of 15 to 20 cm H_2O while the ET tube is extracted. This sigh prevents negative pressure from developing in the airway, which occurs upon tube removal and may cause atelectasis. The baby is then placed in the desired environment (often with nasal CPAP in the case of the VLBW baby) and watched closely for several minutes. The use of pulse oximetry at this time is invaluable. Oxygen saturation should be kept at approximately 88% to 94%. Recent work has shown that higher oxygen saturation levels appear to be correlated with a greater risk of retinopathy of prematurity (ROP).

Upon extubation, there should be no significant respiratory distress, or it should last only momentarily. Signs of respiratory difficulty include tachypnea, retractions, pallor, cyanosis, agitation, and lethargy. If distress is significant, it is prudent to replace the ET tube and repeat the trial in 2 days. If a child fails two attempts at extubation, the authors perform flexible fiberoptic bronchoscopy on the baby to be sure that there are no obstructive lesions in the airway. If the result of this study is negative, one should consider initiating dexamethasone treatment (0.25-0.5 mg/kg per day in two divided doses beginning 48 hours before extubation, continuing for 24 hours after extubation, if successful) to reduce any airway edema. In addition, methylxanthines, such as caffeine citrate or theophylline, may decrease resistance and increase respiratory drive, improving the likelihood of successful extubation. There are no controlled studies that demonstrate the effectiveness of this approach, but it anecdotally appears to benefit some children. One should be aware that the use of dexamethasone, even briefly, may put the child at some neurodevelopmental and growth risk.

If a child cannot be extubated after several repeated attempts or after 8 to 10 weeks of continued ventilatory support, the diagnosis of laryngotracheomalacia or subglottic stenosis must be considered. Some of these infants may not be extubated successfully, and tracheostomy must be considered. The authors do *not* perform a tracheostomy, however, until it is certain that a child cannot be extubated and that this fact has been demonstrated at least four times over several weeks. Such cases are rare but this intervention is preferable to continued ventilation through an ET tube. Often the decrease in dead space and work of breathing provided by tracheostomy results in significant improvement of ventilator settings and even rapid weaning to blow-by oxygen.

Accidental extubation occasionally occurs in all nurseries for a variety of reasons. The tape around the ET may loosen, or the movement of the child may free the tube and dislodge it. If extubation occurs, the authors carefully assess the infant to determine his or her readiness for extubation at the time of the event. If extubation is thought to be days away and the child appears to be exerting excessive effort, the ET tube is immediately replaced. *Allowing the child to become unnecessarily distressed at this point further delays ultimate extubation and should be avoided.* If, however, the child appears comfortable, the authors follow pulse oximetry to be sure that the infant remains well oxygenated and obtain a chest radiograph and arterial blood gas levels. If these are acceptable, the child can remain extubated with very careful observation.

Box 9-3 COMPLICATIONS OF MECHANICAL VENTILATION

Airway Injury
- Tracheal inflammation
- Tracheobronchomalacia
- Subglottic stenosis
- Granuloma formation
- Palatal grooving
- Nasal septal injury
- Necrotizing tracheobronchitis

Air Leaks
- Pulmonary interstitial emphysema (PIE)
- Pneumothorax
- Pneumomediastinum
- Pneumopericardium
- Pneumoperitoneum
- Air embolism syndrome

Cardiovascular
- Decreased cardiac output
- Patent ductus arteriosus (PDA)

Endotracheal Tube Complications
- Dislodgment
- Obstruction
- Accidental extubation
- Airway erosion

Chronic Lung Injury
- Bronchopulmonary dysplasia (BPD)
- Acquired lobar emphysema

Miscellaneous
- Retinopathy of prematurity
- Apnea
- Infection
- Feeding intolerance
- Developmental delay
- Hyperinflation
- Intraventricular hemorrhage (IVH)

Complications of Mechanical Ventilation

The potential complications of neonatal mechanical ventilation are substantial, and a partial list is presented in Box 9-3. Many of these complications can be avoided or minimized with the approaches to care outlined in this chapter. The most commonly seen clinical circumstance that produces immediate concern involves sudden deterioration of an infant on a ventilator. In such circumstances, the child may appear well one moment but rapidly become cyanotic, with pallor, bradycardia, hypotension, and hypercapnea, the next. An approach to this situation is shown in Figure 9-8.

If the physician demonstrates that progression of lung disease is the cause of deterioration, or if the pressures or volumes necessary to maintain the infant are considered

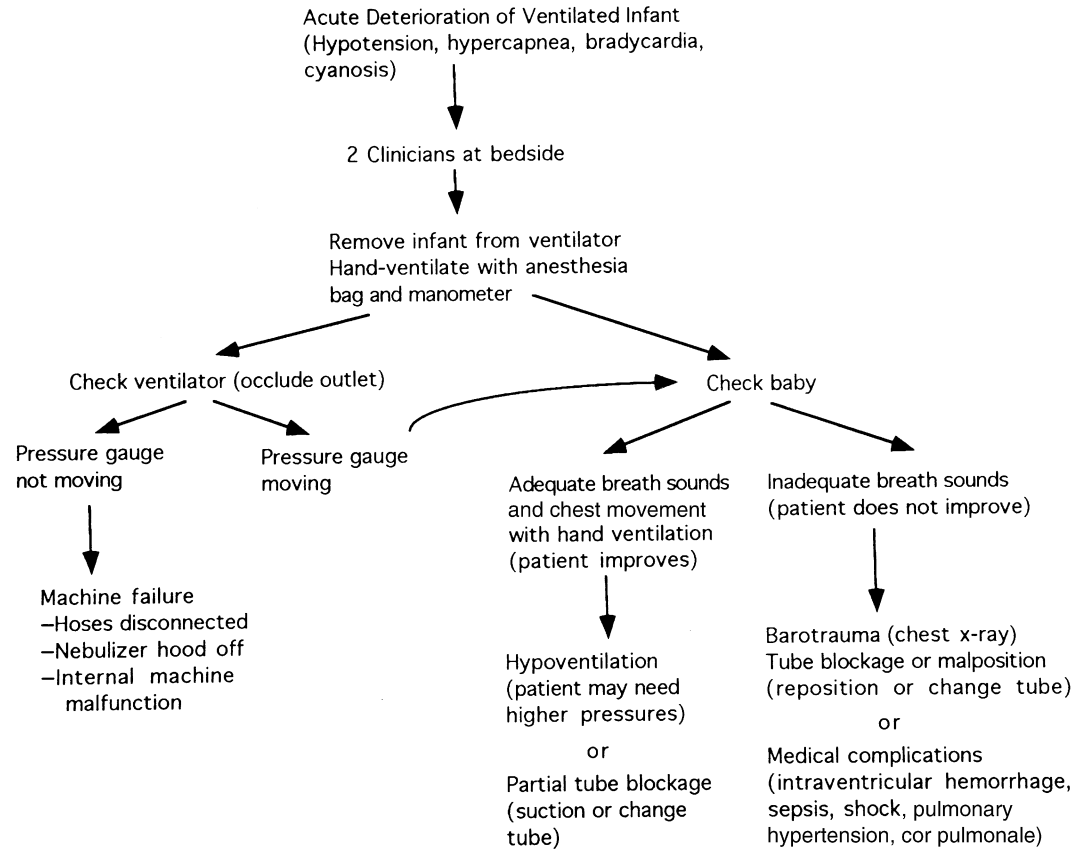

Figure 9-8 ■ Algorithm demonstrating approach to the ventilated infant with sudden, acute deterioration. (Modified from Gottschalk SK, King B, Schuth CR: Basic concepts in positive-pressure ventilation of the newborn. Perinatol Neonatol 4:15, 1980.)

toxic, then one must consider going to a more advanced form of therapy, such as high-frequency ventilation or ECMO. These treatments appear to be effective for some infants who require rescue therapy for severe cardiopulmonary disease. These therapies are discussed in Chapters 11 and 16.

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10 Volume-Targeted Ventilation*

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Despite the introduction of newer strategies such as extracorporeal membrane oxygenation, inhaled nitric oxide, high-frequency ventilation, and partial liquid ventilation, conventional mechanical ventilation remains the primary treatment for respiratory failure in newborns. In the past, this has usually been accomplished with traditional time-cycled, pressure-limited ventilation, in which peak inspiratory pressure (PIP) is set by the clinician and is not exceeded by the ventilator (see Chapter 9). Because PIP may be directly related to the likelihood of developing ventilator-induced lung injury (VILI) including air leaks and chronic lung disease (CLD) in newborn infants, it has been assumed that pressure-limited ventilation decreases barotrauma because of its ability to control PIP. This, however, is an oversimplification not supported by adequate scientific evidence. Moreover, there are now indications to suggest that injury to the neonatal lung may be more related to overdistension of the lung (i e., volutrauma) than to pressure-induced injury (i.e., barotrauma), and it is the amount of gas (tidal volume) delivered to the lungs that may be more critical in the pathogenesis of injury.[1] When tidal volume is appropriate and the lungs are adequately inflated, the use of high airway pressure does not seem to produce lung injury. This observation becomes more clear if one understands the concept of lung pressure-volume hysteresis (see Fig. 2-3).[2]

Animal models show that only six manual inflations of 35 to 40 mL/kg given to preterm lambs injures the lungs and reduces the response to surfactant therapy.[3] Dreyfuss et al.[4]observed significant increases in lung edema and transcapillary albumin flux in rats ventilated at high tidal volumes in contrast to rats ventilated with low tidal volumes and high pressures, who did not have these effects. In another study, high pressure ventilation with high tidal volumes caused a sevenfold increase in lung lymph flow and protein clearance in sheep, whereas high pressure ventilation with a normal tidal volume obtained by chest strapping produced a 35% decrease in lymph flow and protein clearance.[5] Hernandez et al.[6] completely blocked microvascular damage in ventilated rabbit lungs using tidal volume limitation. Evidence for the importance of volutrauma also comes from the adult acute respiratory distress syndrome (ARDS) network trial.[7] Traditional approaches to mechanical ventilation in adults used tidal volumes of 10 to 15 mL/kg in patients with acute lung injury and ARDS. This trial was conducted to determine whether ventilation with lower tidal volumes would improve the clinical outcomes. The use of lower tidal volumes decreased mortality and increased the number of days without ventilator use.

Like *volutrauma* from excessive tidal volume delivery, ventilation at low lung volumes may also cause lung injury. This is seen in preterm newborns with surfactant-deficient lungs and is thought to be related to the repeated opening and closing of lung units with each mechanical breath. This phenomenon has been termed *atelectrauma* and may explain the observation that recruitment of the lung to increase the functional residual capacity protects against VILI.[8,9]

If volutrauma is indeed an important element in the development of VILI, then control of tidal volume delivery may have advantages over control of pressure. This has led to an increasing interest in using "volume-targeted" modes of ventilation instead of pressure-targeted modes in ventilating newborns at risk for VILI.

Broadly speaking, volume-targeted modes of ventilation can be provided in two ways: Volume-controlled ventilation (VCV), in which the primary target is the delivery of a set tidal volume irrespective of lung compliance, or hybrid modes, which are essentially pressure-targeted but aim to deliver the tidal volume within a set range using a computer-controlled feedback mechanism.

Volume-Controlled Ventilation

The first ventilator designed specifically for volume-targeted ventilation in infants was the Bourns LS 104-150, which was modified from an adult ventilator and featured in the first edition of this text (1981). Because of problems with trigger sensitivity, long response times, and lack of continuous flow during spontaneous breathing, this device (and VCV) fell out of favor in the early mid-1980s. Technologic advances in the 1990s enabled reintroduction of this type of ventilation in neonatal and pediatric intensive care units, and the difference between first-generation volume ventilators and the present-day devices is remarkable. These new ventilators incorporate sophisticated

*We thank Dr. Jag Ahluwallia, Consultant Neonatologist, Cambridge, United Kingdom, for guidance in preparing the ventilatory management guideline on volume-targeted ventilation on the Babylog 8000 plus.

devices to trigger and deliver the very small tidal volume required by an infant weighing as little as 500 g.

How does VCV differ from pressure-targeted ventilation? This is best understood by using the concept of hierarchal classification, in which ventilators can be classified by the *control* variable (also called the *parent mode*), which cannot be changed, for example, pressure or volume, as well as the *phase* variables (daughter modes), such as time, pressure, or volume (flow). These can be used to start (trigger), sustain (or limit), and end (cycle) inspiration.[10] At any one time, a ventilator can be used only in either pressure or volume modes. Pressure- and volume-controlled breath types have certain specific characteristics, which are retained even if changes are made in phase variables by altering the trigger, limit, or cycling mechanism. For example, in time-cycled, pressure-limited ventilation (TCPLV), a peak inspiratory pressure (PIP) is set by the clinician, and during inspiration gas flow is delivered to achieve (and not exceed) that target pressure. The volume of gas delivered to the patient, however, is variable depending upon the compliance of the lungs. At lower compliance (such as early in the course of respiratory distress syndrome), a given pressure delivers lower tidal volume compared to later in the course of the disease when the lungs are more compliant. This is illustrated in Figure 10-1. In contrast, the key differentiating feature of VCV is that the primary gas delivery target is tidal volume, which is set by the operator, and the peak inspiratory pressure may vary from breath to breath. Thus at lower compliance higher pressures are generated to deliver the desired tidal volume. As compliance improves, the pressure needed to achieve the set tidal volume is automatically reduced (autoweaning of pressure). This is again illustrated in Figure 10-1.

In "adult" VCV, inspiration is terminated and the machine is cycled into expiration when the target tidal volume is delivered. This gave rise to the term *volume-cycled ventilation*. However, the use of uncuffed endotracheal tubes in newborns results in some degree of gas leak around the tube. Thus true volume cycling is a misnomer in neonatal ventilation, and the terms *volume controlled*, *volume targeted*, or *volume limited* better describe this modality.[11] Many modern ventilators provide the option of using a leak compensation algorithm to at least partially offset the problem of uncuffed endotracheal tubes. There is also

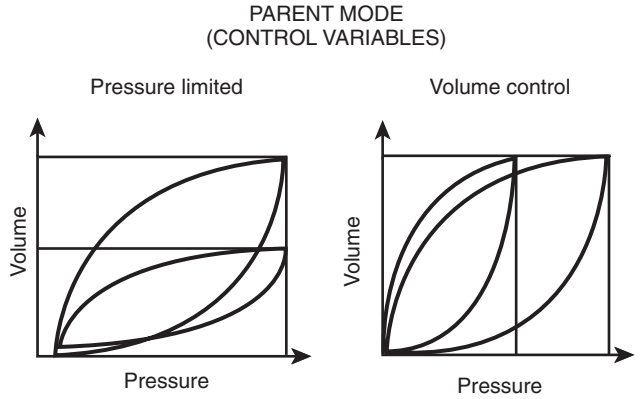

Figure 10-1 ■ Pressure-volume loop showing difference between pressure-limited and volume-controlled ventilation.

a discrepancy between the volume of gas leaving the ventilator and that reaching the proximal airway. Much of this results from compression of gas within the ventilator circuit. This is referred to as *compressible volume loss*. It will be greatest when pulmonary compliance is lowest. Use of semirigid circuits may help offset this discrepancy. Gas volume delivered is also affected by humidification. It is, therefore, critical that the delivered tidal volume is measured as close to the proximal airway as possible (i.e., at the patient wye piece).

Another important feature of VCV, differentiating it from TCPLV, is the way that gas is delivered. In traditional VCV, a square flow waveform is generated (Figure 10-2) and peak volume and pressure delivery are achieved at the end of inspiration.[11] During VCV, inspiratory time is determined by the inspiratory flow rate. As higher flow rates lead to more rapid filling of the lungs, set tidal volumes are achieved faster. This leads to an inverse relationship between flow and inspiratory time in VCV. In contrast, during TCPLV, flow is more rapid and the opening pressure (and most volume delivery) is reached early in inspiration (Figure 10-2). After the target pressure has been reached, flow decelerates rapidly until inspiration is completed. The rapid inspiratory flow allows early pressurization of the circuit and delivery of gas to the alveoli, giving a theoretical advantage if high opening pressures are necessary, such as during the acute stages of respiratory distress syndrome (RDS). The distinguishing features of VCV and TCPLV are summarized in Table 10-1. Some of the newer machines offer the option of decelerating inspiratory flow and an inspiratory "hold" or "pause" with volume ventilation. The intention is to improve oxygenation and decrease the duration of positive pressure. The inspiratory pause must be long enough to allow the pressure to plateau or reach a stable pause pressure. The plateau pressure is more representative of alveolar pressure than is the PIP.

Of the devices presently available, most ventilators for neonatal use measure volume delivery at the proximal airway. This provides a much closer approximation of what will be delivered to the lungs compared to devices that measure volume at the ventilator and provide calculated estimates of what the patient will actually receive. Tidal volume is the volume of gas delivered during inspiration, expiration, or averaged for both respiratory cycles. Normal values in healthy term newborn infants range from 5 to 8 mL/kg body weight and are smaller for preterm infants. In practice, it seems safer to use a range of 4 to 6 mL/kg. When measured over a 1-minute duration, the volume data provide a reference to minute ventilation; normal values in newborns range from 240 to 360 mL/kg/min. Minute ventilation is a surrogate measure of carbon dioxide elimination, although it is alveolar ventilation (minute ventilation minus dead space ventilation) that has a direct inverse relationship to alveolar PA_{CO_2}, or arterial carbon dioxide tension (see Chapter 2).

Detractors of VCV have argued that unlike the fixed PIP used in TCPLV, VCV uses a high inflation pressure to deliver the preset volume in cases of decreased compliance. This was a previous source of anxiety to clinicians because of the perceived risks of barotrauma and its consequences. However, it must be realized that high peak pressure associated with fixed-flow delivery in VCV is a reflection of

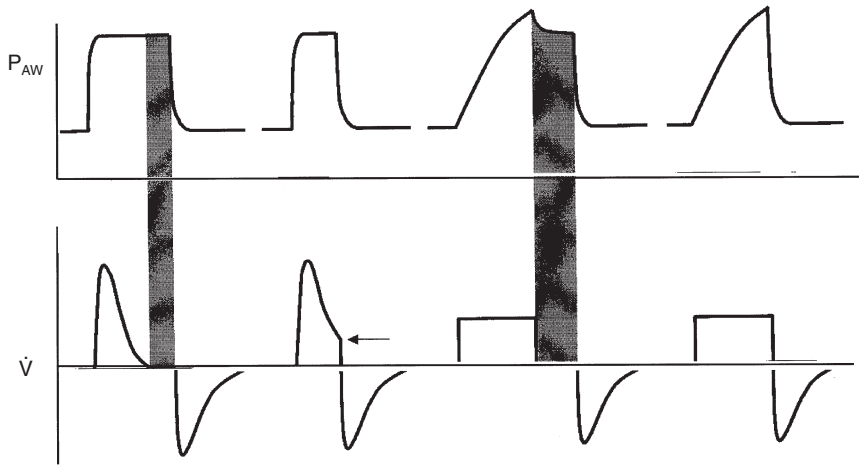

Figure 10-2 ■ Cycles 1 and 2 represent pressure-targeted (pressure-limited) ventilation.
- Set, limited, constant inspiratory pressure level
- Nonlimited, decelerating inspiratory flow
- Control (nondependent) variable: pressure
- Dependent variable: tidal volume
- Cycling mechanisms:
  - Time: pressure control, time-cycled, pressure-limited ventilation (TCPLV) (cycle 1)
  - Flow: pressure-support, flow-synchronized vent (cycle 2)
  - Arrow: termination flow criterion (usually as percentage of peak flow)

Cycles 3 and 4 represent volume-targeted (volume-control, volume-cycled) ventilation.
- Set, limited, constant inspiratory flow rate
- Gradually increasing, "shark fin" inspiratory pressure
- Control (nondependent) variable: flow
- Dependent variable: peak inspiratory pressure
- Cycling mechanisms:
  - Time: volume ventilation with set inspiratory pause time (cycle 3)
  - Volume: volume-control ventilation (cycle 4) (volume may be represented as the area under the flow curve)

Note that the inspiratory plateau period (gray-filled area) may exist during time-cycled modes (cycle 1 in pressure and cycle 3 in volume ventilation). (Acknowledgment to Dr. Akos Kovacs, Clinical Specialist, Visys Health Care System, Hungary, for help in preparing this figure.)

proximal airway pressure rather than peak lung (alveolar) pressure. When the compliance of the patient's lungs improves (increases), the ventilator actually generates less pressure to deliver the same tidal volume, thus leading to automatic reduction of the PIP. Although peak airway pressure is greater for the constant flow pattern seen in VCV, mean airway pressure is less, and it is the latter parameter that should correlate better with the mean lung pressure (assuming that resistance and compliance remain constant throughout the ventilatory cycle). For a single-compartment lung model, if tidal volume is held constant, the risk of barotrauma is the same for pressure-targeted or volume-targeted ventilation, and peak alveolar pressure will be the same. For a two-compartment model with unequal time constants (as in neonatal respiratory distress syndrome [RDS]), it can be shown mathematically that VCV results in a more even distribution of volume and a potentially lower risk of barotrauma.[12,13] Because of these considerations, limiting the peak pressure in volume-controlled devices may be a misconception, as it offsets the major advantage of volume-controlled ventilation in maintaining a constant flow pattern.

It is also a misconception that pressure-limited ventilation of infants is superior to VCV on the basis that it can maintain a constant airway pressure in the presence of leaks around uncuffed endotracheal tubes. The reasoning seems to be that constant pressure implies that the delivered volume remains constant. In addition to the effects of changing lung compliance on tidal volume delivery during pressure-limited ventilation, leaks at the tracheal level can drop the pressure in the trachea and thus affect ventilation just the same as during VCV. This effect may, in fact, be

TABLE 10-1 Distinguishing Features of Volume-Controlled and Pressure-Limited Ventilation

Features	Volume-Controlled	Pressure-Limited
Control (fixed) variable	Volume	Pressure
Phase (changeable) variable		
Inspiratory trigger	Patient or machine	Patient or machine
Inspiratory limit	Flow	Pressure
Inspiratory cycle	Volume or flow	Time or flow
Delivered tidal volume	Constant	Variable
Recorded peak pressure	Variable	Constant
Inspiratory flow waveform	Square	Ramp-descending
Available modes	IMV, SIMV, A/C, PSV	IMV, SIMV, A/C, PSV

A/C, Assist/control; *IMV*, intermittent mandatory ventilation; *PSV*, pressure-support ventilation; *SIMV*, synchronized intermittent mandatory ventilation.

masked during pressure-limited ventilation. Some devices that provide VCV actually provide a way to compensate for leaks by adding additional flow to the circuit to automatically maintain a stable baseline pressure.

Despite different inspiratory flow patterns, VCV, like TCPLV, can be provided as intermittent mandatory ventilation (IMV), synchronized intermittent mandatory ventilation (SIMV), and assist/control (A/C) ventilation. It may also be combined with pressure support ventilation (PSV) during SIMV. Detailed descriptions of each of these modes is given elsewhere in the book (see Chapter 12), but the key features of commonly used methods are discussed here.

Volume-Controlled IMV

As its name implies, in the *volume-controlled intermittent mandatory ventilation (IMV)* mode, the clinician adjusts the ventilator to deliver mechanical breaths at a fixed rate. The patient is still able to breathe independently from the bias flow in the circuit between the mechanically delivered breaths. Such systems do not permit synchronization of the patient's breath with the mechanical breath, but it is possible to superimpose a generated tidal volume on the patient during inspiration or expiration. Asynchrony may result in widely variable tidal volume delivery, alveolar overdistension, and air leaks, and this mode has been associated with intraventricular hemorrhage (IVH) in preterm infants. To prevent these complications, patients often require sedation and occasionally neuromuscular paralysis. In addition, spontaneous breaths are supported only by positive end-expiratory pressure (PEEP).

Volume-Controlled SIMV

Synchronized intermittent mandatory ventilation (SIMV) is an improvement over IMV in achieving inspiratory synchrony in that the ventilator allows the patient to receive mandatory breaths with an onset that is timed to the patient's own spontaneous inspiratory effort. The assisted breaths occur only during windows of time established by the manufacturer at a rate set by the clinician. The time available within each window for patient triggering varies, but it is usually a function of the set respiratory rate. If a patient's inspiratory effort is detected while the window is open, a synchronized breath is delivered. If no patient effort is detected at the time the window closes, the ventilator delivers a mandatory breath. In volume-controlled SIMV, the mandatory breaths delivered by the machine provide the set tidal volume, but the spontaneous breaths taken by the patient are again supported only by PEEP. This can be obviated by combining SIMV with PSV, in which spontaneous breaths can be augmented fully or partially. The use of a low SIMV rate (fewer than 20 breaths/min) without some other means of breath support, such as PSV, may be unwise when discontinuation of mechanical support is imminent for the reasons outlined below.

Volume-Controlled A/C

In the *assist/control (A/C)* mode, each spontaneous breath that exceeds the trigger threshold results in the delivery of a mechanical breath (assist) aimed at delivering the desired tidal volume (Fig. 10-3). If the patient fails to breathe, or if the spontaneous breath fails to exceed the trigger threshold, a mechanical (control) breath is provided at a minimal rate chosen by the clinician to ensure adequate ventilation. A/C ventilation is probably the best mode to use in the acute phase of respiratory failure because it requires the least amount of patient effort and work of breathing. It also has the safety of a guaranteed "back-up" rate to assure adequate minute ventilation in the event of apnea or insufficient patient effort. Weaning during A/C is different than it is for IMV or SIMV because many of the parameters previously set by the clinician are now controlled by the patient. During A/C, as long as the patient is breathing above the control rate, reduction in the mechanical rate

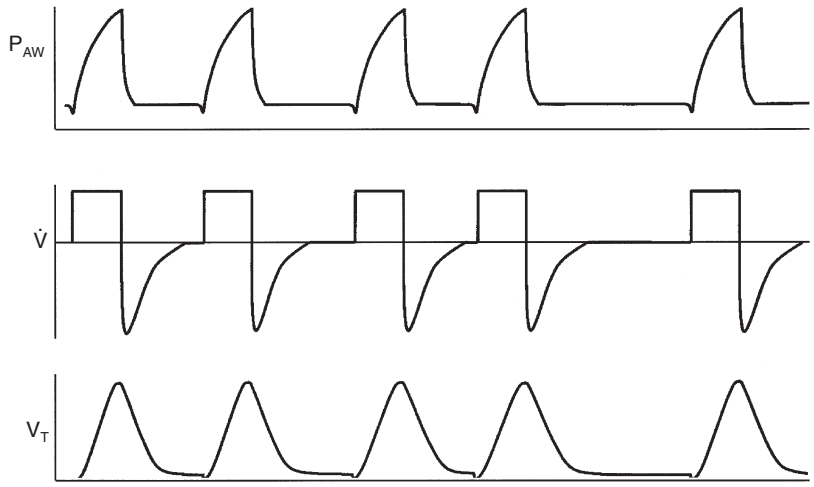

Figure 10-3 ■ Volume ventilation modes: assist/control (A/C) ventilation. Airway pressure, flow, and volume waveforms are shown. All cycles are similar mandatory; the ventilator responds to all detected spontaneous inspiratory effort. Note that the delivered volume is equal during every cycle, and the total rate is controlled by patient effort (plus the minimum set rate delivered if no spontaneous inspiration has been detected.) Measured exhaled tidal volume is always a bit less than inspiratory, representing the leak around the uncuffed endotracheal tube. (Acknowledgment to Dr. Akos Kovacs, Clinical Specialist, Viasys Health Care System, Hungary, for help in preparing this figure.)

brings about no change in ventilator cycling. Unlike pressure-limited A/C, where reduction in PIP is the primary weaning parameter, reduction in tidal volume delivery to a level of 3 to 4 mL/kg or the use of slower-rate SIMV with PSV is the preferred method of weaning with volume-controlled modes.

PSV Combined with Volume SIMV

Pressure-support ventilation (PSV) is a pressure-limited, flow-cycled spontaneous mode of ventilation in which inspiratory flow is variable according to patient effort. It is intended to give the patient an inspiratory pressure "boost" during spontaneous breathing to overcome the imposed work of breathing created by the narrow-lumen, high-resistance endotracheal tube; the ventilator circuit; and the demand valve system, if one is used. PSV can be used as a singular mode (provided the patient has sufficient ventilatory drive), although it is most commonly used in conjunction with SIMV (Fig. 10-4). Because PSV is pressure limited, the tidal volume delivery depends on the respiratory mechanics and may be variable. To overcome this variability, some devices have combined pressure support with a guaranteed minimum tidal volume delivery as in Volume Guarantee® or Volume-Assured Pressure Support® ventilation (see below).

Hybrid Modes Providing Volume-Targeted Ventilation

Both VCV and TCPLV are perceived to have certain advantages and disadvantages (Table 10-2). Attempts have been made to combine the most desirable features of each, resulting in a number of hybrid modalities. These include volume guarantee (VG), Pressure Regulated Volume Control® (PRVC), and volume-assured pressure support (VAPS). They are primarily pressure-targeted ventilation but involve computerized servocontrolled ventilation in which the ventilator has an algorithm that adjusts the rise and fall of pressure to produce tidal volume delivery within a set range. VG and PRVC use the tidal volume of previous breaths as a reference, but follow-up adjustments in peak inspiratory pressure take place on averages of 4 to 6 breaths. VAPS makes intra-breath adjustments of pressure and/or inspiratory time until the desired volume has been provided. All these hybrid modes try to achieve the same goal, the optimization of tidal volume delivery, although each has a different mechanism, and clinicians must familiarize themselves with the specific features of individual machines to maximize efficacy and safety. The commonly available ventilators and features of volume targeting are summarized in Tables 10-3 and 10-4.

Volume Guarantee Ventilation

Volume guarantee (VG) ventilation, available on the Draeger Babylog® 8000 plus ventilator, is a commonly used form of volume targeting. It can be best described as a double or dual loop synchronized modality that ventilates with TCPLV breaths but allows the pressure to be adjusted, using microprocessor technology, to deliver a tidal volume in the range set by the clinician. The operator chooses a target tidal volume and selects a pressure limit up to which the inspiratory pressure (the working pressure) may be adjusted (Figure 10-5). The machine uses the exhaled tidal volume of the previous breath as a reference to adjust the working pressure up or down to achieve the target volume, but this adjustment is made over the next few breaths. The auto-feedback mechanism is an improvement in design from previous iterations but may not always achieve the target volume because of certain characteristics in newborns in whom the respiratory status is rapidly changing and in whom there is always a potential of a large endotracheal tube leak. The feedback loop may have some other limitations as well. For example, because adjustments to PIP are made in small increments to avoid overcompensation and are based on the exhaled tidal volumes, the delivered tidal volume may not compensate for large breath-to-breath fluctuations in the presence of large leaks. Indeed, when the leak exceeds 40%, VG mode no longer functions reliably because of the inability to accurately measure tidal volume.

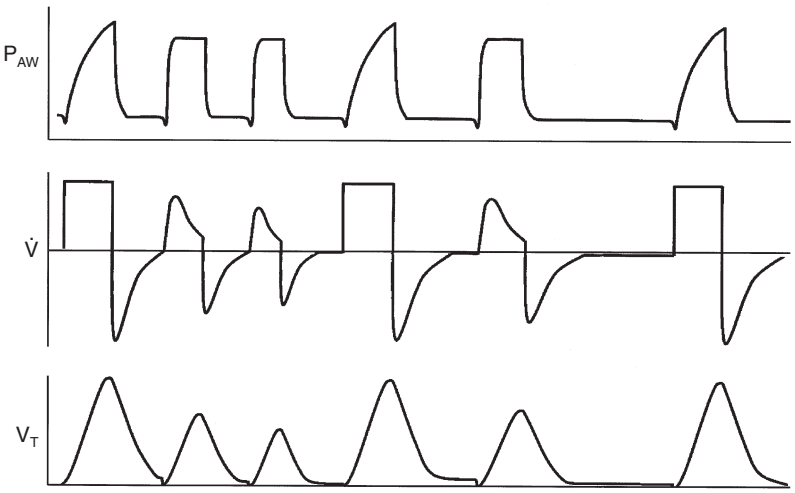

Figure 10-4 ■ Volume ventilation modes: synchronized intermittent mandatory ventilation (SIMV) plus pressure support (PS). Airway pressure, flow, and volume waveforms are shown. Two different waveforms exist. Set number of mandatory (SIMV) cycles plus PS cycles with set inspiratory pressure and nonlimited flow rate. Note that tidal volume during PS is enhanced (compared to continuous positive airway pressure) but is varying and not guaranteed. PS cycles are terminated when inspiratory flow drops to the set level. Inspiratory time and breath rate may vary during PS. For the mandatory cycles, rate and volume are guaranteed, flow is fixed, and peak pressure is patient dependent. The total rate is a sum of the set mandatory plus the spontaneous (PS) cycles. (Acknowledgment to Dr. Akos Kovacs, Clinical Specialist, Viasys Health Care System, Hungary, for help in preparing this figure.)

TABLE 10-2 Perceived Advantages and Disadvantages of Volume-Targeted Versus Pressure-Limited Ventilation

	Volume-Targeted	Pressure-Limited
Advantages	Linear increase in minute volume delivery as VT is increased Autoweaning of proximal airway pressure as lung compliance improves Constant VT delivery regardless of pulmonary compliance in the presence of a substantial leak around the uncuffed endotracheal tube (as used in newborns); inspired tidal volumes may overestimate the actual tidal volume delivered to the lungs	Improves gas distribution by exposing the lungs to set PIP throughout inspiratory cycle Reduces work of breathing by providing high initial flow (pressure control) Limits excessive airway pressure and thus reduces "risk" of barotrauma
Disadvantages	Excessive airway pressure could increase risk of barotrauma Patient-ventilator asynchrony from fixed inspiratory flow, which may cause difference between set flow and patient flow demand leading to "flow starvation" and increased work of breathing	Variable VT delivery; thus risk of excessive volume delivery as compliance improves or inadequate volume delivery if compliance worsens (if no adjustment is made) Inconsistent change in VT with change in PIP and PEEP

PEEP, Positive end-expiratory pressure; *PIP*, peak inspiratory pressure.; VT, tidal volume.

TABLE 10-3 Features of Various Forms of Volume-Targeted Ventilatory Modes*

Ventilation Mode	Features
Volume-control (VC; V.I.P. BIRD Gold, Avea, Siemens Servo 300)	10-1200 mL tidal volume range Flow or pressure triggered Square or decelerating flow waveform Inspiratory pause Volume delivery set on inspired or expired tidal volume as reference
Volume-assured pressure-support (VAPS; V.I.P. BIRD Gold)	Variable flow decelerating waveform Adjustable rise time Target pressure with volume guarantee on breath-to-breath basis Transition to constant flow waveform to deliver volume Flow or volume cycled Inspiratory pause May be used during weaning either in A/C or SIMV with PSV
Pressure-regulated, volume-controlled (PRVC; Siemens Servo 300A, Servo-i)	Pressure-limited, time-cycled mode Closed-loop feedback system Pressure adjusted based on previous four-breath average Must be switched to volume-support mode for weaning
Volume-guaranteed (VG), pressure-limited (Babylog 8000 plus)	Pressure-limited mode Targeted mean tidal volume delivery Volume guarantee based on the previous 8- to 10-breath average Targets expired tidal volume as reference Automated leak compensation

*NOTE: Although often referred to as special types of volume ventilation, PRVC and VG theoretically are time-cycled, pressure-limited modes in which the peak inspiratory pressure setting is not solely user determined but adjusted according to a built-in software algorithm.
A/C, Assist/control; *PSV*, pressure-support ventilation; *SIMV*, synchronized intermittent mandatory ventilation.

TABLE 10-4 Commonly Available Neonatal Ventilators That Provide Volume-Targeted Modes of Ventilation

Ventilator	Available Modes	Features
V.I.P. BIRD Gold and Avea	Volume control Combination modes VAPS	Flow cycling Variable orifice sensor/Heated wire sensor Proximal airway sensor Flow triggering
Bear Cub 750 PSV	Volume-limited, pressure-controlled breaths	Requires properly installed flow sensor
Siemens Servo 300, Servio-i	Volume control Combination modes PRVC Volume support	Flow cycling in all modes Sensor located in machine/wye piece Closed-loop feedback technology "Automode"
Draeger Babylog 8000 plus	Combination mode Volume-guaranteed, pressure-limited	Flow cycling in PSV only with a fixed 15% termination criteria Heated wire sensor

PRVC, Pressure-regulated volume-control; *PSV*, pressure-support ventilation; *VAPS*, volume-assured pressure-support.

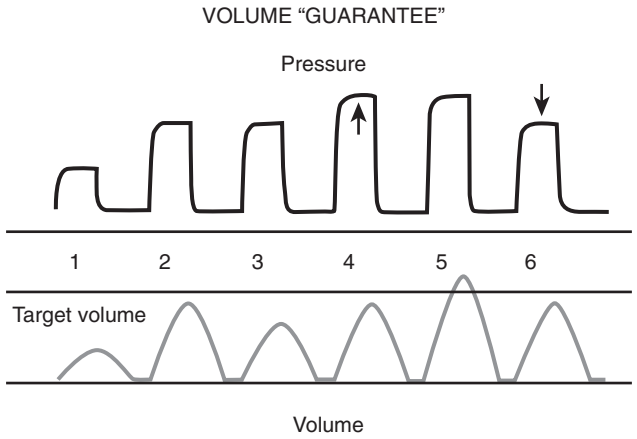

Figure 10-5 ■ Principle of volume guarantee ventilation.
Breath #1: Test breath—the volume that has delivered at a small pressure level is measured.
Breath #2: The ventilator automatically increases the pressure to the necessary level to deliver the target volume based on the calculation from previous breath.
Breath #3: The delivered volume is measured during every breath. During this breath the target volume has not been reached (worsening in lung mechanics).
Breath #4: Ventilator increases pressure level to reach the target volume again.
Breath #5: As lung mechanics improve, the actual pressure will deliver more volume, so the ventilator senses that the target volume is exceeded.
Breath #6: The ventilator answers by automatically reducing the pressure to the level that exactly delivers the target volume ("autoweaning").

The options then are to abandon VG or to correct the problem by replacing the endotracheal tube Moreover, because catch up adjustments in pressures occur every few breaths, it may not work if the ventilatory rate is set at low levels. Clinicians using VG should be aware of these limitations and be prepared to deal with troubleshooting. In this context, the term "guarantee" is somewhat misleading and is better described as a volume "target." Nonetheless, the tidal volume delivery has been documented to be much less variable when different ventilatory modes were combined with VG compared to these modes used without VG.

Potential advantages of VG include less volutrauma, because the clinician sets a tidal volume that is not exceeded, and as lung compliance improves, peak pressures are decreased. Autoweaning of peak pressure should also reduce barotrauma.[14] VG can be used only in conjunction with patient-triggered modes, that is, A/C, SIMV, and PSV. The addition of VG to one of the triggered modes allows the clinician to set a mean tidal volume to be delivered, as well as the standard ventilator settings of PIP, PEEP, inspiratory time, and respiratory rate. The inspiratory pressure is set at the upper desired pressure limit. If this pressure is reached and the set tidal volume is not, an alarm will sound. Automatic pressure changes are made in increments (theoretically) to avoid overcompensation. No more than 130% of the target tidal volume is supposed to be delivered. The usual starting target is a tidal volume of 4 to 5 mL/kg. The pressure limit is set approximately 15% to 20% above the peak pressure needed to constantly deliver the target tidal volume.

If the flow sensor is removed or damaged, the ventilator will default to the set pressure limit. In this mode, because the adjustment of PIP is in response to exhaled tidal volume and adjustments are made in limited increments to prevent overcompensation, the PIP cannot be adjusted instantaneously to compensate for large breath-to-breath fluctuations in respiratory effort. One reason for this lack of variability may be attributable to the fact that VG uses historical exhaled tidal volume data to determine PIP rather than real-time data.

Consequently, although the delivered tidal volume certainly is more consistent than in the absence of VG, it does fluctuate around the target value. The VG modality automatically compensates for changes in compliance, resistance, and spontaneous respiratory effort. VG is useful in infants with periodic breathing and apnea, who are on low-maintenance respiratory support. When used appropriately, the alarm function should alert staff to worsening lung compliance, which may require immediate attention. The PIP is weaned automatically as lung compliance improves. Theoretically, this should lead to faster weaning from mechanical ventilation. Most infants can be extubated when they consistently maintain tidal volume at or above the target value with delivered PIP less than 10 to 12 cm H_2O and with good sustained respiratory effort.

Pressure-Regulated Volume Control Ventilation

Pressure-regulated volume control (PRVC) is another modality of ventilation that attempts to combine the benefits of pressure-limited and volume-controlled ventilation. This is available on Servo 300A and the SERVO-i® Infant ventilators (Maquet). It is a flow-cycled modality that offers the "variable" flow rate of pressure control ventilation with a targeted tidal volume. Like VG, PRVC is also a form of closed loop ventilation in which pressure is adjusted according to tidal volume delivered. The new SERVO-i Infant ventilator features wye-sensor measurements assuring better measurement compared with older prototype machines (Servo 300), which had sensors fixed in the machine rather than near the patient.

The clinician selects a target tidal volume and the maximum pressure to deliver the tidal volume. The microprocessor of the ventilator attempts to use the lowest pressure with a decelerating flow waveform to deliver the set tidal volume. The first breath is delivered at 10 cm H_2O above PEEP and is used as a test breath to enable the microprocessor to calculate the pressure needed to deliver the selected tidal volume based on the patient's compliance. The next three breaths are delivered at a pressure of 75% of the calculated pressure needed. If targeted tidal volume is not delivered, the inspiratory pressure is increased by 3 cm H_2O for each breath until the desired tidal volume is reached (Figure 10-6). If targeted tidal volume is exceeded, the inspiratory pressure is decreased by 3 cm H_2O. Inspiratory pressure is regulated by the ventilator between the PEEP level and 5 cm H_2O below the clinician-set upper pressure limit. In PRVC, the pressure is adjusted based on the average of four breaths, so variations in delivered tidal volume still occur.

The new SERVO-i Infant ventilator has a variety of modes and combination of modes, which are specific for

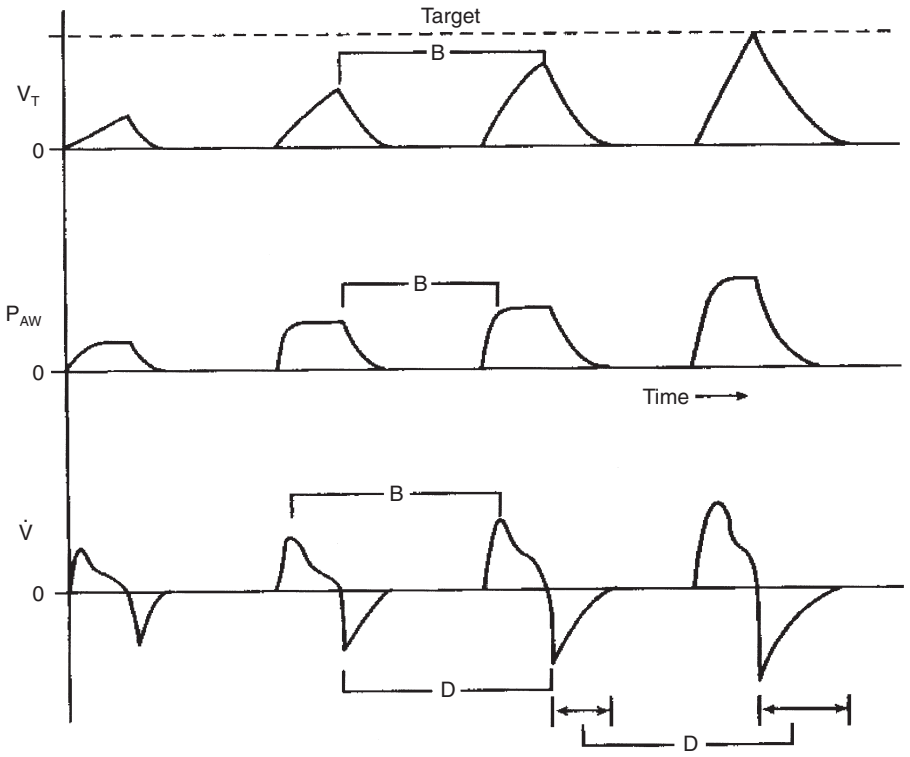

Figure 10-6 ■ Volume, pressure, and flow waveforms for four sequential breaths showing the functioning of pressure-regulated volume-controlled ventilation. Note the progressively increasing PIP, peak inspiratory flow, and inspiratory tidal volume (*B*), and the progressively increasing peak expiratory flow rate (*D*), as well as the duration of expiratory flow. (From Hagus CK, Donn SM: Pulmonary graphics: Basics of clinical application. In Donn SM (ed): Neonatal and Pediatric Pulmonary Graphics: Principles and Clinical Applications. Armonk, NY, Futura Publishing, 1998, pp. 81-127, with permission.)

neonatal ventilation, and clinicians intending to use this machine should familiarize themselves with its specific features.

Volume-Assured Pressure Support Ventilation

Volume-assured pressure support (VAPS) ventilation combines the advantages of pressure and volume ventilation within a single breath and on a breath-to-breath basis. It can be used with both A/C and SIMV or by itself in babies with reliable respiratory drive. It is best described as "variable flow volume ventilation." This is a blended mode with decelerating, nonlimited, variable inspiratory flow with guaranteed tidal volume delivery.

The breath is triggered by the patient. Spontaneous breaths begin as PSV breaths. The ventilator measures delivered volume when inspiratory flow has decelerated to the minimal set value. As long as the delivered volume exceeds the desired level (set by the clinician), the breath behaves like a pressure support breath and is flow cycled. If the preset tidal volume has not been achieved, the breath will transition to a volume-controlled breath; the set flow will persist and the inspiratory time will be prolonged until the desired volume has been reached (Fig. 10-7). If the delivered volume is very far below the desired level, pressure also may be increased.

VAPS can be used both in the acute phase of respiratory illness, in which the patient requires a substantial level of ventilatory support, and when a patient is being weaned from the ventilator, especially in the face of unstable ventilatory drive. In that case, it is designed to supply a back-up tidal volume as a "safety net" in case the patient's effort and/or lung mechanics change.

In summary, VAPS is a hybrid modality of ventilation that optimizes two types of inspiratory flow patterns (VAPS = PSV + VCV). There is also an adjustable rise time that controls the rate of rise of airway pressure and is set by the clinician. The optimal flow acceleration varies with patient dynamics, patient demand, and patient circuit characteristics. Pulmonary graphics are an essential tool for making the appropriate adjustments with VAPS. Thus VAPS is equally suitable for both acute respiratory illness and as a facilitatory modality during weaning because of its advantage in reducing the patient's work of breathing and improving synchrony between patient and ventilator.

Volume Support Ventilation

Volume support ventilation (VSV) is a hybrid modality similar to PSV and PRVC. The volume-supported breath is patient triggered, pressure limited, and flow cycled. It is intended for patients who are breathing spontaneously with sufficient respiratory drive. Similar to PRVC, breath rate and tidal/minute volume are preselected by the clinician; however, inspiratory time is determined by the patient. Like PRVC, the ventilator algorithm adjusts the pressure limit up or down by no more than 3 cm H_2O at a time. Adjustments are made in sequential breaths until the target tidal volume is achieved. The flow, pressure, and volume graphics for a volume-supported breath are similar to those of pressure-supported breaths; however, evidence for efficacy of volume support can be assessed only by evaluating sequential graphic presentations over time, as in PRVC. The tidal volume waveform will increase in a stepwise fashion until the target volume is reached.

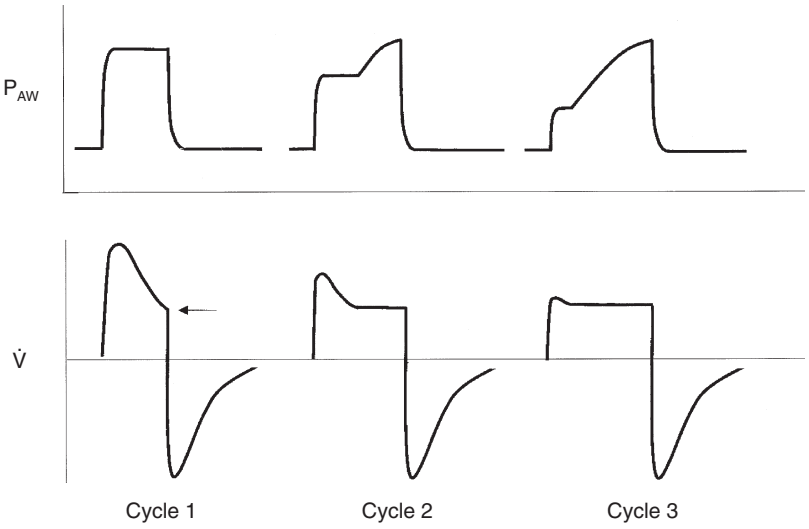

Figure 10-7 ■ Volume-assured pressure-support ventilation. Airway pressure and flow waveforms of three typical settings are shown. **Cycle 1:** Set tidal volume is lower than the delivered volume (because inspiratory pressure has augmented to a relatively high level). Breath is terminated when flow decelerates to the set flow rate (*arrow*). Breath behaves similar to pressure support. **Cycle 2:** At a lower level of pressure augmentation, the set volume is not completely delivered until the decelerating flow reaches the set flow level (transition point). The flow is maintained as long as the set volume is completed. See the typical notch in the middle of the breath. **Cycle 3:** At a minimal pressure augmentation level, the peak flow hardly exceeds the set flow and breath behaves like volume ventilation, except for the nonlimited flow at the very beginning of the breath. (Acknowledgment to Dr. Akos Kovacs, Clinical Specialist, Viasys Health Care System, Hungary, for help in preparing this figure).

Pressure Augmentation

Pressure augmentation is also a hybrid modality that offers the benefit of matching the patient's flow demand while guaranteeing a minimal tidal volume. Pressure augmentation differs from PRVC in the following ways: (1) preset tidal volume is only a minimum and the patient can breathe above this level; (2) the minimal tidal volume is guaranteed by adjustment in flow rather than pressure, which is fixed at a preselected level; and (3) adjustment to flow is made within each breath rather than in several sequential breaths. Pressure augmentation is interactive with the patient and depends upon the patient's flow demand and lung dynamics. Pressure augmentation can be used in either A/C or SIMV modes, in which volume-controlled breaths are selected (Fig. 10-8).

Suggested Ventilatory Management Guidelines

Although a number of neonatal units have now started using VCV modalities to treat newborn populations, until recently no guidelines had been published that were truly evidence-based, other than the trial of Singh et al.[23]. That

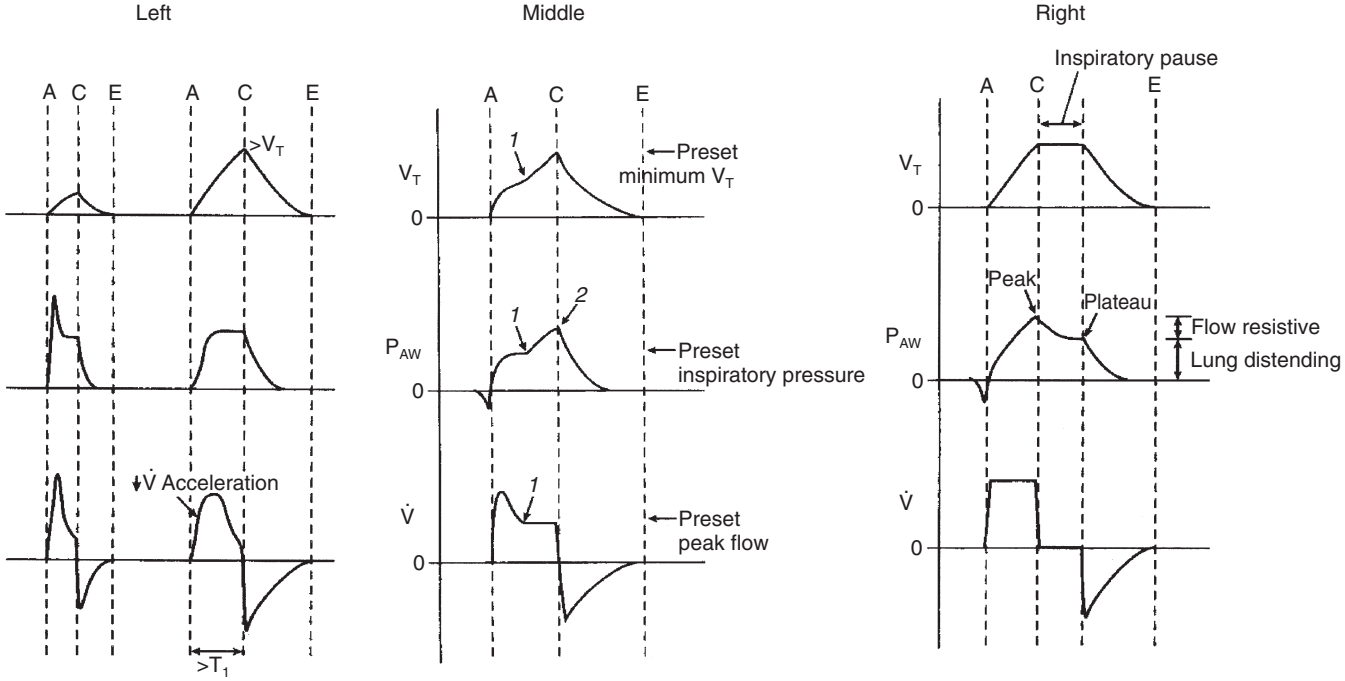

Figure 10-8 ■ Volume, pressure, and flow waveforms (*left*) showing the benefit of slowing flow acceleration when compliance is low and airway resistance is high; (*middle*) for a volume-assured, pressure-supported breath type; and (*right*) for a volume-controlled breath type with an inspiratory pause. *A,* Inspiration begins; *C,* inspiration ends and expiration begins; *E,* expiration ends. (Modified from Hagus CK, Donn SM: Pulmonary graphics: Basics of clinical application. In Donn SM (ed): Neonatal and Pediatric Pulmonary Graphics: Principles and Clinical Applications. Armonk, NY, Futura Publishing, 1998, pp. 81-127, with permission.)

TABLE 10-5 Protocol for Using Volume-Controlled Ventilation (V.I.P. Gold, Avea)

	Sequence of Adjustments
Initial mode	Start in A/C mode Adjust volume to deliver 4-6 mL/kg (measured at proximal endotracheal tube)
Time limit (A/C)	Use flow to adjust inspiratory time to 0.25-0.4 sec
Target ABG	pH: 7.25-7.4 P_{CO_2}: 45-60 P_{O_2}: 50-80
Weaning	Wean by reducing volume as tolerated but continue in A/C with control rate to assure normocapnia and tidal volume delivery at 4-6 mL/kg Switch to SIMV/PS when control rate is less than 30
Weaning to extubation	Decrease rate to 20 Decrease pressure support to have similar VT to previous settings until 10 is reached
Trial of extubation	If infant is tolerating the minimal settings and MAP is less than 8.0 cm H_2O for at least 12 hours or earlier self-extubation Load and start methylxanthine

ABG, Arterial blood gas; *A/C*, assist/control; *MAP*, mean airway pressure; *PS*, pressure-support; *SIMV*, synchronized intermittent mandatory ventilation.

study compared VCV to TCPLV in low-birth-weight babies, using a strict protocol. On the basis of that trial (and a previous similar trial), guidelines now can be recommended for VCV because it appears to be safe and effective. The guidelines for other volume modalities (esspecially VG and PRVC), are based mostly on product literature,[14,15] although some centers have acquired sufficient knowledge to share their experiences and make management recommendations.[16] It is also imperative that the operator be well versed in these techniques and any characteristics that may be unique to the device being used. It should be realized that the pathophysiology of underlying lung conditions that give rise to respiratory failure in newborns is characterized by changing pulmonary mechanics, either naturally or in response to treatment or complications, and the initial ventilatory settings almost always need to be adjusted. Proper clinical use requires close monitoring of the indices of gas exchange (blood gases, minute ventilation), pulmonary mechanics (compliance and resistance) and hemodynamics to gauge the safety and efficacy of the ventilator strategy being applied. Online breath-to-breath pulmonary waveforms and mechanics displays may provide useful information about the trends in pulmonary function and allow the operator to make adjustments in the ventilatory settings. A brief summary of the clinical management protocol for VCV and VG is given in Table 10-5 and Box 10-1.

In VCV (Table 10-5), we generally initiate ventilation in the A/C mode using an inspiratory tidal volume of 4 to 6 mL/kg (measured at the proximal endotracheal tube) as the reference range to achieve the target blood gases. However, for monitoring and further adjustments in tidal volume delivery, we use expired tidal volume as the reference, which probably provides a more accurate measurement of the gas delivery to the lungs. We do not administer neuromuscular paralyzing agents, because A/C is both synchronized and relies to a great extent on spontaneous breathing. For weaning, we use low rate SIMV mode (10-20 breaths/minute) combined with PSV to augment spontaneous breathing and prevent increased work of breathing. In the beginning, the amount of pressure support provided delivers a full tidal volume breath (pressure support [PS] max) and with further improvement in spontaneous breathing, we sequentially reduce the PSV to half its initial value until a tidal volume of 3 to 4 mL/kg is reached (pressure support [PS] min). Most babies can be extubated from this level of support if regular respiratory drive is demonstrated.

In VG ventilation, the initial ventilation is started in the synchronized, intermittent, positive-pressure ventilation (SIPPV) mode with a trigger sensitivity set at 1, which is the most sensitive setting (Box 10-1). This may need subsequent adjustment to reduce the effect of leak-induced auto-triggering. The starting tidal volume reference range is between 4 and 6 mL/kg, which can be adjusted. This will need further adjustment during the course of ventilation based on the results of blood gas analyses. It takes the Babylog between six and eight breaths to reach the targeted tidal volume, the exact time depending on the respiratory rate. If the PIP being used to deliver the desired tidal volume is several cm H_2O below PINSP (where PINSP is the

Box 10-1 PROTOCOL FOR USING VOLUME GUARANTEE (VG) MODE OF VENTILATION ON DRAEGER BABYLOG[14]

1. Press "vent mode" and select triggered mode of ventilation (SIMV, SIPPV = A/C, PSV)
2. Set trigger sensitivity at most sensitive
3. Set TI, TE (therefore back-up rate for apnea), F_{IO_2}, PINSP, PEEP, flow rate
4. Press <VG>; preset VT set by—and + buttons (start value 4-6 mL/kg[7,8])
5. Connect Babylog to the infant
6. Select <Meas 1> or <VG> screen
7. Check to see delivered VT and PIP used by Babylog to delivery target VT
8. Adapt PINSP to actual PIP

A/C, Assist/control; *PEEP*, positive end-expiratory pressure; *PINSP*, maximum allowed pressure; *PIP*, peak inspiratory pressure; *PSV*, pressure-support ventilation; *SIMV*, synchronized intermittent mandatory ventilation; *SIPPV*, synchronized intermittent positive pressure ventilation; *VG*, volume guarantee.

maximum allowed pressure), then the set PINSP may be left as is. This extra available peak pressure can be used by the ventilator if lung compliance decreases (or resistance increases, endotracheal tube leak increases, or respiratory effort decreases). If the PIP used by the ventilator is close to or equal to the set PINSP, the set PINSP should be increased by at least 4 to 5 cm H_2O. This will allow the ventilator some leeway in delivering the desired tidal volume even if compliance decreases. Once appropriate levels of tidal volume have been established, weaning should be an "automatic" process, with the amount of pressure deployed by the ventilator to provide the set tidal volume decreasing as the infant recovers. When the peak airway pressure used is very low, the infant may be ready for extubation.

Clinical Evidence

Compared to TCPL, VCV is relatively new to the neonatal intensive care unit. Not many controlled studies describe its safety and efficacy, although most published trials concerning this mode are indeed favorable.

In a recent Cochrane review, McCallion et al.[17] identified eight randomized trials comparing the use of VCV to TCPLV in newborns. Only four met the eligibility criteria for inclusion in the meta-analysis. These four trials recruited a total of 178 preterm infants. The four trials are summarized below.

The first reported randomized controlled trial of true VCV versus TCPLV, which controlled tidal volume delivery in both arms of the trial, was conducted by Sinha et al.[18] Fifty preterm infants weighing 1200 or more grams with RDS were randomly allocated to either VCV or TCPLV using the VIP BIRD® (Bird Products Corp, Palm Springs, Calif.). Tidal volume delivery was set at 5 to 8 mL/kg in both groups so that the only difference was the ventilatory modality, and thus the way in which tidal volume was delivered. The two groups were compared for the time required to achieve success criteria using the alveolar-arterial oxygen gradient ($AaDO_2$) or the mean airway pressure. Infants randomized to VCV met the success criteria faster (mean time 65 vs. 125 hours; $p < 0.001$) and had a shorter total duration of ventilation (mean time 122 vs. 161 hours; $p < 0.001$). These babies also had a significantly lower incidence of large intraventricular hemorrhages and abnormal periventricular echo densities on ultrasound scans. There were no differences between the study groups in other complications associated with mechanical ventilation. Because of technological limitations in the minimum tidal volume delivery, infants less than 1200 g could not be included in this first trial.

In another study performed contemporaneously, Piotrowski and colleagues[19] compared PRVC to TCPLV. Sixty newborn babies weighing less than 2500 g and needing ventilation for RDS or congenital pneumonia were randomized to receive PRVC or TCPLV by IMV. The primary outcome measures were duration of mechanical ventilation and the incidence of chronic lung disease (CLD). Pulmonary air leaks and IVH were considered major adverse outcome events. Duration of mechanical ventilation and incidence of CLD were similar in the two groups; however, the PRVC group had a lower incidence of IVH greater than grade 2 ($p < 0.05$), and fewer infants receiving PRVC had air leaks (3 vs. 7). In a subgroup of infants weighing less than 1000 g, the duration of mechanical ventilation and incidence of hypotension were reduced in the PRVC group ($p < 0.05$).

The third study in this meta-analysis came from Keszler and Abubakar,[20] who tested the hypothesis that VG would maintain the tidal volume and $PaCO_2$ within a target range more consistently than TCPLV used alone in the A/C mode. Eighteen preterm infants were randomized and the Draeger Babylog 8000 plus ventilator was used for both groups. VG significantly reduced the incidence of large tidal volume breaths (greater than 6 mL/kg) more consistently but also significantly reduced the incidence of hypocarbia. They hypothesized that the use of VG had the potential to reduce the pulmonary and neurologic complications of mechanical ventilation.

On a similar theme, Lista et al.[21] evaluated the lung inflammatory response in preterm infants with RDS, who were mechanically ventilated with and without VG, by measuring pro-inflammatory cytokines (IL-6, IL-8, TNF-α) in tracheobronchial aspirate fluid. Fifty-three preterm infants (gestational ages 25-32 weeks) were randomized to be ventilated using PSV with VG (tidal volume = 5 mL/kg) and PSV without VG using the Draeger Babylog 8000 plus ventilator for both. The trial found a significant difference in IL-8 and IL-6 concentrations on day 3 between the two groups. Infants who received PSV alone required 50% more ventilation (12.3 ± 3 vs. 8.8 ± 3 days), although this difference was not statistically significant because of the small sample size.

These four trials included in the Cochrane review used different ventilators and techniques but shared the common aim of investigating the putative advantages of controlling tidal volume delivery in the "optimal" range among premature infants who required mechanical ventilation during the first 72 hours of life. No significant difference was found for the primary outcome of death before discharge. None of the four trials reported the combined outcome of death or CLD. Analysis of the trials, however, showed that VCV resulted in a significant reduction in the duration of ventilation (weighted mean difference [WMD], 2.93 days [−4.28, −1.57]) as well as the rate of pneumothorax (risk reduction [RR] 0.23 (0.07, 0.76); risk difference [RD] −0.11 (−0.20, −0.03); number needed to treat [NNT] 9). There was also a significant difference in the rate of severe (grade 3 or 4) intraventricular hemorrhage favoring VCV [typical RR 0.32 (0.11, 0.90); RD −0.16 (−0.29, −0.03); NNT 6]. There was a reduction in the incidence of CLD (supplemental oxygen at 36 weeks) among surviving infants, of borderline statistical significance (typical RR 0.34 [0.11, 1.05]; RD −0.14 [−0.27, 0.00]; NNT 7.)[17] Long-term outcomes were not addressed.

Subsequent to this meta-analysis, another trial was published, this time enrolling even smaller preterm babies.[22] In this largest trial published so far, Singh et al. compared the safety and efficacy of VCV to TCPLV in very-low-birthweight (VLBW) infants who had respiratory failure at birth and required mechanical ventilation. The results are the most recent at this time on this subject and should only strengthen the findings of the meta-analysis in support of VCV.

In this study, 109 newborns 24 to 31 weeks' gestation, and weighing 600 to 1500 g at birth were randomized to receive either VCV or TCPLV. All infants in this study were treated with the VIP Gold® ventilator (Viasys Healthcare Systems, Palm Springs, Calif.) using a standardized protocol designed for this study. In both groups, ventilator variables were set to target an exhaled tidal volume (V_{Te}) of 4 to 6 mL/kg, which was monitored and adjusted on an hourly basis. In the VCV group, delivered tidal volume was adjusted, and in the TCPL group, the peak inspiratory pressure was adjusted.

During the acute phase of illness, all infants were placed in A/C. Targeted blood gas indices, including a pH of 7.25 to 7.40, $PaCO_2$ 4.5 to 6.5 kPa (35-49 mm Hg), and PaO_2 7 to 10 kPa (50-75 mm Hg) were used during the initial stage. Subsequently, $PaCO_2$ was permitted to rise to 8 kPa (60 mm Hg) if the pH remained higher than 7.20. Once the infants were recovering from acute illness (PIP less than 16 cm H_2O and FIO_2 less than 0.3), the ventilatory mode was changed to SIMV with PSV. The two modalities were compared by determining the time required to achieve either an $AaDO_2$ of less than 100 torr or a mean airway pressure (Paw) less than 8 cm H_2O.

Secondary outcomes included mortality, duration of mechanical ventilation, and complications associated with ventilation. The mean time to reach the success criteria was 23 hours with VCV vs. 33 hours with TCPL ($P = 0.15$). This difference, however, was more striking in babies weighing less than 1000 g (21 vs. 58 hours; $P = 0.03$). Mean duration of ventilation with VCV was 255 hours vs. 327 hours with TCPLV ($P = 0.60$). No significant difference was found in the incidence of complications between groups. However, all deaths in the first week of life were related to respiratory disease and occurred exclusively in infants randomized to TCPLV. This was unexpected, because the groups were closely matched for severity of RDS.

Although the modality of ventilation did not show an independent effect on survival on multivariate analysis, there was a trend toward better survival among babies treated with VCV (odds ratio, 0.5; 95% cardiac index [CI], 0.2-1.2; $P = .10$). These findings should be interpreted with caution because of the sample size. One explanation for this difference might lie in the way in which flow (and hence volume) is delivered. During TCPLV, there is rapid flow delivery, resulting in a sharp rise in airway pressure and delivery of volume early in the inspiratory phase. Theoretically, this should favor the expansion of the more compliant areas of the lung, possibly leading to nonhomogeneous gas delivery. In VCV, there is a slower but more sustained rise in inspiratory pressure, with peak volume delivery occurring at end-inspiration. This might result in more uniform filling of the lung and less atelectrauma. A further benefit might accrue from autoweaning.

Although a similar tidal volume target was selected for both groups, changes in the TCPLV group required a clinical decision, which may not have been performed as rapidly. A masked follow-up study of these infants at a median postconception age of 22 months showed a continued trend toward better survival and clinical respiratory outcomes in the babies who had received VTV.[23] The incidence of severe disability was also no higher in the volume group, but the study was not powered to address this outcome. This study is unique in that no other randomized studies of volume-targeted ventilation have evaluated outcomes after discharge, which is an important consideration when evaluating the performance of any specific ventilatory modality or strategy. In the previous report, the authors had found trends toward improved survival, faster weaning, and decreased duration of ventilation favoring VCV. This follow-up study has provided further evidence that VCV is safe and efficacious in the management of RDS in VLBW babies. The trend toward improved survival without CLD in the VCV group has a clinical correlate, because fewer children from this group were receiving inhaled bronchodilators and steroids for treatment of respiratory symptoms at follow up.

Other studies have also looked at the efficacy of VCV. Weiswasser and colleagues[24] examined differences in pulmonary vascular resistance (PVR), cardiac index (CI), and dynamic compliance (C_{dyn}) in healthy and a surfactant-deficient (induced by saline lavage) neonatal piglet model. Animals were randomly assigned to VCV or TCPLV using perflourocarbon liquid ventilation. Although there was no significant difference in healthy lungs, in the surfactant-deficient model, C_{dyn} was significantly higher and PVR was significantly lower in the VCV group after 180 minutes of liquid ventilation. Cardiac index declined significantly in both groups irrespective of ventilatory modality.

Hummler et al.[25] performed a crossover study to compare volume-controlled SIMV with pressure-limited SIMV in a population of 15 mechanically ventilated babies exhibiting frequent hypoxemic episodes. Although there was no significant difference between the two groups with respect to primary outcome measure (time with functional oxygen saturation [SpO_2] less than 80%), babies randomized to volume-controlled SIMV maintained tidal volume better during episodes of desaturation, and bradycardia was less frequent in the volume-controlled SIMV group.

Volume guarantee (VG) is a widely used method of providing volume-targeted ventilation but is the least studied in clinical trials. Of the published trials of VG, most are small crossover trials relating to endpoints based on short-term physiological changes. There is a lack of published data about relevant long-term clinical outcomes. Cheema and Ahluwalia[26] first investigated the feasibility and efficacy of VG in 40 premature newborn infants (mean birth weight 1064 g, gestation 27.9 wk) with RDS, in a 4-hour crossover trial. They found that the mean PIP and mean Paw using VG with either SIPPV or SIMV was lower than that with either SIPPV or SIMV alone. No untoward effects were noted during the study period. VG, as used in this study, seemed to be a feasible ventilation modality for neonatal patients and achieved equivalent gas exchange using statistically significant lower PIP both during early and recovery stages of RDS.

In another study, Herrera et al.[27] compared the effects of SIMV with VG and conventional SIMV on ventilation and gas exchange in a group of VLBW infants recovering from RDS. Nine infants were studied for two consecutive 60-minute intervals in a crossover trial. The authors concluded that VG led to automatic weaning of mechanical support and enhancement of spontaneous respiratory

effort during short-term use. However, the study was based on a short-term observation period in relatively stable babies. There was an upward trend in the transcutaneous P_{CO_2} tensions in the infants given VG.

Abubakar and Keszler[28] in a short crossover trial, showed that breath-to-breath tidal volume variability was significantly reduced with VG compared to with assist-control, SIMV, or PSV alone. In another randomized trial by the same authors comparing A/C with A/C plus VG, the VG group maintained tidal volume and P_{CO_2} within a target range more consistently. The authors concluded that VG reduced hypocarbia and excessively large tidal volumes.[29] Next, they compared the effect of A/C plus VG with SIMV plus VG in a short crossover trial. Infants in the SIMV plus VG group had higher variability of tidal volume and increased work of breathing.[30] A more recent study has shown that VG is feasible in the initial stabilization of infants greater than 25 weeks' gestation, and that it halves the incidence of hypocarbia compared to SIMV, but at the same time VG in this study was not effective in reducing hypercarbia in babies less than 25 weeks' gestation, suggesting that the universal protocol for VG may need modification for ventilating smaller babies.[31]

There have been two randomized controlled trials of PRVC. Although a subgroup analysis of infants less than 1000 g in the first trial, as described earlier, showed a reduction in the duration of ventilation in the PRVC group, there was no difference in short-term survival, duration of ventilation, or the incidence of CLD.[19] Another randomized, controlled trial compared PRVC with SIMV in a group of 213 ventilated infants and found no difference in short-term survivors, duration of ventilation or the incidence of CLD.[32]

Summary

VCV and other "volume targeted" modalities such as VG, PRVC, and VAPS are new to neonatal intensive care and represent a departure from traditional TCPLV. Not surprisingly, there are only a few published randomized controlled clinical trials testing these modalities in the newborn population. Nonetheless, the evidence so far is highly encouraging. It appears that the consistency of tidal volume delivery during VCV in the face of varying lung compliance and the auto-weaning of airway pressure may be clinically advantageous, especially in conditions in which lung compliance can change rapidly, such as after surfactant treatment of RDS. Volume-targeted modalities have in common an objective to control tidal volume delivery in an attempt to provide optimal lung inflation. Stability of tidal volume delivery may be beneficial, especially in extremely low-birth-weight infants, who are at increased risk of sustaining complications associated with mechanical ventilation. Although the benefits of VCV in the published studies have been restricted to short-term outcomes such as duration of ventilation, pneumothorax, and intraventricular hemorrhage, these are still important findings and should not be ignored. The preliminary trials also have laid the groundwork for larger multicenter trials of a sufficient size to be able to address the question of whether VCV improves the long-term respiratory and neurodevelopmental outcomes of infants requiring mechanical ventilation.

Future Directions

The development of microprocessor-based respiratory technology and sophisticated yet miniature transducers has resulted in new modes of volume-targeted ventilation for treatment of neonatal respiratory failure. This further expands the therapeutic range and enables customization of ventilator management based on specific pathophysiology and patient responses. However, many questions remain unanswered and further studies are required to confirm the safety and efficacy of VCV with respect to both short-term and long-term outcome measures, such as the impact on CLD.[33]

The volume-controlled modes are new and represent a departure from the time-honored TCPLV. The wide range of choices now available should not intimidate the clinician but should represent a challenge to determine the best clinical indications, as well as the limitations of each. Clinical information on newborns is limited, and the opportunity to design and implement randomized, controlled clinical trials may never be better. Before embarking on such studies, it is imperative that clinicians familiarize themselves with individual ventilator specifications, as well as differences among the many available commercial devices. Gone are the days when all neonatal lung diseases can be treated alike.

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11 High-Frequency Ventilation

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First described in the 1970s, high-frequency ventilation (HFV) is a form of mechanical ventilation that uses small tidal volumes, sometimes less than anatomic dead space, and very rapid ventilator rates (2-20 Hz or 120-1200 breaths/min). Potential advantages of this technique over conventional mechanical ventilation (CMV) include the use of lower proximal airway pressures, the ability to adequately and independently manage oxygenation and ventilation while using extremely small tidal volumes, and the preservation of normal lung architecture even when using high mean airway pressures.[1-6] HFV's ability to sufficiently oxygenate and ventilate the fragile preterm lung with airway pressures that are lower than that used with CMV, as well as its use for alveolar recruitment and distribution of medicines such as inhaled nitric oxide (iNO), makes it a crucial constituent of neonatal respiratory therapy. In this chapter, current HFV techniques and technology are described and their application in the newborn with pulmonary dysfunction is discussed.

Currently, there are three general types of HFV: high-frequency positive-pressure ventilation (HFPPV), which is produced by conventional or modified CMVs operating at rapid rates; high-frequency jet ventilation (HFJV), which is produced by ventilators that deliver a high-velocity jet of gas directly into the airway; and high-frequency oscillatory ventilation (HFOV), which is produced by a device that moves air back and forth at the airway opening and produces minimal bulk gas flow. Ventilators that deliver HFPPV, because of small internal compressible volumes and high gas flow rates, may simply be more efficient at moving small tidal volumes of gas into and out of the lung. HFJV and HFOV appear to enhance both the distribution and diffusion of respiratory gases. Both shift the transition point between convective and diffusive gas transport progressively in a cephalad direction from the acinus into the large airways. The net effect of this shift is efficient CO_2 elimination relatively independent of mean lung volume.[7]

Conventional pulmonary physiology tells us that the amount of gas available for gas exchange, the alveolar volume, is the product of the tidal volume delivered into the airway minus anatomic dead space ($V_A = V_T - V_D$). If this relationship is true, tidal volumes near anatomic dead space should produce little if any alveolar ventilation. In an attempt to clarify the mechanisms of HFV gas exchange at tidal volumes less than anatomic dead space, Chang[8] demonstrated that multiple modes of gas transport occur, including bulk convection, high-frequency "pendelluft," convective dispersion, Taylor-type dispersion, and molecular diffusion. Whatever the HFV system, the presumed linear relationship between ventilator rate and CO_2 elimination is no longer valid with this mode of ventilation. In fact, during HFV, CO_2 elimination improves with decreasing ventilator frequency as long as the inspiratory-to-expiratory time ratio (I:E) is held constant.

Although paradoxical at first blush, this inverse relationship reflects the impact of an increasing inspiratory time as frequency is lowered; this results in higher delivered gas volumes. In 1980, Slutsky et al.[9] reported a review of possible gas transport mechanisms during HFV. They suggested that CO_2 elimination during HFV varies according to the product of frequency[a] and tidal volume[b], with *b* greater than 1 and the value of *a* less than 1. Since then, many other theoretical and practical reviews have been published. The theoretical mechanisms of gas exchange during HFV are beyond the scope of this clinical chapter. For those interested, there are a number of excellent review articles, as well as a review of physiologic principles in Chapter 2.[10-15]

Types of High-Frequency Ventilators

Currently only a small number of HFV devices are approved by the United States Food and Drug Administration (FDA) for clinical use. Even though the number of HFVs is small, the classification or taxonomy of these ventilators is confusing and at times inconsistent. Froese and Bryan[13] classified HFV into three categories based on the character of exhalation: active, passive, and hybrid. In this chapter we use the more traditional, clinical classification of HFPPV, HFJV, and HFOV. Table 11-1 lists all the current FDA-approved HFV devices. A number of other HFV devices have been studied and are currently being used throughout the world. This chapter focuses primarily on those machines currently approved for clinical use in the United States and Canada.

High-Frequency Positive-Pressure Ventilators

High-frequency positive-pressure ventilators (HFPPVs) usually are CMVs adapted to operate at rapid rates. This includes a group of ventilators often referred to as high-frequency flow interrupters. The term *flow interrupter* originally was used to describe a group of ventilators that were neither true oscillators nor true jets. Some had jet-type

TABLE 11-1 FDA-Approved High-Frequency Ventilator Devices in the United States and Canada

Trade Name	Type of Ventilator	Exhalation Characteristics
SensorMedics 3100A	HFOV	Active
Dräeger Babylog 8000	HFOV	Active
Bunnell Life Pulse	HFJV	Passive
Infrasonics	HFPPV	Passive (hybrid: Venturi-assisted)

HFOV, High-frequency oscillatory ventilator; *HFJV*, high-frequency jet ventilator; *HFPPV*, high-frequency positive-pressure ventilator.

injectors but delivered their bursts of gas not directly into the airway but into the ventilator circuit some distance back from the trachea and endotracheal tube. For this reason, these machines also were called *setback jets*. For the purposes of our discussion, we consider all of these hybrid machines as HFPPVs.

Because all conventional pressure-preset neonatal ventilators will cycle at rates up to 150 breaths/minute (min), all of them can be used to produce HFPPV. The only neonatal HFPPV device available in the United States that is designed to cycle at more rapid rates is the Infant Star HFV (Nellcor Puritan Bennett, Pleasanton, Calif.). Although no longer in production, the Infant Star HFV is still widely used. This device (Fig. 11-1) has been referred to as both a jet and an oscillator. Because it has neither an injector in the airway like a jet ventilator nor the active exhalation of an oscillator, it is neither. This ventilator has a set of microprocessor-controlled pneumatic valves that alter inspiratory flow to achieve preset peak inspiratory pressures (PIPs). Although there is a Venturi system on the exhalation valve to facilitate expiration and prevent inadvertent positive end-expiratory pressure (PEEP), exhalation is still passive. This ventilator has been used in clinical trials to treat severe pulmonary air leaks and lung diseases unresponsive to CMV.[16-18] It was approved by the FDA for these purposes.

The term *HFPPV* most often refers to mechanical ventilators operating at rates between 60 and 150 breaths/min (1-2.5 Hz). Sjostrand[19] pioneered this technique in Sweden using specially designed ventilators with extremely low compressible volumes. He and his colleagues studied more than 2000 adults and children during surgery and 32 neonates with respiratory distress syndrome (RDS).[20] He concluded that in most clinical situations, HFPPV provided adequate respiratory support. In 1980, Bland et al.[21] reported improved outcomes in 24 infants with RDS using conventional volume preset infant ventilators operating at

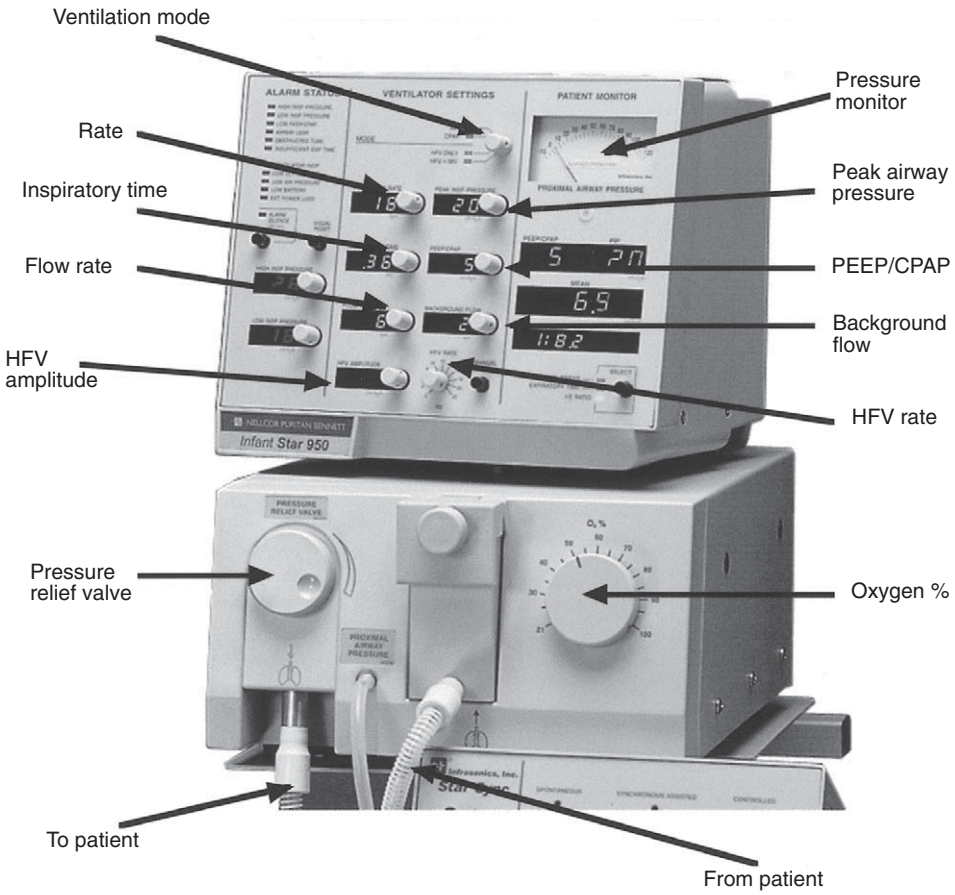


Figure 11-1 ■ The Infant Star neonatal ventilator. This is a time-cycled, pressure-limited ventilator that provides high-frequency ventilation (HFV) using high-frequency positive-pressure ventilation principles. It uses a Venturi system to facilitate expiration. Operational frequency range is from 120 to 1320 breaths/min. Pressure wave amplitude is adjusted by changing ventilator flow from 4 to 120 L/min. Inspiratory time is set as 18 milliseconds. *PEEP/CPAP,* Positive end-expiratory pressure/continuous positive airway pressure.

rates ranging from 60 to 110 breaths/min. In 1991, a multicenter randomized trial compared HFPPV using rates of 60 breaths/min, to CMV using rates up to 40 breaths/min. The infants treated with HFPPV had fewer pulmonary air leaks.[22] Thome and colleagues[23] compared two different types of HFPPV: that produced using the Infant Star HFV system to that produced using the Dräger Babylog neonatal ventilator at rapid rates. The Infant Star system operates at much higher frequencies, and the authors hypothesized that this HFV system would produce fewer treatment failures. In fact, outcomes using both types of HFPPV were similar, except that babies treated with the Infant Star HFV had significantly more air leaks. In the "Sy-Fi" study, Craft and colleagues[24] again compared the Infant Star system to CMV in extremely low-birth-weight (ELBW) infants and found no difference in air leaks or other pulmonary outcomes.

Since the 1980s HFPPV using conventional pressure-preset ventilator systems has become a common therapy in neonatal intensive care units throughout the world. The technique seems simple and easy. In most cases, HFPPV requires no special equipment. As with many allegedly simple and easy therapies, however, things may not be as simple and easy as they first seem. Today, CMVs routinely operate at rates up to 150 breaths/min. However, few of these machines were designed with such frequencies in mind. In vitro and in vivo studies of conventional pressure-preset infant ventilators show that all have maximum operating frequencies beyond which their performance deteriorates.[25-30]

The first such in vitro study measured delivered tidal and minute volumes as ventilator rates increased progressively from 20 to 150 breaths/min.[25] All the machines tested had maximal effective rates beyond which minute ventilation decreased exponentially. For the compliance and resistance values studied, these maximum effective rates ranged from 75 to 100 breaths/min (Fig. 11-2, *A*). A subsequent animal study showed remarkably similar results. This study also noted that as CMV rates increased and minute ventilation decreased, functional residual capacities progressively increased.[26] Hird et al.[30] studied human neonates and confirmed such gas trapping at higher rates as well, in particular in paralyzed infants. Fontan et al.[28] studied rabbits and saw predictably reduced compliance and tidal volume values at higher rates. When in vitro studies of ventilator performance were repeated using currently available neonatal ventilators, performance was more consistent as rates increased, but marked intra-device variability was demonstrated at similar pressures (Fig. 11-2, *B*).[31] These studies all suggest that CMVs cycling at the upper limits of their frequency range to produce HFPPV require higher, not lower, airway pressures to maintain adequate gas exchange. This apparent violation of conventional wisdom is a stimulus to review some of the determinants of gas transport during mechanical ventilation.

During inspiration, the time required for gas to travel from one end of the airway to the other depends on a ventilator's peak inspiratory pressure (PIP), inspiratory gas flow, and pressure-flow waveforms (compliance of the lung and resistance of the airways). During expiration, the time required for lung emptying depends mainly on lung and chest wall elastic recoil, expiratory resistance, and the ventilator's set positive end-expiratory pressure (PEEP). If inspirations or expirations are long enough, proximal and distal airway pressures equilibrate and gas flow stops. Conditions are static. The volume of gas delivered into or out of the lung is determined by the pressure change in the lung and lung compliance ($\Delta V = \Delta P \times C_L$). As ventilator rates increase, inspiratory and expiratory times decrease. Eventually, there is inadequate time for proximal and distal airway pressures to equilibrate. Gas flow is continuous. Conditions are no longer static. They are dynamic. The volume of gas delivered into or out of the lung becomes a function of flow rate and time.[32,33]

The key timing factors of gas transport depend upon lung compliance and airway resistance. The product of lung compliance and airway resistance, measured in seconds, is called its *time constant* (see Chapter 2). Time constants describe the time it takes for proximal and terminal airway pressures to equilibrate. After one time constant, there is 63% equilibration; after two, 84.5%; after three, 95%. After five time constants, there is 99% pressure equilibration between the proximal and terminal airways.[34] When inspiratory time is shortened beyond three time constants, a pressure gradient develops between the proximal and terminal airways. As inspiratory time becomes shorter, this pressure gradient progressively increases. Because the tidal volume delivered to the terminal airways is also a function of this gradient, it too becomes a function of inspiratory time. As the pressure gradient between the proximal and terminal airways increases, the volume of gas delivered into the terminal airways decreases in a predictable way.

Time constants apply equally to inspiration and expiration. Because airway resistance is always greater during expiration, expiratory time constants are always longer. Experimental evidence suggests that this difference between inspiratory and expiratory resistances increases as ventilator rates increase.[28] Expiratory times less than three time constants do not allow adequate lung emptying and ultimately result in increasing functional residual capacity levels and gas trapping. In summary, because of the high ventilator rates used with HFPPV, inadequate gas delivery during inspiration and incomplete lung emptying during expiration can become two major factors limiting its effectiveness at adequate gas exchange.

One can assess for these limiting factors, because today it is relatively easy to estimate respiratory mechanics and the impact of ventilator manipulation at the bedside.[35-38] Most conventional neonatal ventilators now display measurements of tidal volume, minute ventilation, airway pressures, and respiratory cycle timing, as well as basic measurements of respiratory mechanics. The simultaneous tracings of proximal airway pressures, gas flows, and volume delivery show whether or not time constants are violated and create a potential environment for suboptimal gas exchange and/or gas trapping. For example, when gas flow patterns during inspiration reach a plateau, proximal and distal airway equilibration has occurred and prolonging the inspiratory time beyond this point only serves to increase airway pressures. Conversely, decreasing inspiratory time below this point decreases delivered tidal volume and likely would lead to suboptimal ventilation. Expiratory flow patterns provide similar information

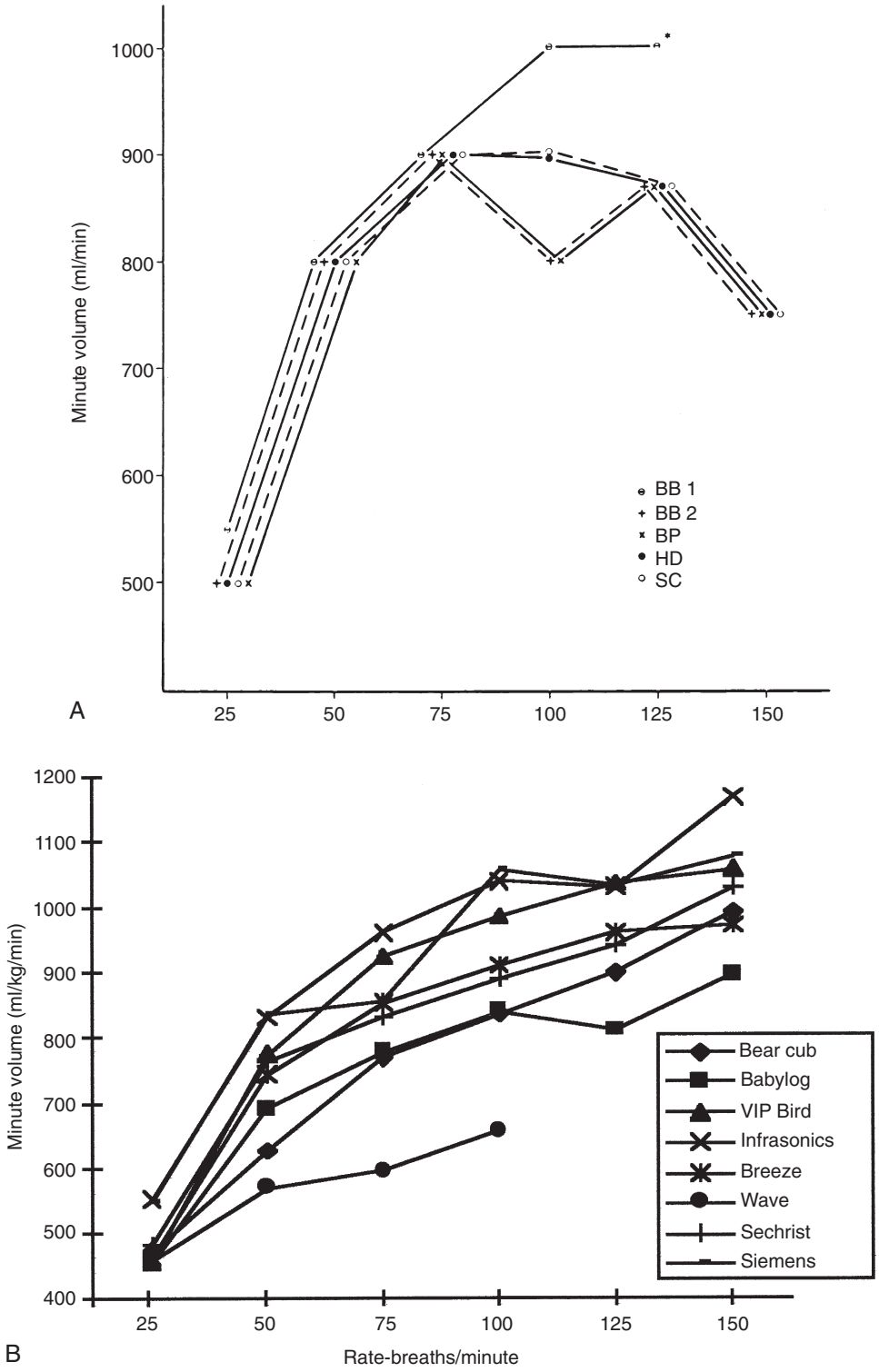


Figure 11-2 ■ Minute volume effects of increasing ventilator rates from 25 to 150 breaths/min (horizontal axis). **A,** Ventilators examined: Babybird 1 (BB1), Babybird 2 (BB2), Bourms BP200 (BP), Healthdyne (HD), and Sechrist (SC). Ventilator settings: peak inspiratory pressure = 25 cm H2O; positive end-expiratory pressure = 5 cm H_2O; inspiratory-to-expiratory ratio (I:E) = 1:2 (beyond 75 breaths/min, BB1 minute volumes were measured at 1:1 I:E ratio; flow = 10 L/min. **B,** Ventilators examined: Bournes Bear Club, Dräger Babylog 300, VIP Bird, Infrasonics Infant Star, Newport Breeze, Newport Wave, Sechrist 100V, and Siemens 300. Studies were performed using a lung simulator at fixed compliance and resistance values: peak inspiratory pressure = 25 cm H_2O; positive end-expiratory pressure = 5 cm H_2O; I:E ratio = 1:2. (**A** from Boros SJ, Bing DR, Mammel MC, et al: Pediatrics 74:487, 1984; **B** from Mammel MC, Bing DR: Clin Chest Med 17:603, 1996.)

regarding lung emptying and gas trapping. Bedside respiratory system mechanics measurements are useful adjuncts to HFPPV (see Chapter 18) and, when used properly, they can accurately predict the clinical effects of HFPPV and prevent inadvertent gas trapping.[38]

High-Frequency Jet Ventilators

High-frequency jet ventilators (HFJV) deliver short pulses of pressurized gas directly into the upper airway through a narrow-bore cannula or jet injector. HFJVs are capable of maintaining ventilation over wide ranges of patient sizes and lung compliances. These systems have negligible compressible volumes and operate effectively at rates from 150 to 600 breaths/min (2.5-10 Hz), with the most common rates, 240 to 420 breaths/min, being less than those typically used in HFOV.[39] Exhalation during HFJV is a result of passive lung recoil. An open ventilator-patient circuit is essential, and the HFJV is used in combination with a CMV to provide optimal oxygenation. Tidal volumes are difficult to measure but appear to be equal to or slightly greater than anatomic dead space.[40]

In addition to tidal volumes delivered through the jet injector, gases surrounding the injector are pulled or entrained into the airway with each jet pulse. The high-flow jet pulse produces a Venturi effect that creates an area of negative pressure at its periphery, entraining ambient gases into the airway. Because of high gas velocities, Venturi effects, and pressure gradients within the delivery system, pressure monitoring is difficult with HFJV. Airway pressures must be measured far enough downstream from the jet injector to minimize Venturi effects. Pressures measured upstream from the jet injector are meaningless unless such effects have been accounted for. Jet ventilation using the Bunnell device is administered via a triple-lumen endotracheal tube adapter. This adapter, shown schematically in Figure 11-3, houses the jet injector port and the pressure monitoring port.

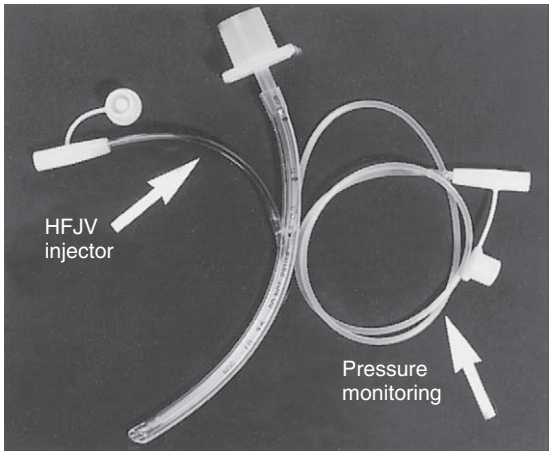


Figure 11-3 ■ Triple-lumen endotracheal tube for use with high-frequency jet ventilation (HFJV; Hi-Lo jet tube, National Catheter Corporation, Division of Mallinckrodt, Inc.). The HFJV infector and pressure monitoring ports are labeled. The pressure monitoring port measures pressure at the distal end of the endotracheal tube; the HFJV infector enters the lumen of the tube approximately 7 cm above the monitoring port.

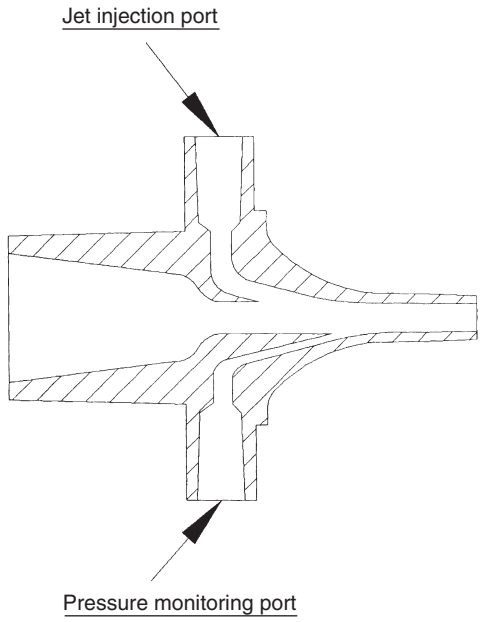


Figure 11-4 ■ Schematic representation of the triple-lumen endotracheal tube adapter designed for use with the Bunnell Life Pulse jet ventilator. This adapter incorporates a standard lumen for connection to a conventional ventilator circuit, a jet injection port, and a pressure monitoring port. This adapter eliminates the need for reintubation prior to initiation of jet ventilation.

Jet ventilators have been tested extensively in laboratory animals and have been used clinically in adults and neonates.[41-54] The Bunnell Life Pulse jet ventilator (Bunnell Inc., Salt Lake City, Utah) was designed specifically for infants (Figure 11-4). Using the triple-lumen endotracheal tube adapter, this device delivers its jet pulse into the endotracheal tube through the adapter's injector port, then servocontrols the background pressure, or driving pressure, of the jet pulse to maintain a constant predetermined pressure within the endotracheal tube. This device is approved for clinical use in neonates and infants. With HFJV, CO_2 removal is achieved at lower peak and mean airway pressures than with either HFPPV or HFO.[3,44,45,55] Although effective in homogeneous lung disorders, such as respiratory distress syndrome (RDS), only one randomized multicenter trial has demonstrated a beneficial pulmonary effect (lower rates of chronic lung disease) with the use of early HFJV over CMV in RDS.[53]

HFJV appears to be most effective in non-homogeneous lung disorders where CO_2 elimination is the major problem, such as air leak syndromes (i.e., pulmonary interstitial emphysema [PIE].)[50] It also appears to be safe and effective when used in neonatal transport and can be used with simultaneous delivery of inhaled nitric oxide (iNO).[56]

High-Frequency Oscillators

High-frequency oscillators (HFOs) are a type of HFV that use piston pumps or vibrating diaphragms, operating at frequencies ranging from 180 to 2400 breaths/min (3-40 Hz), to vibrate air in and out of the lungs.[13,57] During HFOV, inspiration and expiration are both active (proximal airway pressures are negative during expiration). Oscillators produce little bulk gas delivery. A continuous

flow of fresh gas rushes past the source, generating or powering the oscillations. This bias gas flow is the system's only source of fresh gas. A controlled leak or low-pass filter allows gas to exit the system (Fig. 11-5).[57] The amplitude of the pressure oscillations within the airway determine the tiny tidal volumes that are delivered to the lungs around a constant mean airway pressure. This allows avoidance of high peak airway pressures for ventilation as well as maintenance of lung recruitment by avoidance of low end-expiratory pressures.

As with HFJV, pressure monitoring in HFOV is a problem. During HFOV, airway pressures usually are measured either at the proximal end of the endotracheal tube or within the ventilator itself. Many practitioners question the clinical relevance of such measurements, as they are some distance away from the patient; the relationship of intra-pulmonary pressures measured during HFOV to those measured during CMV is difficult to assess accurately. Depending upon the size and resonant frequency of the lung, alveolar pressures can be the same, lower, or even higher than those measured in the trachea.[57-60]

HFOs have been tested extensively in animals and humans.[1,2,4,57-80] Today the most commonly used neonatal HFO is the SensorMedics 3100A oscillator (Cardinal Health, Yorba Linda, Calif.), which is approved for use in both the United States and Canada. This ventilator has been approved for clinical use in neonates and provides ventilation and oxygenation, with no need for combination with CMV like the HFJV. This device produces its oscillations via an electronically controlled piston and diaphragm. Frequency (3 to 15 Hz or 180-900 breaths/min), percent inspiratory time, and volume displacement can be adjusted, as well as resistance at the end of the bias flow circuit (Fig. 11-6). Variations in bias flow rate and the patient circuit outflow resistor control mean airway pressures. Ventilation is proportional to the product of frequency and the square of the tidal volume ($f \times V_T^2$), thus a decrease in frequency or increase in tidal volume by way of an increase in set amplitude should cause increased carbon dioxide removal.[81]

There are other HFOs that are not currently used in the United States. The Hummingbird BMO 20N and Hummingbird II (Senko, Tokyo, Japan) are two fairly well-known HFOs. Both are mechanical piston-driven devices. The BMO 20N was the primary ventilator used in the National Institutes of Health (NIH)–sponsored multicenter HFO-RDS (HiFI) trial. Even though this ventilator was used in a large nationwide clinical trial and currently is used extensively in Japan, it is not approved for clinical use in the United States. Another newer HFO device, the Dräger Babylog 8000 (Dräger Medical, Lübeck, Germany), is approved for use in Canada. This ventilator is based on "membrane oscillation," in which a continuous flow from 10 to 30 L/min is modulated by high-frequency oscillation of the exhalation valve membrane (Fig. 11-7). Frequency (5-20 Hz or 300-1200 breaths/min) and pressure amplitude are adjustable. Mean airway pressure is adjusted by automatic modulation of the active expiration, the continuous flow rate, and alteration of the I:E ratio. This ventilator is unique in its ability to measure and monitor airway pressures and tidal volumes at the airway opening during ventilation. A bench comparison of this device to the SensorMedics 3100A suggests that the Dräger ventilator in its current form is best suited for use in patients weighing less than 1500 to 2000 g because of its inability to generate large enough tidal volumes and variation in I:E ratios with frequency changes.[82]

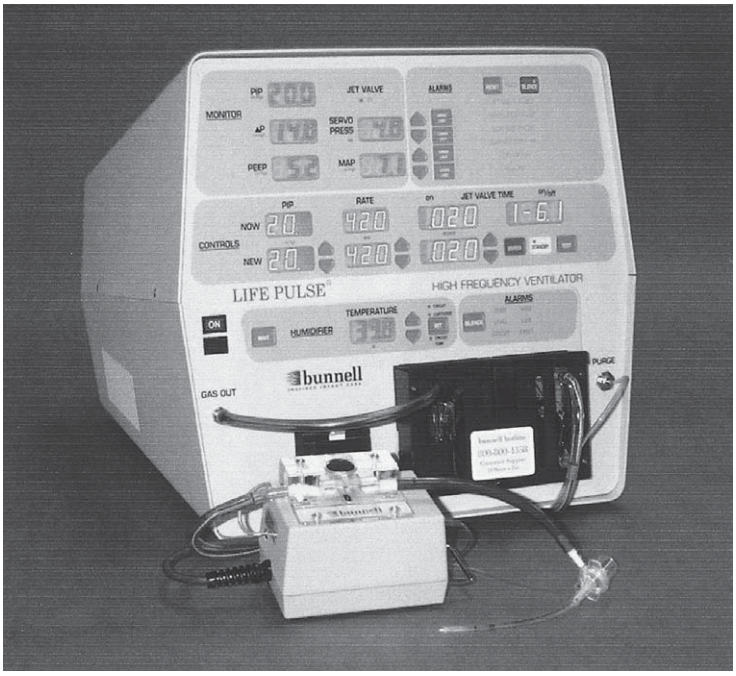
Clinical Applications of HFV

Elective Versus Rescue High-Frequency Ventilation

HFV has been studied in animal models for over 30 years. The majority of animal data supports the superiority of HFV over CMV, both in terms of short-term physiology and pressure exposure, and in lung pathology over days to weeks. Animal studies suggest that HFV works at lower proximal airway pressures than CMV, reduces ventilator-induced lung injury and lung inflammatory markers, improves gas exchange in the face of air leak syndromes, is synergistic with surfactant, and decreases oxygen exposure.* Unfortunately, these findings have not been consistently reproduced in the human studies of HFV versus CMV, either when looking at HFV as an initial, elective mode of ventilation or as a rescue mode of ventilation when CMV has failed to provide adequate gas exchange.

To date there have been 16 randomized controlled clinical trials of elective use of HFV versus CMV for the treatment of neonates with respiratory insufficiency, primarily in babies with respiratory distress syndrome of prematurity.† The studies include HFV in the form of HFPPV, HFJV, and HFOV. The majority of the studies (11 of 16) were unable to demonstrate any significant difference in pulmonary outcomes between babies treated with HFV versus CMV. The remainder of the studies demonstrated a small, yet significant reduction in chronic lung disease (CLD) in the HFV treated groups.[53,69,74,76,78] In 2007, the Cochrane database provided a review and meta-analysis of clinical trials of elective HFOV versus CMV in preterm infants with acute pulmonary dysfunction.[91] The review demonstrated no evidence of effect on mortality and no clear advantage to the preferential use of elective HFO over CMV as the initial ventilation strategy in premature babies with respiratory distress. High volume strategy of HFOV, piston-oscillators, lack of lung protective strategies in the CMV groups, early use of HFO (less than 6 hours), and inspiratory: expiratory ratio of 1:2 was associated with the trials that demonstrated a reduction in chronic lung disease in the HFO groups. The Cochrane Database also reviewed the elective use of HFJV versus CMV, and in the three studies reviewed concluded that there may be a decreased risk of CLD in the elective HFJV groups.[92] However, the authors cautioned these apparent positive findings with the fact that one study had increased adverse neurologic outcomes in the HFJV group. Overall, grouped analysis of all randomized, controlled studies to date would not support the selective use of early and elective HFV over CMV in premature babies with respiratory insufficiency.

*References 1-4, 6, 60, 61, 64, 68, 83-89.
†References 23, 24, 49, 52, 53, 67, 69, 73-80, 90.



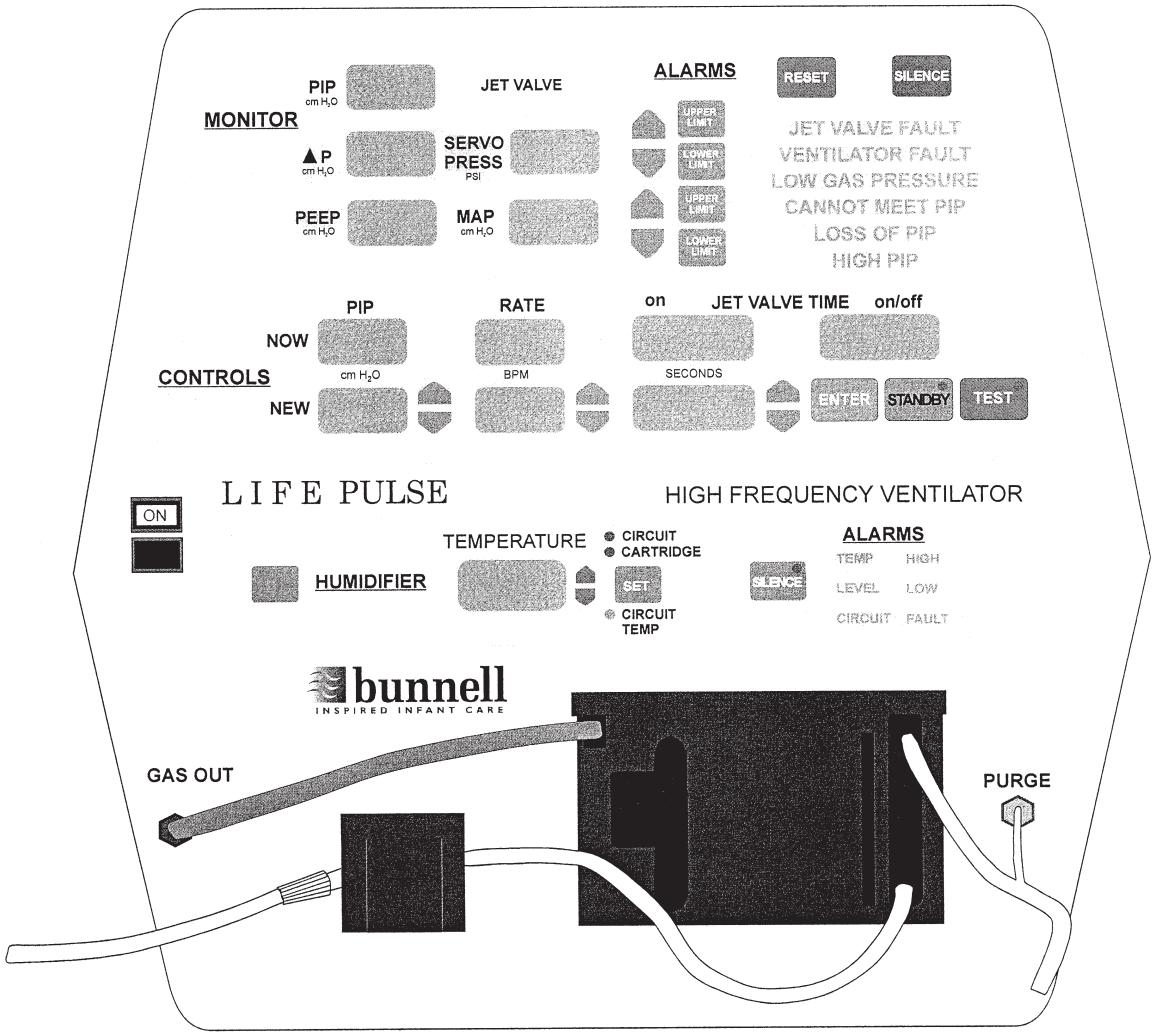


Figure 11-5 ■ The Bunnell Life Pulse jet ventilator. This microprocessor-controlled, pressue-limited, time-cycled ventilator servocontrols delivered airway pressure as measured at the endotracheal tube tip. Frequency range is from 240 to 660 breaths/min. Pressure range is from 8 to 50 cm H_2O. Inspiratory time is adjustable from 0.02 to 0.034 second.

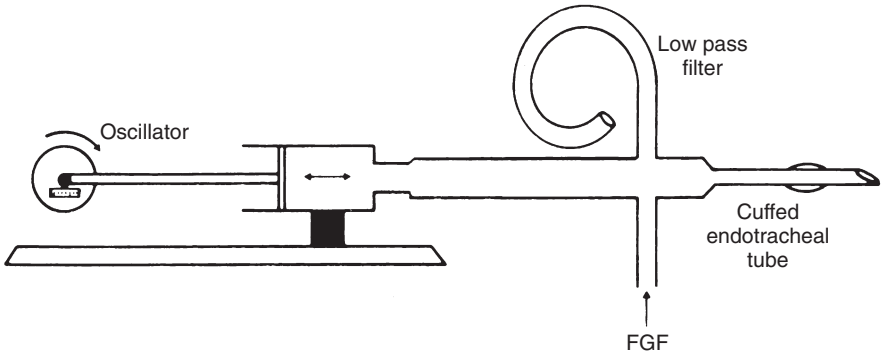


Figure 11-6 ■ High-frequency oscillator. Fresh gases enter the system proximal to the endotracheal tube (FGF). Excess gas and mixed expired gases exit via a low-pass filter. (From Thompson WK, Marachak BE, Froese AB, et al: J Appl Physiol 52:543, 1982.)

One of the early HFV versus CMV studies, the HiFI study, raised concerns as the HFOV-treated group demonstrated increased incidence of intraventricular hemorrhage (IVH) and/or periventricular leukomalacia (PVL).[67] More alarming, the neurodevelopmental outcomes at 16 to 24 months postterm age were significantly worse in the HFO-treated group.[93] Two subsequent large, multicenter, randomized trials by Courtney et al.[76] and Johnson et al.[75] demonstrated no difference in rates of IVH or PVL between the HFOV- and CMV-treated groups. This contradictory data raised concerns for potential users of these modalities. However, recently more data has been published on the long-term neurodevelopment and respiratory outcomes of babies treated with elective HFV versus CMV.

Truffert et al.[94] and Marlow et al.[95] have now provided long-term neurodevelopmental follow-up at 2 years of age from their initial randomized controlled trials of HFOV versus CMV in preterm babies with RDS. Both studies concluded that elective use of HFOV does not portend any worsening of the long-term neurologic status. Truffert and colleagues actually state that early use of HFOV may in fact be associated with a better neuromotor outcome at 2 years of age. Marlow and colleagues also report on long-term respiratory outcomes from their study, and although common in both cohorts, there was no difference in the prevalence of respiratory symptoms between the HFOV- and CMV-treated children. Needless to say, although valuable, this is follow-up data from only two of the many studies performed and more follow-up data is necessary before widespread generalizations can be made regarding predicted long-term outcomes. Again, the short-term and long-term data is conflicting, and this newer follow-up data would not change the supported notion that there is no proven benefit to elective use of HFV versus CMV in babies with pulmonary insufficiency.

So if elective use of HFV has not demonstrated any advantage over CMV, what about the use of rescue HFV when CMV appears to be failing to provide adequate gas exchange? To date, there are four randomized, controlled trials in premature and term infants assessing HFV as a rescue technique after failing CMV.[50,54,96,97] The data set is limited and includes two studies using HFJV and two studies using HFOV. In the two trials treating premature infants, the HiFI trial and Keszler's trial, improvement of ongoing pulmonary interstitial emphysema (PIE) was noted in the HFV groups versus those who remained on CMV; however, there was no difference in overall pulmonary outcomes.[50,96] In the two trials treating older preterm babies (more than 34 weeks), there was notable improvement in gas exchange and treatment success in the HFV groups; however, there was no significant difference in the incidence of CLD or death between those rescued with HFV versus those who remained on CMV.[54,97] Further review of rescue HFV versus CMV in the Cochrane database demonstrates that there is no long-term benefit conferred on the patient by using rescue HFOV or HFJV over continued CMV.[98-100] Of note, most of these HFV rescue trials were performed when the administration of exogenous surfactant and maternal antenatal steroids were not routine standard of care. More importantly, there has been no long-term neurodevelopment or pulmonary outcome follow-up data published from these rescue trials. Therefore, because of the limited number of studies and lack of long-term follow-up data, routine use of rescue HFV over continued CMV would not be supported.

Lung Protective Strategies With HFV: Limiting Pressure While Optimizing Volume

Much progress has been made in the treatment of neonatal respiratory failure over the past few decades. In particular, antenatal steroids and exogenous surfactant replacement have decreased neonatal mortality and morbidity in premature infants.[101-103] However, lung injury and pulmonary morbidities secondary to mechanical ventilation remain an ongoing problem in the care of premature infants. Of most concern, chronic lung disease (CLD) develops in up to one third of preterm infants with respiratory distress syndrome who receive positive-pressure mechanical ventilation.[104] Clearly, dilemmas still remain regarding optimization of both timing and mode of mechanical ventilation to decrease neonatal pulmonary morbidities. HFV has been explored aggressively as a potential ventilation strategy that would avoid the large tidal volumes (volutrauma) and repetitive shear stress of the expansion and collapse with each CMV breath (atelectrauma) that contributes to the development of CLD.

Although the body of literature comparing HFV and CMV is sizeable, it is difficult to compare one study to another because there is significant variation in ventilation strategies. In particular, when meta-analyses are performed, the heterogeneity amongst randomized controlled trials becomes obvious. The meta-analysis performed by Bollen and colleagues[105] demonstrated that variation in ventilation strategies in both the HFV and CMV groups most

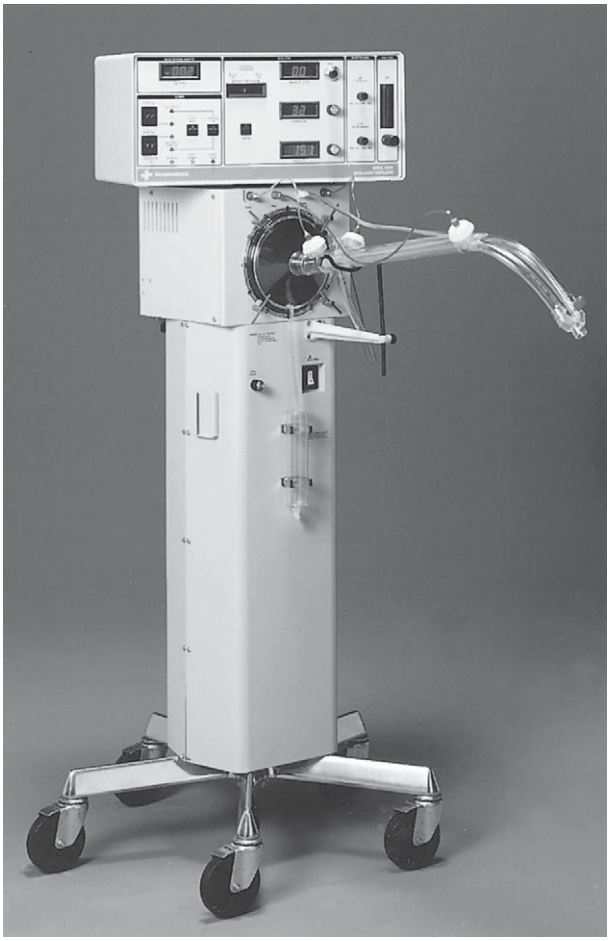
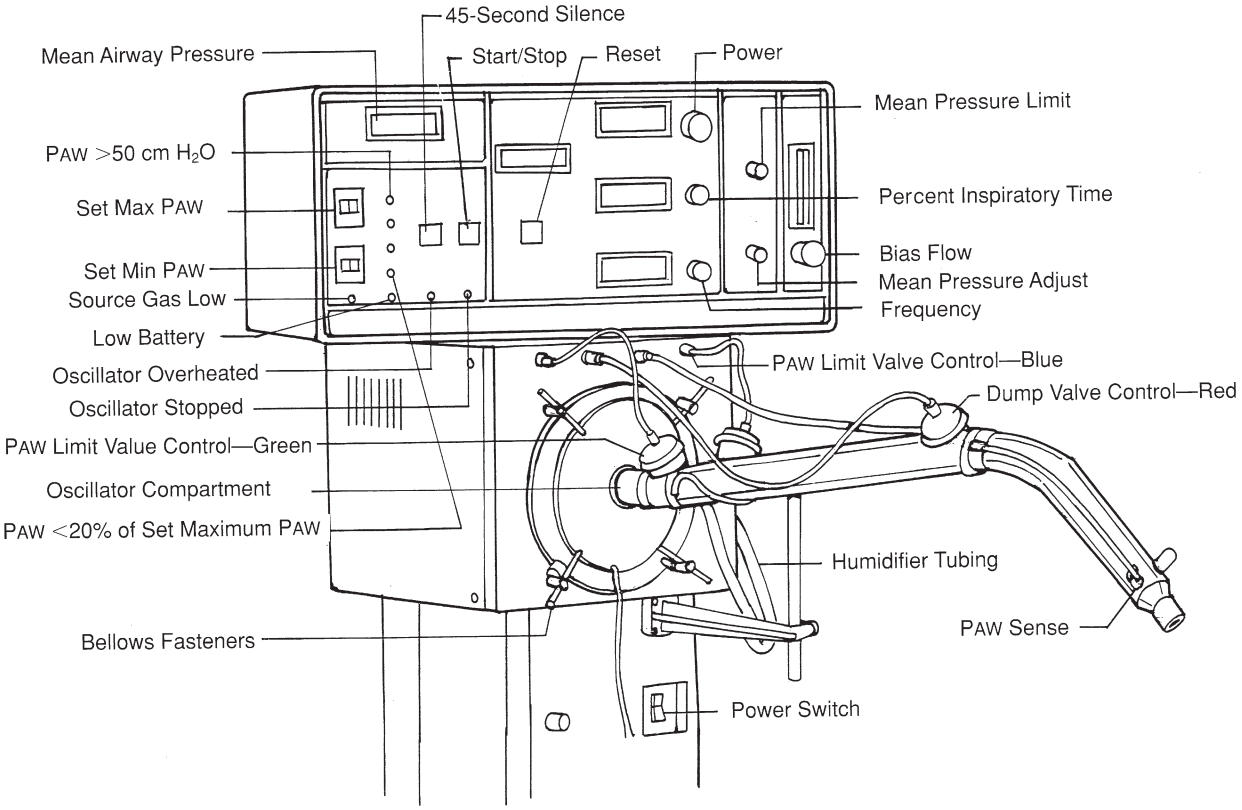


Figure 11-7 ■ The SensorMedics 3100A high-frequency oscillator. This electronically controlled and powered ventilator uses a sealed piston with adjustable volume displacement to generate oscillations into the airway. Frequency is adjustable from 180 to 900 breaths/min (3-15 Hz). Mean airway pressure can be set between 3 and 45 cm H_2O; oscillatory pressure is adjustable to greater than 90 cm H_2O. Inspiratory time can be set from 30% to 50% of the total cycle.



likely explains the observed differences in outcomes as compared with other variables. These findings lead to key questions: Would the outcomes of these studies be different if all had employed similar ventilation strategies, and what would be the most appropriate HFV and CMV ventilation strategies? The search for the optimal lung-protective strategy is ongoing.

Animal models have shown that low tidal volume and increased positive end-expiratory pressure (PEEP) during CMV will lessen ventilator-induced lung injury (VILI).[106-109] With HFV, animal studies have demonstrated that recruiting the lung to ensure open and stable alveoli can attenuate VILI.[86,110] This approach of reducing tidal volume to avoid VILI has been termed *permissive hypercapnia*. The approach of recruiting and stabilizing the open alveoli has been termed *optimal lung volume* or *open lung* strategy. Taken together, these two concepts have been termed *lung protective ventilation*. However, there is much debate as to how to actually employ lung protective ventilation strategies at an infant's bedside, because there are no strict criteria or guidelines and much of the guiding data is from adult literature.[111,112] Nonetheless, most studies and reviews refer to an "open lung" strategy when there is a predefined F_{IO_2} target of 0.25 to 0.40 or less being targeted as a surrogate for optimal lung recruitment.[113,114] To that end, tidal volumes of less than 7 mL/kg with high ventilator rates and "permissive hypercapnia" on laboratory evaluation are generally considered to be "lung protective" with the goal to limit lung volume and alveolar overdistension (see Chapters 13 and 15).

HFV on the surface would appear to be an ideal ventilator for a lung protective strategy because it delivers very small tidal volumes at low airway pressures while maintaining lung recruitment around a constant mean airway pressure. The fact is the randomized clinical trials to date do not demonstrate benefits of HFV over CMV in terms of long-term morbidities and mortality.[1,92,98-100,105] These findings, or lack thereof, have been ascribed to the inconsistent, and at times, poorly defined ventilation strategies in both the HFV or CMV arms.[115,116] Although we have many ventilator tools, there is little neonatal data to guide us down one "best path" for optimum treatment. Thus ventilation strategies vary greatly from NICU to NICU across North America and the world. Astutely, Van Kaam and Rimensberger[116] point out three key research questions that have yet to be answered in neonates: (1) Is low tidal volume CMV less injurious to the lung than traditional tidal volumes, (2) would recruitment maneuvers and higher levels of PEEP further optimize low tidal volume CMV, and (3) would the use of HFV over CMV demonstrate decreased morbidities and mortality if the same lung protective strategy was used in both groups? If these questions are resolved, the "best path" may become clearer in the future.

Applications of HFV in Specific Diseases

Respiratory Distress Syndrome

Respiratory distress syndrome (RDS) continues to be the primary form of respiratory failure requiring treatment with mechanical ventilation in neonates. Treatment of acute RDS is based on principles of lung volume recruitment and optimization, and is described in detail below.

Air Leak Syndromes

Today HFV is generally accepted as a safe and effective treatment for severe pulmonary air leaks. This application was one of the original clinical uses of HFV, sometimes with dramatic results (Fig. 11-8).[43,44,63] There are very few randomized controlled trials evaluating the management of air leak syndromes with HFV versus CMV. A British trial compared the incidences of pulmonary air leaks in 346 neonates treated with either HFPPV or CMV. Twenty-six percent of the infants treated with CMV developed air leaks compared to 19% of those who received HFPPV.[22] Mortalities, durations of ventilation, and incidences of CLD and intraventricular hemorrhage were similar. Keszler et al.[50] compared HFPPV and HFJV in 144 infants with severe PIE. Sixty-one percent of those treated with HFJV improved compared to only 37% treated with HFPPV. Forty-five percent of those who did not respond to HFPPV and were transferred to HFJV improved, whereas only 9% of the infants who did not respond to HFJV and were transferred to HFPPV improved. In addition, HFJV appeared to ventilate patients using lower proximal airway pressures. In another multicenter HFOV-RDS trial (the HiFO study), the effect of HFOV in the treatment of air leak was examined.[96] Air leaks, either PIE or pneumothorax, were present in 26 (30%) of 86 patients randomized to HFOV and in 22 (24%) of 90 patients randomized to CMV. Although a low-pressure strategy might be presumed in a study of this type, HFOV patients still required higher airway pressures for gas exchange. Air leaks occurred in 42% of HFOV patients who entered the study without air leak compared to 63% of CMV patients ($p < 0.05$). Although HFOV patients who entered the study with air leaks tended to do better than their counterparts treated with CMV, the differences were not significant.

Of all the forms of HFV considered thus far, HFJV has been the most successful with respect to the incidence and treatment of air leak syndromes. All things considered, most forms of HFV appear to lessen the incidence of ventilator-associated pulmonary air leaks and improve the outcome of preexisting pulmonary air leaks. The question remains, why do pulmonary air leaks improve during HFV? One theory is that HFV produces smaller pressure fluxes within the distal airways. Pressures in the upper airway equilibrate and gas is delivered distally at a more constant distending pressure. Pressure differentials between airway and intrapleural space lessen. There is less stretching of the injured tissue. Less gas escapes during peak inspiration and there are greater opportunities for self-repair.

The low occurrence rates of bronchopleural and tracheoesophageal fistulas in neonates preclude the ability to perform adequate randomized clinical trials of management with HFV versus CMV. However, a few studies have formally evaluated the amount of air leak through these types of fistulas using HFV versus CMV. In the management of infants with bronchopleural fistula, Gonzales and colleagues[117] showed a decrease in chest tube air leak when using HFJV versus CMV. Goldberg et al.[118] and Donn et al.[119] report similar experiences in managing infants with

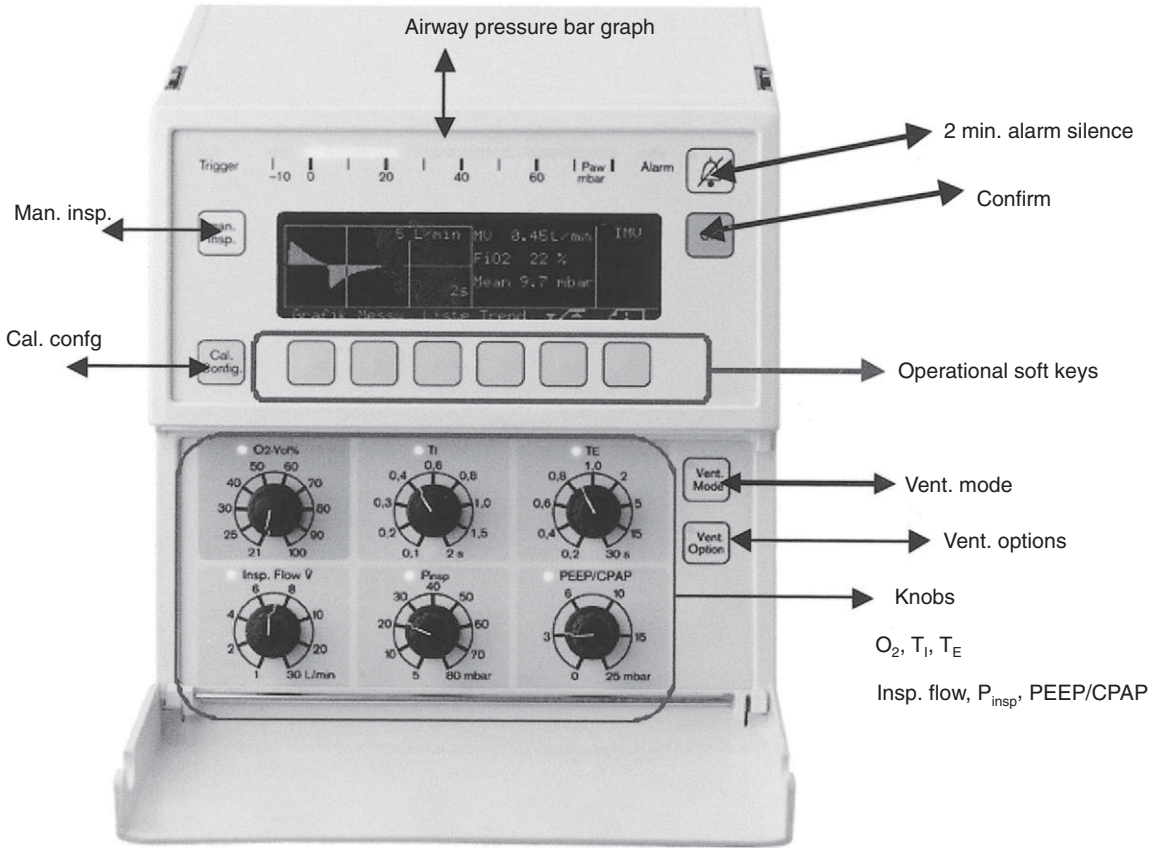


Figure 11-8 ■ The Dräger Babylog 8000 neonatal ventilator. This ventilator provides both conventional and high-frequency ventilation using the same platform. Frequency is adjustable from 0 to 1200 breaths/min (0-20 Hz). Mean airway pressure is adjusted using the positive end-expiratory pressure/continuous positive airway pressure (PEEP/CPAP) control knob. Amplitude is set from 0% to 100%, with the resulting delivered pressures and tidal volumes displayed. Pressures, respiratory cycle timing, tidal and minute volumes, and basic respiratory system mechanics are measured or calculated during ventilation and displayed. Peak pressure is adjustable from 1 to 80 cm H_2O; PEEP from 0 to 25 cm H_2O. Ventilator functions are selected using the vent mode, vent option, and operational soft keys.

tracheoesophageal fistulas with HFJV. Furthermore, case reports, such as that by Bloom et al.,[16] and animal studies, such as that by Orlando et al.,[120] relay findings of an observed benefit to the use of HFV in the ventilatory stabilization of patients with tracheoesophageal or bronchopleural fistula. Although these findings are positive, the lack of randomized controlled trials makes it difficult to provide an evidence-based recommendation for the use of HFV over CMV in the treatment of bronchopleural or tracheoesophageal fistulas. As such an evidence base may never exist, the evidence available does support a trial of these therapies in these difficult conditions when more conventional approaches are failing.

Pulmonary Hypoplasia, Persistent Pulmonary Hypertension, and Inhaled Nitric Oxide

Infants with various forms of pulmonary hypoplasia may derive at least some short-term benefit from HFV. Some of these infants have associated, equally lethal, abnormalities. In such situations, HFV may provide a brief respite for diagnostic studies to identify potential survivors or confirm diagnoses for family members. In congenital diaphragmatic hernia (CDH), HFV may be a useful "bridge" therapy to cannulation for extracorporeal membrane oxygenation (ECMO). In the hypoplastic lung, because the number of gas-exchanging units is small, it is only logical to assume that ventilation at rapid rates using low tidal volumes would be most effective. Because of the variety of conditions associated with pulmonary hypoplasia and their relative rarity, controlled studies are difficult to design or perform, and clear evidence-based guidelines simply are not available.

Infants with pulmonary hypoplasia associated with CDH may derive some benefit from HFV. To date there are no controlled studies, only clinical anecdotes. There are many early case reports of infants with pulmonary hypoplasia associated with CDH treated with HFV. Most of the patients improved initially but had poor long-term outcomes if the hypoplasia was severe.[44,121] In most of the patients, arterial blood gas measurements improved at lower proximal airway pressures; however, few patients survived. These reports predated ECMO.

Carter et al.[122] studied 50 infants referred for ECMO who were first treated with HFOV. Forty-six percent improved and did not require ECMO. Four infants had pulmonary hypoplasia associated with CDH. None responded positively to HFOV. All required ECMO. Baumgart et al.[123] reviewed results of 73 neonatal ECMO candidates who first were treated with HFJV. Nine infants had pulmonary hypoplasia associated with CDH; only three survived. deLemos et al.[124] reviewed the outcomes of 122 neonatal ECMO candidates first treated with HFO.

Fifty-three percent did not require ECMO; however, only 5 of 20 patients who had pulmonary hypoplasia associated with CDH responded positively to HFOV and did not require ECMO. A smaller series of 12 infants, described by Stoddard and colleagues,[125] showed much better outcomes with HFO. Eleven of the 12 babies with CDH did not require ECMO and ultimately survived. Migliazza and colleagues[126] report in their retrospective review of 111 babies with CDH that treating these babies with early HFOV as part of the preoperative stabilization minimizes pulmonary morbidities. Despite reports of success, overall, HFV has not been terribly successful in the treatment of severe pulmonary hypoplasia associated with CDH, at least as an independent treatment. As with other forms of pulmonary hypoplasia, however, HFV often can stabilize critically ill patients until their ultimate prognosis becomes clear. Another common use of HFV is in conjunction with inhaled nitric oxide (iNO) as a treatment for severe respiratory failure secondary to persistent pulmonary hypertension. Detailed discussion regarding the current evidence to support this combined therapy in preterm and term neonates can be found in Chapter 14.

Clinical Guidelines

Most clinical guidelines are, by their nature, arbitrary; they reflect the experiences, biases, and at times, idiosyncrasies of their authors. Many clinicians do not consider HFV first-line therapy in the neonatal population; however, many quickly move to it when problems develop during CMV.[127] Some practitioners use HFV early in the course of uncomplicated RDS. Likewise, some wean to extubation from HFV. Others choose a return to CMV prior to extubation. Because of these many clinical variations and the lack of data from which to generalize, the following guidelines must be tempered by experience and modified as new information becomes available. What follows is a description of HFV use in a variety of situations, using two different HFV strategies: (1) limiting pressure exposure, which is used in air leaks and most other rescue situations; and (2) optimizing lung volume, which is used in RDS or other conditions where diffuse atelectasis is a major issue.

Limiting Pressure Exposure

High-Frequency Jet Ventilators

The only high-frequency jet ventilator (HFJV) currently in general use for neonates is the Bunnell Life Pulse. With this machine, initiating HFJV is always the same, regardless of the clinical condition. First, the endotracheal tube hub is replaced by an adapter. The adapter can be used with an endotracheal tube as small as the standard 2.5-mm tube. Patients are then reconnected to the CMV at their previous settings. The jet ventilator is activated and set in its standby mode. The jet injector and pressure monitoring lines are connected to their respective ports on the endotracheal tube. The ventilator's internal pressure transducers now measure airway pressures within the endotracheal tube. These values appear on the ventilator's front panel. They are the baseline CMV settings. When CMV rates and airway pressures are not extremely high, pressures measured at the proximal and distal ends of patients' endotracheal tubes usually are similar. During HFJV, however, these pressures often are quite different. Airway pressures should be measured at the adapter or endotracheal tube tip. Once baseline airway pressures are established, arterial blood gases should be analyzed. The HFJV rate initially is set at 420 breaths/min, using the shortest possible inspiratory time of 0.02 seconds (these are the default settings programmed into the ventilator). PIP is set at the same level used during CMV. End-expiratory pressure is controlled by the PEEP control and background flow of the CMV circuit.

Many use a CMV background or "sigh" rate of 5 to 10 breaths/min to maintain lung volume and prevent atelectasis, which is a common problem during low tidal volume–constant airway pressure ventilation. Little information is available regarding the effectiveness of this strategy. During HFOV with the Dräger Babylog in an animal model, "sigh" breaths were useful during lung recruitment but not after recruitment was complete.[128] The PIP of the CMV background breaths should be lower than the PIP of the HFJV breaths. If it is not, these background breaths will interrupt the cycling of the HFJV. When treating respiratory failure unaccompanied by significant air leaks, we set mean airway pressure (Paw) at the same level or higher than that used during CMV; this is accomplished by adjusting the PEEP level on the associated conventional ventilator. When treating air leak syndromes, we use lower Paw levels than that when on CMV, usually lowered by 2 cm H_2O, and do not use CMV background rates. Once HFJV settings are established, mean airway pressures should adjusted as necessary to maintain a balance between the lowest possible pressure and oxygen exposure.

After initiating HFJV, some patience is required. During HFJV, airway pressures equilibrate more slowly than during CMV. One must allow adequate time for the system's servomechanisms to adjust the HFJV driving pressure to achieve the targeted pressures. Patients usually stabilize within 15 to 30 minutes. After this initial equilibration period, interval arterial blood gases are measured. Usually CO_2 elimination improves, and it does so at lower mean airway pressures. Oxygen requirements may transiently increase. Because this strategy is designed to minimize pressure exposure, increases in F_{IO_2} may be necessary to eliminate air leaks. Most commonly, HFJV is a rescue therapy; relatively short-term exposure to HFJV (generally a few days) often will result in substantial clinical improvement. As patients improve, HFJV peak inspiratory pressure (HFJV-PIP) can be decreased in increments of 1 to 2 cm H_2O while ideal pH and P_{aCO_2} values are maintained. One should also aim to decrease F_{IO_2} levels as arterial oxygen saturation values allow. As "weaning" progresses, expect to see radiographic evidence of losses in lung volume. There is often an HFJV-PIP "threshold," usually 8 to 10 cm H_2O below previous maximum HFJV-PIP values, at which blood gas values progressively deteriorate, likely reflecting a significant loss in lung volume. If this occurs, a CMV background "sigh" rate of 5 to 10 breaths/min with an increase in HFJV-PIP levels of 2 to 4 cm H_2O may help resolve this problem. After stabilization for several hours, HFJV-PIP level may again be decreased. When HFJV-PIP values are below 20 cm H_2O and F_{IO_2} values fall below 0.4, consider returning to total CMV support.

As mentioned above, using a pressure-limiting strategy will usually result in an increase in the F_{IO_2} required on HFJV versus CMV. Likely, the increased oxygen requirements are the result of less than optimal lung volume. This is by design; the assumptions underlying this therapeutic approach are that allowing some loss of lung recruitment will hasten the resolution of air leak, although this has never been studied. In fact, there are no published data to guide us in assessing whether this planned reduction in overall lung volume will add to potential lung injury from atelectrauma while helping to lessen air leaks via the lower-pressure strategy. In practice, we will still target an F_{IO_2} of 40% or less during this type of treatment. As in homogenous lung disease, alterations in Paw followed by radiographic evaluation and blood gas assessment are our best surrogates for producing and assessing changes in lung volume and oxygen requirements.

The mechanics of returning to CMV are simple. Set the jet ventilator to standby mode. Set the CMV rate to 60 breaths/min (an arbitrary number). Adjust CMV-PIP levels to deliver tidal volumes of 4 to 6 mL/kg or use a volume-targeted CMV mode. Adjust F_{IO_2} levels as necessary to maintain arterial oxygen saturation values greater than 85%. If, after returning to CMV, the patient's general condition worsens or F_{IO_2} or P_{aCO_2} levels increase significantly, consider a return to HFJV for at least another 24 hours. The response to a variety of clinical situations is summarized in Table 11-2.

High-Frequency Oscillatory Ventilators

Today the most commonly used neonatal high-frequency oscillatory ventilator (HFOV) is the SensorMedics 3100A. With this device, in contrast to HFJV, use of an endotracheal tube adapter is not necessary; infants receive HFOV and CMV through the same endotracheal tube. Initial HFO frequency for a premature infant is commonly set between 10 and 15 Hertz. This ventilator's "power" control sets the amplitude of its airway pressure oscillations (ΔP), the prime determinant of CO_2 removal. Increasing airway pressure amplitude increases chest wall movement and decreases P_{aCO_2} values. Decreasing airway pressure amplitude decreases chest wall movement and increases P_{aCO_2} values. Initially, the amplitude control is set at a level that adequately produces "jiggling" of the chest and abdomen; often it can be as high as 35 to 40 cm H_2O. Some physicians simply use a visual assessment as to adequacy of the chest wall movement to set the initial amplitude value and others use an amplitude value of approximately double the mean airway pressure as a starting point and adjust as necessary for adequate chest wall movement. After assessment of the initial P_{aCO_2} value on HFOV, the amplitude is then adjusted up or down as necessary to produce the desired P_{aCO_2} levels, with assessment of P_{aCO_2} values every 15 to 30 minutes until stabilized within the goal range. One should take note of the ratio of the amplitude to airway pressure, because air trapping may be evidenced by the need for an amplitude value that is more than three times the airway pressure.

During HFOV (as well as HFJV), airway pressure, or Paw, is the main determinant of lung volume. Small changes in Paw can produce large changes in lung volume, either overdistension or atelectasis. The airway pressures are measured within the oscillator circuit, not in the endotracheal tube or proximal airway. These pressures may or may not reflect the actual pressures within the patients' airways. Airway pressures are rapidly damped across the HFO circuit and further within the airways (Fig. 11-9). Once the desired oscillatory amplitude is established, Paw is adjusted to equal or exceed that used during CMV. Once the patient stabilizes and/or starts to improve, airway pressures should be decreased; Paw, if P_{aCO_2} values are normal and arterial oxygenation is adequate at F_{IO_2} levels less than 0.4 to 0.5; and ΔP, if P_{aCO_2} levels are subnormal. During HFOV weaning, there often is a Paw threshold, similar to the PIP threshold seen during HFJV, at which patients suddenly develop respiratory acidosis or show labile oxygen requirements. This threshold usually appears when mean airway pressures reach between 8 and 10 cm H_2O. When this occurs, consider a 1 to 2 cm H_2O increase in Paw to stabilize lung volume. If things do not improve, a brief (15- to 30-second) increase in mean airway pressure of 5 to 10 cm H_2O simulates a sustained inflation maneuver as used in the laboratory to re-recruit the airways. When continuously measured S_{aO_2} or P_{aO_2} increases to the desired level, pressures are returned to baseline. Although some clinicians extubate patients directly from HFOV, very little

TABLE 11-2 Gas Exchange and Ventilator Adjustments During High-Frequency Ventilation

Problem	HFOV	HFJV
Inadequate oxygenation with atelectasis/ poor lung expansion on x-ray	Increase Paw by 1-2 cm H_2O *or* SI, then decrease after improvement	Increase Paw or SI Add IMV "sigh" breaths with increased PIP during IMV
Inadequate oxygenation with lung overexpansion on x-ray, ± hypercarbia	Decrease Paw by 1-2 cm H_2O Repeat x-ray	Decrease Paw and IMV rate until MAP falls by 1-2 cm H_2O Repeat x-ray
Hypercarbia with normal lung volumes on x-ray	Increase amplitude/power or decrease frequency	Increase PIP or increase rate if PIP at maximum
Hypocarbia	Decrease amplitude/power or increase frequency	Decrease PIP or increase Paw
Hyperoxia	Decrease F_{IO_2} to 0.3- 0.4 or less, then Paw	Decrease F_{IO_2} to 0.3-0.4, then Paw (or IMV rate if present)

HFOV, High-frequency oscillatory ventilator; *HFJV*, high-frequency jet ventilator; *HFPPV*, high-frequency positive-pressure ventilator; *IMV*, intermittent mandatory ventilation; *PEEP*, positive end-expiratory pressure; *PIP*, peak inspiratory pressure; *SI*, sustained inflation; *Paw*, mean airway pressure.

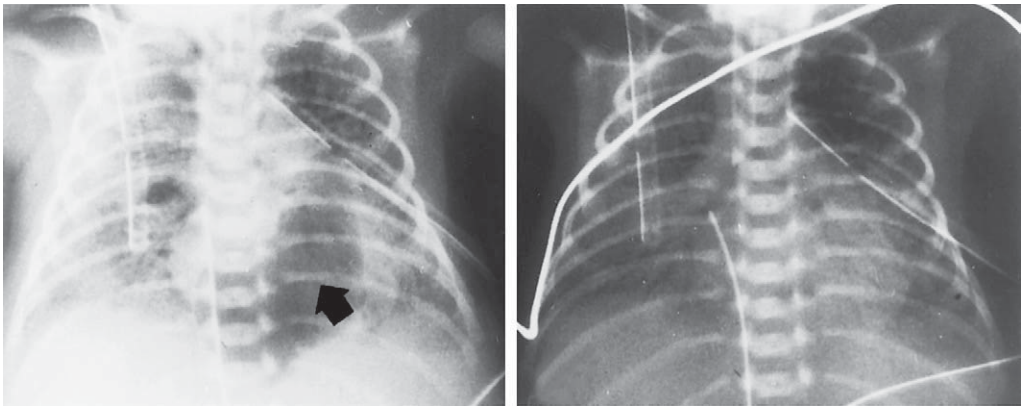


Figure 11-9 ■ Chest roentgenogram of a 1300-g infant with severe hyaline membrane disease before (**A**) and 4 hours after (**B**) high-frequency jet ventilation (HFJV). Pulmonary interstitial emphysema and air trapped within the pulmonary ligament (*arrow*) markedly decreased after HFJV. (From Pokora T, Bing D: Pediatrics 72:27, 1983.)

published data exists regarding this technique. Others return patients to CMV and wean to the point of extubation using conventional techniques. Responses to a variety of clinical situations are summarized in Table 11-2.

Optimizing Lung Volume

The strategy for optimizing lung volume is critical. As was described previously in this chapter, adequate recruitment of lung volume may be the key to protection and preservation of lung architecture as well as to potentiate exogenous surfactant.[84,88,110,129,130] Because lung volumes are difficult to assess at the bedside, other surrogates must be employed. Respiratory inductive plethysmography (RIP) has been studied in animals and recently in neonates to define the inspiratory and expiratory pressure-volume (P-V) relationship.[131,132] A study in lambs reported direct estimation of lung volume change during HFV using RIP.[132] Although more precise and informative than Sa_{O_2} measurements, RIP is not yet part of mainstream neonatal ventilator management. Therefore, Sa_{O_2} measures and chest x-ray expansion are used most commonly as surrogates for changes in lung volume. Although a bedside, direct volume measure would be desirable, none is currently available; however, Sa_{O_2} has been shown to be an acceptable alternative.[114,131]

Currently there are two established techniques for optimizing lung volume during HFV: sustained inflation (SI) and gradually increased mean airway pressure. The first strategy uses sustained lung inflations at relatively high mean airway pressures (15 to 30 seconds in duration) at varied intervals.[65,84] The second strategy involves gradual stepwise increases in mean airway pressures until arterial oxygen saturation values increase significantly.[68,69,74-76] The SI technique for lung recruitment, which has been studied extensively in the laboratory during HFOV and found to be extremely effective, has not been widely introduced into clinical practice. A number of reasons may account for this clinical reluctance. Because the SI rapidly recruits volume, which is difficult to measure at the bedside, the lung might be inadvertently overdistended. The rapid increase in intrathoracic pressure could impair cardiac output or adversely alter intracranial blood flow. Stepwise gradual pressure increases may prevent these problems. Still, a technique that fully inflates the lung, allowing ventilation to move from the inspiratory limb of the pressure-volume curve to the expiratory limb, should facilitate effective ventilation and oxygenation at lower pressures by exploiting the physiologic advantages of lung hysteresis. The delineation of an individual patient's pressure-volume relationship is still difficult, but has been done successfully in neonates (Fig. 11-10).

With SI, the lung may be maximally inflated, moving ventilation onto the expiratory limb of the pressure-volume (P-V) relationship. This then allows maximal preservation of lung volume at lower pressures, with the potential for the greatest protection from VILI. The lung changes

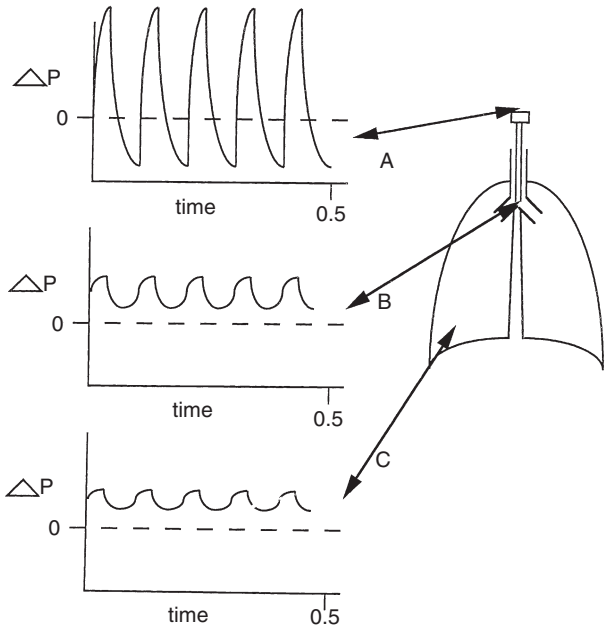


Figure 11-10 ■ Airway pressure drip across the airway using high-frequency oscillatory ventilation, adapted from unpublished observations using the SensorMedics 3100A. **A,** Pressure measured at the proximal endotracheal tube. **B,** Pressure measured at the carina. **C,** Pressure measured in the distant airways.

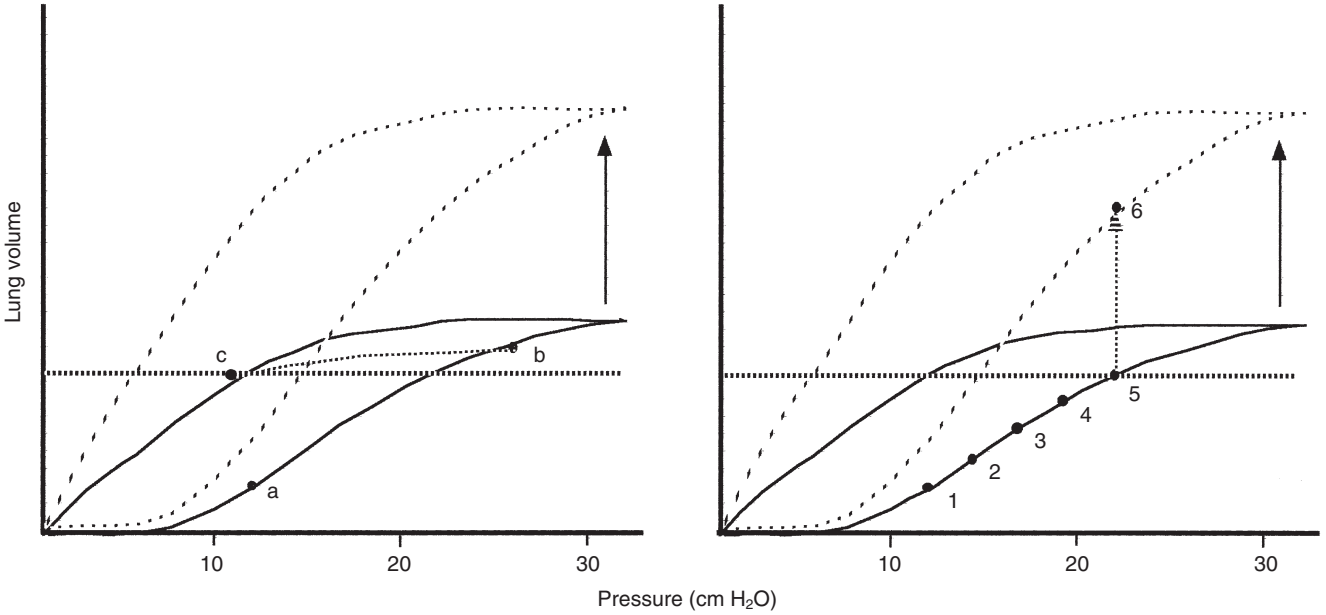


Figure 11-11 ■ Schematic representation of two different approaches to achieving alveolar expansion and the theoretical effect of a sudden improvement in lung compliance. The horizontal dashed line indicates the desired mean lung volume. The solid curve is a pressure-volume (P-V) relationship of a surfactant-deficient lung prior to the development of structural injury. The dashed line shows the P-V curve of the lung after some recovery has occurred. In the left panel, a brief sustained inflation from opening pressure (point a) to pressure point b inflates the lung to the desired volume. Pressure is then decreased to point c, moving to the deflation limb of the curve. In the improved lung, volume at point c is still maintained within the desired range at low pressure. In the right panel, progressive increases in mean airway pressure occur on the inflation limb (points 1-5). Target volume is achieved but at higher pressure. If the lung then improves, rapid overdistension could occur when pressure is maintained but volume increases (point 6). (Adapted from Froese AB: Neonatal and pediatric ventilation: Physiological and clinical perspectives. In Marini JJ, Slutsky AS (eds): Physiological Basis of Ventilatory Support. New York, Marcel Dekker, 1998, p. 1346.)

rapidly during the course of illness; theoretically, providing ventilation on the descending limb of the P-V relationship, as seen with SI, offers potential protection from these rapids changes. Figure 11-11 schematically demonstrates this potential advantage using basic physiologic principles.

High-Frequency Jet Ventilators

High-frequency jet ventilation (HFJV) is initiated as previously described. The only difference in this strategy from the previous pressure-limiting strategy is the higher Paw levels used, initially 2 cm H_2O higher than that used during CMV, with adjustments targeted to recruit lung volume and decrease oxygen requirements. In surfactant deficiency syndromes, surfactant is administered either immediately after intubation or during CMV. At this time, there is no convincing evidence that surfactant administration is either more efficient or safer during any form of HFV, although adequate volume recruitment prior to instillation clearly improves surfactant distribution and function.[129,130] Again, a triple-lumen adapter is attached to the existing endotracheal tube. The jet ventilator is activated and set to its standby mode. Inspired oxygen concentrations are maintained at the same level used during CMV. Set HFJV rates at 420 breaths/min and inspiratory times at 0.02 second. Initially, HFJV-PIP levels are the same as those used during CMV. PEEP levels are adjusted on the conventional ventilator to produce mean airway pressures 2 to 3 cm H_2O higher than those used during CMV. Mean airway pressure levels are increased in increments of 1 to 2 cm H_2O until arterial oxygen levels no longer increase. When initial recruitment is complete, PIP levels must be weaned rapidly to avoid hypocarbia. When oxygen saturation levels are satisfactory, an initial decrease in Paw of 2 cm H_2O is made to prevent overdistension and to shift the P-V relationship to the expiratory portion of the curve. Then F_{IO_2} rather than Paw should be decreased to prevent atelectasis. When F_{IO_2} levels fall to 0.4 or less, further decreases in Paw and PIP may be made.

HFJV removes CO_2 very efficiently, possibly more so than HFO.[56,57] If hypocarbia and alkalosis develop, decreasing PIP seems to be the best remedy. If F_{IO_2} requirements increase, it is likely a consequence of diminished lung volume. Remedies here include stepwise increases in Paw, a brief SI, or adding a CMV background "sigh" rate. Use of a background IMV rate of 3 to 5 breaths/minute provides a simple and quick way to assess adequacy of lung volume recruitment. If addition of this slow IMV rate, with ventilator PIP 2 to 3 cm H_2O below that set during HFJV, results in a fall in F_{IO_2} over the next 30 minutes, this is an indication that more recruitment of lung volume (through an increase of 1-2 cm H_2O in Paw) should be tried. The slow IMV rate is left unaltered for 15 to 30 minutes after making this Paw change, then it is discontinued. If F_{IO_2} remains stable, sufficient lung volume recruitment has been achieved. If F_{IO_2} falls after discontinuation of IMV, this suggests that further recruitment is necessary. A technique for finding optimal Paw levels is shown in Table 11-3. When Paw falls to 8 to 10 cm H_2O and PIP levels to less than 20 cm H_2O, an attempt to return to CMV may be made in the fashion previously described. Alternatively, one can continue to decrease Paw to 6 to 7 cm H_2O. If F_{IO_2}

TABLE 11-3 Optimal Mean Airway Pressure During High-Frequency Jet Ventilation

	IMPACT OF CHANGE	
Change Made	**Sao_2 Goes Up or Unchanged**	**Sao_2 Goes Down**
Add IMV rate	Paw is inadequate Raise PEEP 1-2 cm H_2O, wait for SaO_2 to stabilize at new level, then stop IMV rate again to test new Paw level	Paw is adequate May be impeding cardiac output or causing lung overdistension; stop or reduce IMV rate
Stop IMV	Paw is adequate Maintain IMV = 0, or go to 1-3 breaths/min with smaller tidal volume and modest I-time	Paw is inadequate Return to IMV rate = 5-10 and raise PEEP 1-2 cm H_2O; wait for SaO_2 to stabilize at new level; then try to stop IMV again to test new Paw level

IMV, Intermittent mandatory ventilation; *Paw*, mean airway pressure; *PEEP*, positive end-expiratory pressure.

remains 30% or less, some clinicians would extubate directly to nasal CPAP.

High-Frequency Oscillatory Ventilators

Although the goal of treatment is different, use of high-frequency oscillatory ventilators (HFOVs) is similar to the techniques described for minimizing pressure exposure. The key difference is that higher, not lower, mean airway pressures are applied early. The ventilator frequency and amplitude is set as previously described; Paw initially is set 2 to 3 cm H_2O higher than that used during CMV. Recruitment of lung volume may be accomplished by Paw increases in increments of 1 to 2 cm H_2O until oxygen saturations rise to greater than 95% (or measured arterial oxygen levels no longer rise), or by increasing Paw by 5 to 10 cm H_2O above baseline for 10 to 30 seconds as an SI maneuver. HFOV is continued during the SI. Using either technique, mean airway pressure should be reduced after improvement in oxygenation is seen. As noted earlier, this will maximize the effects of lung hysteresis. If stepwise pressure increases are used, reduction in Paw in increments of 1 to 2 cm H_2O is made every 1 to 2 minutes. Just as the initial pressure increases begin to show effect above the lung's opening pressure, oxygenation should be easily maintained as long as pressures remain above the lung's closing pressure. Because neither of these procedures can be accurately predicted and lung volume changes can only be estimated, careful clinical observation at the bedside is the only solution. After lung recruitment and pressure adjustment, decrease F_{IO_2} to less than 0.4, and then continue to wean Paw. Amplitude is adjusted upward, then rate downward, for CO_2 retention, and vice versa for hypocarbia. Increasing oxygen requirements suggest either impaired cardiac output or loss of lung volume. When mean airway pressures fall to 8 to 10 cm H_2O, consider returning to CMV in the fashion previously described or proceeding to extubation from HFOV as pressures continue to fall.

Problems, Complications, and Questions Without Answers

Will HFV become the preferred means of support for neonates with respiratory failure? To date, there is inadequate information to make this leap. There are a number of practical problems associated with the clinical use of any HFV. Although approved for general use, HFVs are still, in many respects, experimental devices. Each HFV system is different. Generalizations and recommendations developed for one system may or may not apply to the next.[82,133] There are few standards; however, high-frequency ventilation, whether in the form of HFPPV, HFOV, or HFJV, is used in virtually all neonatal intensive care units today. Many different HFV systems are in use around the world; a "best" device has not been identified. HFJV and HFOV can be extremely effective in many different clinical situations, but both systems have their complications and their limitations.

In the absence of a good technique for monitoring lung volumes at the bedside, can HFV produce lung overdistension by quietly trapping gas? We know HFV produces higher end-tidal volumes at lower proximal airway pressures.[134] Increased end-tidal lung volumes would seem to mean increased end-tidal alveolar pressures. Under such circumstances, Paw exceeds mean proximal airway pressures. Such silent distending pressure is commonly referred to as *inadvertent PEEP* (see Chapter 2). Because this pressure cannot be easily measured, the extent to which it produces problems is a conundrum. In some circumstances, it probably causes substantial difficulty with ventilation.

Does HFV produce lung underdistension? Under normal circumstances, small monotonous tidal volumes delivered at relatively constant pressures result in progressive atelectasis. Early HFOV primate studies document that this does occur. To combat this problem, many clinicians periodically vary tidal volumes using either manual or mechanical "sigh" breaths or periodic SI maneuvers. These techniques recruit alveoli and prevent atelectasis. Is this a better technique than simply increasing Paw? What is the best way to vary tidal volume during HFV? Is SI better than gradual increases in Paw? A bedside technique for rapid accurate assessment of changes in lung volume is needed to resolve these issues. The studies to fully answer these questions have yet to be done.

High-frequency techniques initially were frequently associated with previously rare complications. A number of early reports linked tracheal inflammation and tracheal obstructions to various forms of HFV.[43,44,135-137] These complications were serious and at times fatal. They occurred in both adults and neonates. Initially these lesions were

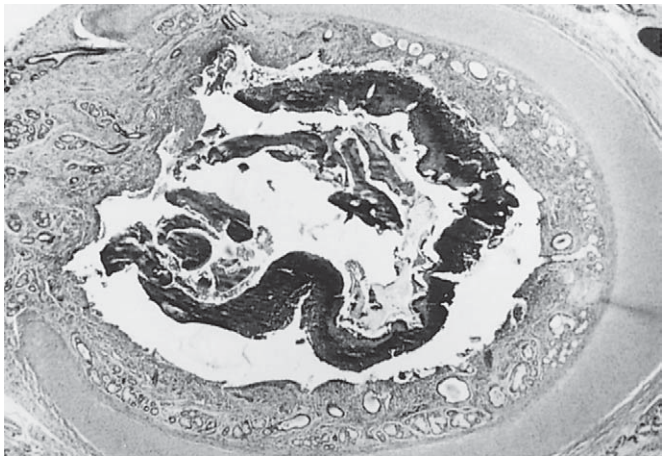


Figure 11-12 ■ Photomicrograph of fatal necrotizing tracheobronchitis. This section was obtained from the trachea just above the carina. The entire mucosal surface has become necrotic and completely obstructs the tracheal lumen.

believed to result from inadequate humidification of respiratory gases. This no longer appears to be the entire answer. Ophoven et al.[138] compared the tracheal histopathology seen in animals after CMV and HFJV using different humidification systems. Although humidity was important, regardless of the humidification system used, HFJV always produced more inflammation and damage in the proximal trachea than did CMV. The histologic injury patterns observed in these animals were virtually identical to those seen in human patients exposed to HFJV.

Similar animal studies compared the tracheobronchial histopathology seen after HFPPV, HFJV, and CMV.[139] HFJV and HFPPV produced nearly identical tracheal lesions. This unique tracheal injury now is referred to as *necrotizing tracheobronchitis (NTB)* (Fig. 11-12). This problem has been extensively studied in the laboratory. It now appears that NTB is associated with a number of factors and occurs during all forms of HFV. Ventilator rates and ventilatory strategies, airway humidification, F_{IO_2} levels, the severity of the underlying illness, duration of ventilation, alterations in epithelial permeability, and infections all seem to play roles.[55,140-148]

A review from the presurfactant era suggested that between 2% and 4% of HFV-treated patients have either clinical or microscopic evidence of NTB.[138] No data is available to assess the impact of surfactant administration on the incidence of NTB. Although it also occurs during CMV, NTB continues to be more likely during HFV. Acute hypercapnia, respiratory acidosis, and a sudden decrease in chest wall movement during HFV signal possible NTB until proven otherwise. Aggressive airway suctioning, use of airway bronchoscopy and reintubation can be potentially life saving. In practice, we rarely see acute NTB today, likely due to both improved equipment and a low threshold for reintubation when early CO_2 retention is detected.

The most serious potential side effect of HFV is an increase in long-term neurologic injury resulting from early periventricular leukomalacia or severe intraventricular hemorrhage. This concerning finding, originally reported in the HiFI trial, was also seen in a study of HFJV reported by Wiswell et al.[52,67] These injuries seem to be linked to the strategy of ventilation used in these studies. Neither of these studies delineated a standardized technique for lung volume recruitment and alkalosis during treatment was common. As noted previously in this chapter, meta-analysis of randomized trials of HFV has concluded that, in studies using a "high lung volume" strategy, there is no evidence of increased neurologic injury. Clearly, the dictum of *primum non nocere* should be followed here.

Summary

HFV is an exciting and useful form of mechanical ventilation. In some circumstances it can produce gas exchange at lower airway pressures than during CMV, and it allows safer application of high mean airway pressures when necessary for oxygenation. This technique is superior to CMV in airway leak syndromes and may be a useful rescue technique and/or bridge to ECMO. It has clear but limited usefulness as a rescue or temporizing measure in pulmonary hypoplasia, persistent pulmonary hypertension, and other forms of neonatal respiratory failure unresponsive to CMV. In neonatal RDS, HFV, perhaps in association with surfactant therapy, may yet play a major role in improving long-term pulmonary outcomes. Today HFV is no longer a treatment in search of a disease, but neither is it the panacea for all forms of neonatal respiratory failure that many initially hoped it would be. Although HFV is a now-standard method of neonatal respiratory support, we still need larger, randomized, controlled studies with extremely detailed ventilatory strategies to address how we can best apply this therapy across the spectrum of newborn respiratory illness.

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12 Special Ventilation Techniques I: Patient-Triggered Ventilation

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Advances in ventilator technology have extended the application of techniques that were not previously available in the neonatal intensive care unit to newborns who require mechanical ventilation for respiratory support. This chapter reviews two of these techniques: synchronized ventilation and pressure-support ventilation (PSV). These neonatal ventilatory modalities have become popular for the management of infants with respiratory failure.

Synchronized Ventilation

The development and implementation of mechanical ventilation are the events most closely associated with the emergence of modern neonatal intensive care. Although assisted ventilation has been the mainstay of treatment for patients with respiratory failure of all causes, it has not been free of complications in the newborn. Although the term *assisted ventilation* has been used, mechanical ventilators available since the mid-1960s used intermittent mandatory ventilation (IMV), and they essentially function independently of the infant. Time-cycled, pressure-limited (TCPL) ventilators deliver a mechanical breath at a preset interval, irrespective of the spontaneous ventilatory effort of the infant. It is therefore not surprising that infants often exhibit asynchronous or dyssynchronous breathing, during which their own spontaneous breaths are out of phase with the mechanically delivered breaths.

Asynchrony may result in several deleterious effects. Efficiency of gas exchange may be impaired when an infant attempts to exhale against positive pressure or, alternatively, when an infant attempts to inhale during the exhalation phase of the mechanical cycle.[1] Asynchrony has been shown to contribute to air trapping and pneumothorax, thus increasing pulmonary morbidity and prolonging recovery.[2] Even central nervous system function may be adversely impacted.[3] Perlman et al.[4] demonstrated that preterm infants who were breathing asynchronously with mechanical ventilation displayed tremendous variability and irregularity of both arterial blood pressure waveforms and cerebral blood flow velocity, which were associated with a high incidence of intraventricular hemorrhage. They also reported that these abnormalities could be ablated with the use of pancuronium, presumably because it prevents the infant from "fighting" the ventilator, but this is obviously not a satisfactory long-term solution (see Chapter 28).

Until relatively recently, clinicians have had limited means to deal with asynchrony. One mechanical method was to reduce the arterial carbon dioxide tension ($PaCO_2$) by increasing the ventilator parameters (especially ventilatory rate and pressure) in an attempt to "capture" the infant (i.e., decreasing $PaCO_2$ will suppress respiratory drive). Alternatively, pharmacologic agents, such as sedatives, analgesics, and even anesthetics, were used to alter or suppress spontaneous breathing. Ultimately, agents such as pancuronium or curare were sometimes used to induce pharmacologic paralysis. Each of these maneuvers is not without potential risks to the infant, including barotrauma, drug toxicity, and even skeletal muscle atrophy.[5] It was finally shown that asynchrony could be correctable if the patient's spontaneous effort and the onset of mechanical inspiration could be coordinated. Indeed, patient-triggered ventilation (PTV), which achieves synchronization between spontaneous and mechanical breaths, had been in use for many years in adult and older pediatric populations, but technologic limitations precluded its use in the neonatal population until only the last two decades.

Advances in microprocessor technology and ventilator design have overcome the obstacles in detecting and responding to the spontaneous effort of even the smallest preterm infants. These advances have enabled clinicians to use synchronized ventilation in the neonatal intensive care unit and have allowed the prospect of reducing pulmonary morbidity and improving outcomes for newborns who require mechanical ventilation. Synchronized ventilatory modes are characterized by the delivery of a mechanical breath in response to a signal derived from the patient representing spontaneous respiratory effort. Collectively, these modes have been referred to as PTV and include *synchronized intermittent mandatory ventilation (SIMV)*, *assist/control (A/C) ventilation*, and *PSV*. Hybrid modalities of ventilation are also being used in clinical practice.

Intermittent Mandatory Ventilation

Figure 12-1 shows the relationship between spontaneous and mechanical breaths during intermittent mandatory ventilation (IMV). When synchrony occurs, it is merely a random event. Even if the infant initiates a breath simultaneously with mechanical inspiration, differing inspiratory times may result in the development of asynchrony during the expiratory phase. For some breaths, the infant may be attempting to exhale against the full pressure of a mechanical inspiration.

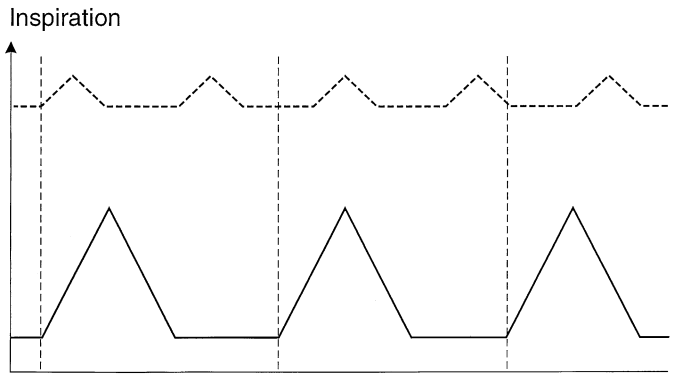

Figure 12-1 ■ Intermittent mandatory ventilation. The upper graph represents spontaneous patient breaths, and the lower graph represents mechanical ventilator breaths. Note the random occurrence of synchrony, because patient and ventilator essentially function independently of one another. (Courtesy David Durand, MD.)

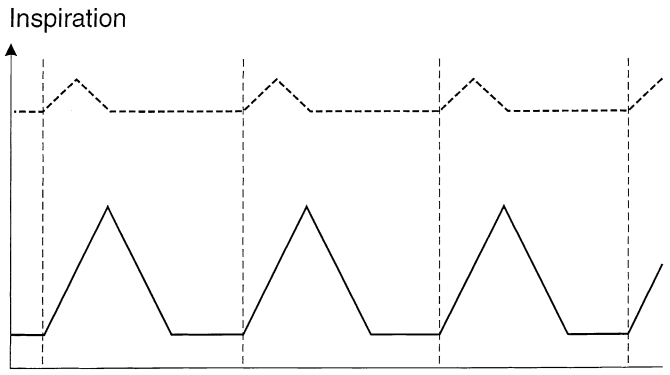

Figure 12-3 ■ Assist/control ventilation. The upper graph represents spontaneous patient breaths, and the lower graph represents mechanical ventilator breaths. Each spontaneous breath that meets threshold criteria results in the delivery of a nearly simultaneous mechanical breath; however, expiratory asynchrony occurs when inspiratory times for the patient and ventilator are not identical. (Courtesy David Durand, MD.)

Synchronized Intermittent Mandatory Ventilation

In synchronized intermittent mandatory ventilation (SIMV), the mechanically delivered breaths are synchronized to the onset of spontaneous patient breaths. During SIMV, the patient may breathe spontaneously between mechanical breaths from the continuous bias flow in the ventilatory circuit, but these breaths are supported only by positive end-expiratory pressure (PEEP). Figure 12-2 shows the improvement SIMV offers over IMV. Each mechanical breath is initiated in response to the onset of the patient's own respiratory effort; this results in inspiratory synchrony. However, unless the inspiratory times are identical, the patient may terminate his or her own effort and begin exhalation while the ventilator is still in the inspiratory phase. This again results in partial asynchrony.

Assist/Control Ventilation

Additional improvement in synchronized ventilation is achieved through the use of assist/control (A/C) ventilation. This mode involves either the delivery of a synchronized mechanical breath each time a spontaneous patient breath meeting threshold criteria is detected (assist) or the delivery of a mechanical breath at a regular rate in the event that the patient fails to exhibit spontaneous effort (control). This is shown schematically in Figure 12-3. Note that spontaneous and mechanical breaths have been completely synchronized to the onset of inspiration; however, once again, expiratory dyssynchrony may occur if the breath is time cycled. This problem can be overcome with the use of a second signal detection system that determines when patient inspiratory effort is about to cease and then synchronizes the termination of the mechanical breath to this event. This is referred to as *flow cycling*, in which a flow-derived signal is also used to terminate inspiration and to permit the total synchronization of spontaneous and mechanical breaths throughout the entire respiratory cycle (Fig. 12-4). The patient and ventilator are completely in phase for every breath.

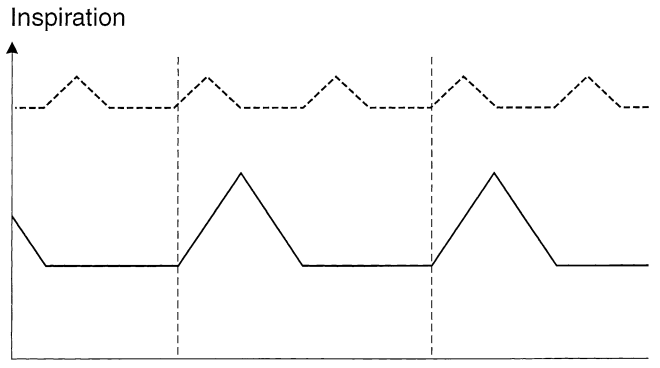

Figure 12-2 ■ Synchronized intermittent mandatory ventilation. The upper graph represents spontaneous patient breaths, and the lower graph represents mechanical ventilator breaths. The onset of mechanical inspiration is synchronized to the onset of patient inspiration; the patient breathes spontaneously between mechanical breaths. Note that dyssynchrony can develop during the expiratory phase because the inspiratory times of the patient and ventilator differ. (Courtesy David Durand, MD.)

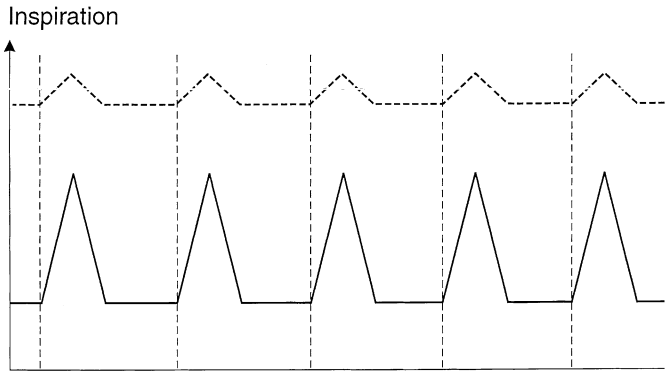

Figure 12-4 ■ Assist/control ventilation. The upper graph represents spontaneous patient breaths, and the lower graph represents mechanical ventilator breaths. This system synchronizes inspiration by sensing patient effort. It also synchronizes expiration by terminating inspiration in response to a decline in airway flow. This results in complete synchronization of the functioning of the baby and ventilator throughout the entire respiratory cycle. (Courtesy David Durand, MD.)

Signal Detection

The key element involved in the success of any synchronized system is the ability to detect the onset of the spontaneous inspiratory effort of the patient and to respond immediately with the delivery of a mechanical breath. The signal "event" needs to be an accurate measure of respiratory effort, but it should minimize any artifacts that may result from other sources. Signals have been derived from abdominal movement, thoracic impedance, and airway pressure or flow changes.

Detection of abdominal movement requires the use of an applanation transducer, such as the Graseby capsule, which is affixed to the abdominal wall.[6] The placement of the transducer is critical to its proper performance and often requires replacement if the patient's position changes. In addition to being subject to movement artifact (such as hiccups), this system may not work in all infants, especially those who lack paradoxical chest and abdominal movements. It is not possible to measure tidal volumes directly, and there is no expiratory synchronization. However, autocycling does not occur (see later), and although the technique is relatively easy to master, the methodology has largely been abandoned.

Recording of thoracic impedance signals requires placement of electronic leads on the chest wall.[7] Drying of the electrode gel and erroneous lead placement may interfere with appropriate signal detection, and tidal volume measurement is not possible. The Sechrist SAVI ventilator (Sechrist Industries, Anaheim, Calif.,) detects thoracic impedance signals. Again, this technique seems to have fallen in popularity since its inception.

Two methods for processing flow-derived signals presently are available. The first involves the use of a hot wire anemometer to convert temperature differences to flow volumes.[8] This method is used in the AVEA ventilator (Viasys Healthcare, Yorba Linda, Calif.), shown in Figure 12-5. Another method uses a variable orifice differential pressure transducer (pneumotachograph) for detection of minute changes in airway flow (as little as 0.2 L/min).[9] Both methods enable the measurement of tidal volume, use of flow changes to synchronize expiration, and adjustment of trigger sensitivity to compensate for endotracheal tube leaks. The last of these features is particularly desirable because one disadvantage of flow-derived signals is autocycling, in which endotracheal tube (or other) leaks may be erroneously interpreted by the system as spontaneous effort, and this error can result in false triggering of mechanical breaths. Use of the flow-derived signal also allows for complete inspiratory and expiratory synchronization by flow cycling. This feature measures the decline in inspiratory airway flow. The clinician can adjust the flow termination point to end a mechanical breath when flow declines to 0% to 25% of peak flow (Fig. 12-6). This is clinically advantageous in preventing gas trapping and inversion of the inspiratory/expiratory ratio when a baby is breathing very rapidly. Clinicians should be aware of the distinction between *flow triggering* (in which changes in airway flow initiate a mechanical breath) and *flow cycling* (in which changes in airway flow terminate the inspiratory phase of a mechanical breath).

Figure 12-5 ■ AVEA ventilator. (Photo courtesy Viasys Healthcare.)

Changes in airway pressure may create a signal that can be used to trigger ventilation.[10] One such system was incorporated in the Newport Wave E200 ventilator (Newport Medical Instruments, Inc., Newport Beach, Calif.), but a subsequent model of this device, the E500Wave, now incorporates flow triggering. It is more difficult for a baby to trigger with a pressure signal than with a flow signal.

Table 12-1 summarizes the triggering methods. Advantages and disadvantages of each are shown.

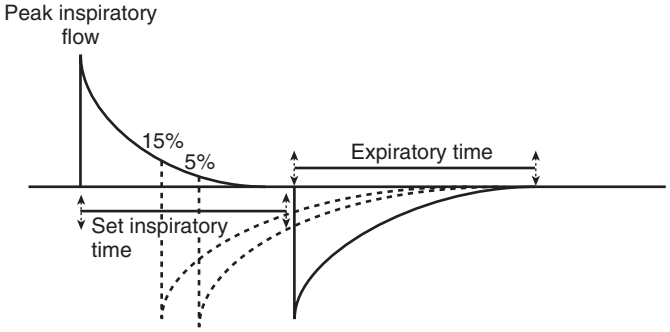

Figure 12-6 ■ Flow cycling. The graph represents the relationship between flow and time for one ventilator cycle. Flow termination refers to a point on the decelerating inspiratory flow curve at which expiration is triggered; it is a percentage of peak inspiratory flow. The higher the termination setting (e.g., 15%), the shorter the inspiratory time; conversely, the lower the termination sensitivity setting (e.g., 5%), the longer the inspiratory time. If the breath was time-cycled, the inspiratory phase would end after the set inspiratory time (*solid line*).

TABLE 12-1 Patient-Triggered Ventilation: Trigger Signals

Signal	Detector	Typical Response Times (msec)	Advantages	Disadvantages
Abdominal motion*	Applanation transducer (Graseby capsule)	40-60	Ease of use; no autocycling; one sensitivity setting only	Placement critical; requires paradoxic chest/abdomen movement; artifactual triggering; no tidal volume measurements
Airway flow	Differential variable orifice	25-50	Ease of use; expiratory synchrony; measures tidal volumes and minute ventilation	Autocycling (lower); patient must exceed trigger pressure transducer
	Heated wire anemometer	5-100	Ease of use; measures tidal volumes and minute ventilation	Autocycling (higher); patient must exceed trigger threshold
Airway pressure	Pressure transducer	40-100	Ease of use	Higher trigger threshold
Thoracic impedance*	Electrocardiogram leads	40-80	Ease of use; active expiration terminates inspiratory cycle	Erroneous lead placement; drying of contact gel; no tidal volume measurements

*Infrequently used.

Trigger Delay

Trigger delay, also referred to as the *system response time*, is the interval between signal detection and the rise in pressure at the proximal airway. For a system to work well, trigger delay must be minimal. As an example, a baby whose own inspiratory time is 0.2 second (200 msec) will already be halfway through the inspiratory phase if the trigger delay is longer than 100 msec. Thus, the longer the trigger delay, the higher the work of breathing.

Clinical Problems

Although PTV represents a major advance in technology, several potential clinical problems may arise with its use. False triggering may occur under several circumstances. Systems using abdominal movement, for instance, may inappropriately respond to nonrespiratory motion, such as hiccups (which also can be problematic for flow and pressure triggering). Systems that use changes in airway pressure or flow to detect inspiratory effort are prone to autocycling, which results in the inadvertent delivery of a mechanical breath. Autocycling may result from the presence of excessive condensation ("rainout") in the ventilator circuit or from endotracheal tube leaks. Among three tested flow-triggered ventilators, the V.I.P. BIRD had the lowest rate of autocycling from endotracheal tube leaks in an earlier study.[11] Autocycling also can occur with detection of cardiac impulses by systems that trigger as a consequence of changes in thoracic impedance.[7]

More important, *failure* of a ventilator to trigger represents a significant clinical problem. It can occur under any circumstance in which the patient does not achieve threshold sensitivity, or it may be a system mechanical problem. Improper placement of the Graseby capsule or chest leads, failure of detection of very small spontaneous breaths, or obstruction or occlusion of transducers all may result in failure to detect patient effort.

Some of the current ventilators appear to perform better in one mode than another. The Babylog 8000 (Dräger, Lübeck, Germany), for example, was shown to have a higher reliability of triggering in SIMV than in A/C ventilation. However, it also produces more asynchronous breathing in SIMV than either the Bear Cub/CEM (Viasys Healthcare, Yorba Linda, Calif.) or the Infant Star with STAR SYNCH SIMV (Infrasonics, San Diego, Calif.).[8] Recent refinements in computer software have overcome many of these problems.

Some of the popular infant ventilators offering patient triggering in the United States are listed in Table 12-2. In addition to available modes and type of signal detector, other features are described.

Clinical Applications

Virtually every form of SIMV or A/C ventilation has been shown to improve gas exchange and eliminate or markedly decrease asynchronous ventilation in the newborn infant. Figure 12-7 shows the impact of synchronization on pulmonary mechanics testing. Note that during IMV (Fig. 12-7, *A*), pressure-volume and flow-volume loops demonstrate tremendous breath-to-breath variability in delivered tidal volumes, despite relatively constant peak inspiratory pressures. During SIMV (Fig. 12-7, *B*), there is considerable improvement in the consistency of the mechanical breaths. When the ventilatory mode is switched to A/C (Fig. 12-7, *C*), complete synchronization is achieved, and each breath is nearly identical. These mechanical changes have been shown to result in improved oxygenation, but without concomitant increases in mean airway pressure and without adverse effects on ventilation. In addition, many ventilators now offer PSV combined with pressure-targeted and volume-targeted SIMV to attain full synchronization during spontaneous breathing that is mechanically supported.

Early clinical experience with PTV suggested that prolonged support of the very-low-birth-weight infant (gestational age less than 28 weeks) might not be feasible because of patient fatigue. Mitchell et al.[12] reported a clinical observation of 22 preterm infants treated consecutively with the SLE 250 Newborn ventilator (SLE Instruments, Surrey, UK) in the patient-triggered mode. The trigger threshold of the device was a change in flow exceeding 0.4 L/min. A control breath was delivered in the event of the occurrence of apnea lasting 7 seconds (thus an effective control rate of only 8.5 breaths/min). Eight of the 22 infants could not tolerate PTV. The median gestational age was 27 weeks and

TABLE 12-2 Patient-Triggered Infant Ventilators

Ventilator	Manufacturer	Modes	Proximal Flow Sensor	Monitor Interface
AVEA	Cardinal Health (Yorba Linda, Calif.)	Pressure (A/C, SIMV) Volume (A/C, SIMV) TCPL (A/C, SIMV) CPAP/pressure support	Yes (hot wire anemometer)	Color display, touch screen Waveforms, loops, trends, monitor screen
Evita 4	Dräger Medical (Lübeck, Germany)	BiPAP (pressure A/C, SIMV) Volume (A/C, SIMV) Autoflow MMV CPAP/PSV APRV	Yes (hot wire anemometer)	Color display, touch screen Waveforms, loops, trends
Galileo	Hamilton Medical (Bonaduz, Switzerland)	Pressure (A/C, SIMV) Adaptive pressure ventilation (A/C, SIMV) Pressure support DuoPAP APRV	Yes (differential pressure)	Color display, touch screen Waveforms, loops, trends
Servo-*i*	Maquet Critical Care (Solna, Sweden)	Pressure (A/C, SIMV) Volume (A/C, SIMV) PRVC (A/C, SIMV) CPAP/pressure support/volume support Auto mode NIV/NCPAP BiVent (APRV)	Yes (differential pressure)	Color display, touch screen Waveforms, loops, trends

A/C, Assist/control; *APRV,* airway pressure release ventilation; *BiPAP,* biphasic positive airway pressure; *CPAP,* continuous positive airway pressure; *DuoPAP*, dual positive airway pressure ventilation; *MMV,* mandatory minute ventilation; *NIV,* noninvasive ventilation; *PRVC,* pressure-regulated volume control; *PSV,* pressure-support ventilation; *SIMV,* synchronous intermittent mandatory ventilation; *TCPL,* time-cycled, pressure-limited.

the median birth weight was 1080 g in this group compared with 32 weeks and 1600 g, respectively, in the successfully treated group.[12] In a follow-up study by Hird and Greenough,[13] 56 infants with a median gestational age of 29 weeks were examined for the causes of failure of PTV. Factors found to affect PTV adversely included development of expiratory asynchrony, long trigger delays, very short inspiratory times, and use of PTV early in the course of disease.[13] These investigators also compared the Dräger Babylog 8000 ventilator with the SLE 250 Newborn system and found a shorter trigger delay in the former. Again, difficulty was encountered in maintaining support of infants with a gestational age less than 28 weeks because of a lack of sustained spontaneous breathing during the acute phases of respiratory distress syndrome.[14]

Technologic advances solved the problem of providing adequate support for the extremely preterm infant. Improvements in trigger sensitivity and provision of an adequate control rate during A/C ventilation have extended the benefits of synchrony to even the smallest patients. Visveshwara et al.[7] summarized a 3-year experience with PTV using a prototype of the Sechrist SAVI, which uses thoracic impedance to both initiate and terminate mechanical breaths. Although this experience was nonrandomized and historically controlled, PTV was associated with a shorter duration of mechanical ventilation and oxygen therapy. It also was associated with a decreased incidence of severe intraventricular hemorrhage. Infants who were included in this observation had birth weights that ranged from 450 to 1250 g. Among the six infants who could not be maintained on PTV, two had apnea (one from sepsis and one from grade IV intraventricular hemorrhage), one had seizures, and three had insufficient respiratory effort.[7]

Servant et al.[9] investigated the prototype flow synchronizer that eventually was incorporated into the V.I.P. BIRD infant/pediatric ventilator.[9] This study examined the safety and feasibility of applying flow-synchronized A/C ventilation to a group of preterm infants in the recovery phase of respiratory distress syndrome. Patients weighing 480 to 1400 g were studied during consecutive 1-hour periods of IMV, A/C ventilation, and IMV and were compared for multiple variables. During flow-synchronized A/C ventilation, infants exhibited a higher total rate of mechanical breaths (as a result of triggering) and improved oxygenation (at the same mean airway pressure); no adverse effects on ventilation, tidal volume, or vital signs were seen. The study also evaluated the performance of an expiratory trigger, which stopped the inspiratory phase of a mechanical breath when inspiratory flow decreased to 25% of peak flow. This enabled complete synchronization, even in expiration. When the expiratory trigger function isused, the breath is flow-cycled and the patient sets his or her own inspiratory time.

A significant observation of this study was the relatively short inspiratory times exhibited by the patients. The smaller the baby, the shorter was the inspiratory time. The 480-g infant consistently triggered expiration after inspiratory times of only 0.15 to 0.18 second. The flow

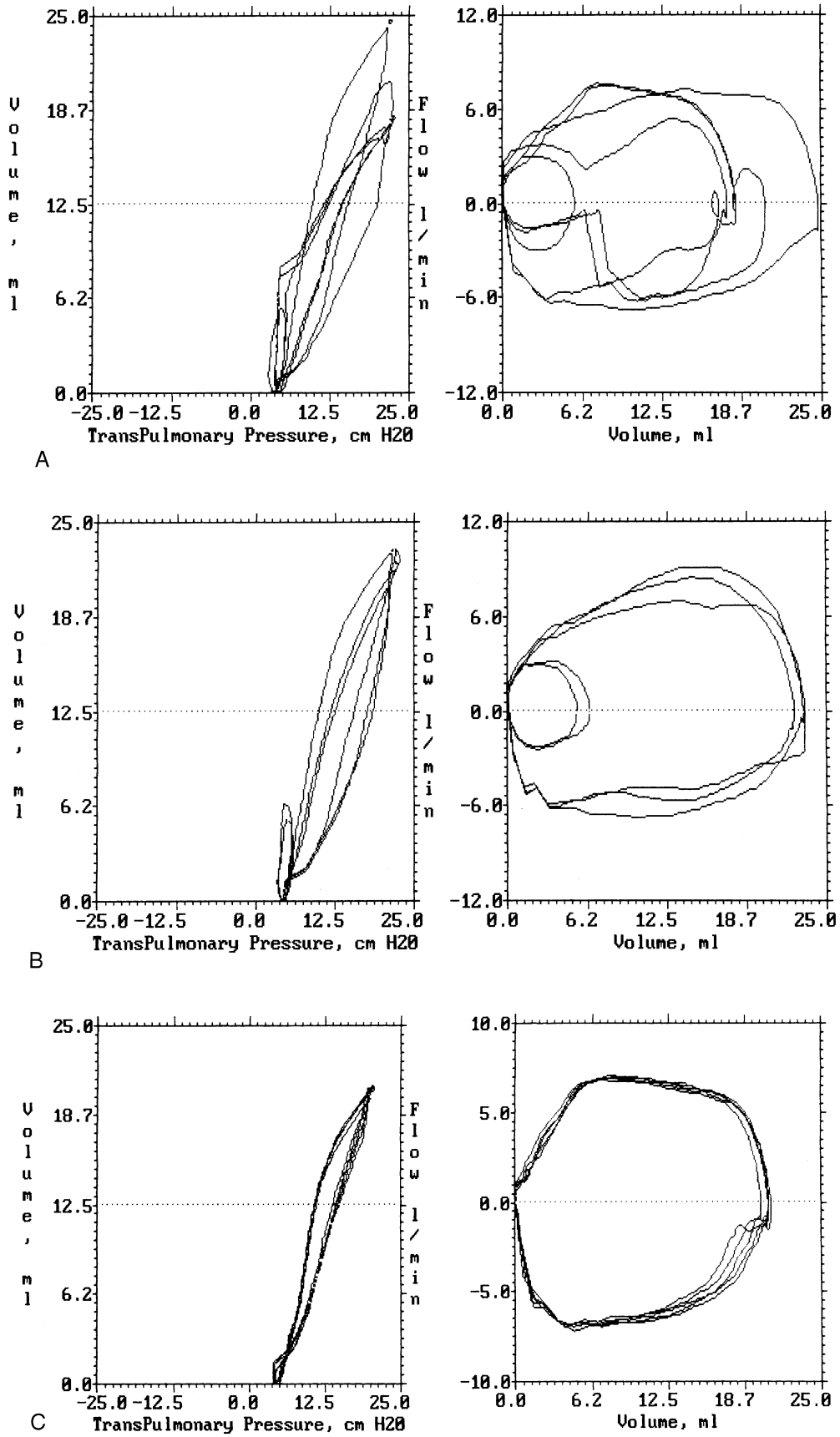

Figure 12-7 ■ Impact of synchronization on pulmonary mechanics. **A,** Pressure-volume and flow-volume relationships during intermittent mandatory ventilation. Note the inconsistency of tidal volume delivery despite nearly identical peak inspiratory pressures for each breath. This demonstrates an effect of asynchrony. **B,** Pressure-volume and flow-volume relationships during synchronized intermittent mandatory ventilation. Note the differences between spontaneous (smaller) and mechanical (larger) breaths. Mechanical breaths are nearly identical to one another as a result of synchrony. **C,** Pressure-volume and flow-volume relationships during assist/control ventilation. Because each spontaneous breath results in the simultaneous delivery of a mechanical breath, a single reproducible loop representing total synchrony between infant and ventilator is created.

synchronizer used in this study responded to changes in airway flow of 0.2 L/min; the transducer weighed only 11.8 g and increased ventilatory dead space by only 0.5 to 0.8 mL.[9]

This prototype flow synchronizer subsequently was incorporated into the V.I.P. ventilator line with one modification. Termination sensitivity, fixed at 25% on the prototype, was made adjustable from 0% to 25% in 5% increments. This enables the clinician to tailor inspiratory times to each individual patient's needs. For example, if an infant is breathing rapidly, longer inspiratory times increase the risk of air trapping and inversion of the inspiratory/expiratory ratio. By selecting a higher termination sensitivity, inspiration is shortened. Figure 12-6 shows the relationship between termination sensitivity and inspiratory time.

Several randomized controlled trials have examined the impact of PTV on preterm infants with respiratory distress syndrome. The first study, conducted by Chan and Greenough,[15] randomized 40 infants to either PTV (SLE HV 2000 ventilator, Specialized Laboratory Equipment, Surrey, England) or IMV after the acute phase of respiratory distress syndrome to determine which modality provided more rapid weaning. Infants were randomized after they had been weaned to a ventilatory rate of 40 breaths/min (from 60 breaths/min) at constant peak pressure and inspiratory time. Further weaning was accomplished with a reduction in peak inspiratory pressure in the PTV group and with a reduction in ventilatory rate in the IMV group. PTV resulted in a 50% reduction in the duration of time from weaning to the first extubation. Three patients, all less than 28 weeks of gestation, did not tolerate PTV and were switched to IMV. The investigators concluded that PTV is more advantageous than IMV for weaning preterm infants with a gestational age greater than 27 weeks.[15] A similar study performed by Donn et al.[16] examined the impact of PTV and IMV on 30 infants weighing from 1100 to 1500 g who were randomized at the start of treatment for respiratory distress syndrome. Entry criteria included the need for mechanical ventilation and severity of disease sufficient to warrant surfactant replacement therapy. After enrollment, patients were randomized to PTV using the V.I.P. BIRD in the A/C mode or to conventional IMV. Groups were demographically and medically comparable. Infants randomized to PTV had a much shorter time to extubation (mean 119 hours; range 15 to 650 hours) than those randomized to conventional IMV (mean 271 hours; range 17 to 746 hours) (P = .0152, Mann-Whitney U-test). Although the sample sizes were small, trends suggested a decreased incidence of chronic lung disease in the PTV group. In the studies by Chan and Greenough and Donn et al., no increases in acute ventilator complications were observed in the groups that received the new PTV therapy.[15,16] Donn et al. also reported a statistically significant cost reduction of approximately $4400 per patient in hospital costs for infants assigned to PTV.[16]

A large multicenter open trial of PTV was conducted by Baumer.[17] Although the results of this trial did not show benefits of PTV compared to conventional TCPL IMV, the study had numerous methodologic design flaws, limited investigator experience, and used multiple devices. The higher incidence of pneumothorax in the group treated with PTV further suggests that an inappropriate weaning strategy was used.[18] A single center study performed by Beresford et al.,[19] using the SLE ventilator, did not report an increased incidence of air leak.

Most of the studies have demonstrated short-term physiologic benefits of synchronized ventilation. Several recent publications have nicely summarized the subject.[20-22] Future investigation will need to focus upon long-term advantages, particularly improved pulmonary and neurologic outcomes. Other issues will need to be addressed, including the optimal triggering system and weaning strategy.[23]

Pressure-Support Ventilation

Continuous-flow TCPL ventilation has been the primary method of ventilation for newborns since the 1970s. Even at that time, there was an awareness that infants had specific ventilation needs that could not be met with the use of adult ventilators, despite many attempts by clinicians to modify these devices. The design of an infant volume-targeted ventilator addressed some of the problems that previously existed, including response time, limited ventilator rate, and system and circuit compliance issues. However, technologic limitations included triggering difficulties, inadequate monitoring, and inability to wean with a slow consistent approach. Further attempts at volume-targeted ventilation were abandoned in favor of a system (TCPL) that did not require triggering and delivered consistent peak airway pressure, which was easier to control and monitor. TCPL IMV provided continuous bias flow, from which the infant could breathe spontaneously, allowing a consistent approach to weaning.

The 1990s began a "new era" in infant ventilation. The V.I.P. BIRD infant/pediatric ventilator was introduced, which not only provided TCPL but also allowed the clinician to select volume-targeted ventilation modes (see Chapter 10). The difference between volume ventilation in the late 1960s and the 1990s is remarkable. The development of microprocessor technology and the availability of accurate flow and pressure transducers have made significant improvements in ventilator design and performance. In conjunction with engineering developments, enhancements in ventilator modalities included SIMV and pressure-support ventilation (PSV), which was first introduced in 1981.[24]

Description and Classification

Pressure support is a patient-triggered, pressure-limited, flow-cycled mode of ventilation designed to assist a patient's spontaneous effort with an inspiratory pressure "boost." Pressure support can be used in conjunction with other modes, such as SIMV, or it can be applied independently. Pressure support is generally applied during weaning to reduce the imposed work of breathing created by high-resistance endotracheal tubes, the ventilator circuit, and the demand valve in demand systems. At the highest level of pressure support, known as PSMAX, complete ventilatory support (i.e., a full tidal volume breath) is provided and patient respiratory muscle work is reduced to almost zero.[25] The lowest level of PSV (PSMIN) is the

pressure necessary to overcome the imposed work of breathing. Intermediate levels can be used to provide partial support (Fig. 12-8).

Most neonatal pressure-support systems are flow triggered. The patient initiates an inspiratory effort that results in an acceleration of airway flow. The trigger sensitivity is set by the clinician to the lowest possible level that avoids autocycling. In ventilators that monitor pressure proximally, triggering sensitivity may be improved; this is in contrast to ventilators that sense pressure from within the ventilator, on either the inspiratory or expiratory side.[26] Further improvement in triggering can be achieved if pressure is sensed at the distal tip of an endotracheal tube.[27] Another factor that can affect trigger sensitivity is the stability of the baseline pressure or positive end-expiratory pressure (PEEP). In pressure-triggered systems, if an airway leak is present, the baseline may drift. This may result in autocycling and necessitates setting the trigger sensitivity to a higher level. Ventilators that incorporate a leak compensation system have improved sensitivity. Flow triggering reduces trigger delay.[24] Although the baseline may not drift, trigger sensitivity may need to be adjusted to avoid autocycling.

Once the breath is triggered, flow is delivered to the patient airway and pressure rises rather quickly to the selected pressure-support setting. The patient's effort is the primary determinant of the amount of flow delivery that affects the rise in pressure. Other factors that are controlled by the ventilator include peak flow availability, the pressure support setting, and the specific pressure support algorithm applied by the ventilator. Earlier pressure support systems proved inadequate when applied to patients who had low compliance, high resistance, or who required smaller endotracheal tubes. Problems associated with pressure overshoot and premature termination have been addressed, especially with ventilators designed for use on small infants and children. Flow acceleration of pressure support breaths has even been modified in newer systems. Algorithms have been incorporated for matching flow delivery for low-compliance, high-resistance applications. A feature on some ventilators is an adjustable inspiratory rise time.[24] Rise time adjustments alter the slope of the inspiratory pressure wave form by controlling the acceleration of inspiratory flow. It is a qualitative variable and differs among manufacturers in the way it is adjusted. Because it is flow cycled, the end of a pressure support breath can also be regulated by the patient. The breath is terminated when the inspiratory flow decreases to a certain percentage of peak flow. The specific percentage varies among different ventilators; for those designed to be used in the infant population, the endpoint is usually 5% to 25% of peak flow. The occurrence of a very short inspiratory time secondary to an early termination may result in ineffective tidal volume delivery. Every ventilator that has PSV capabilities also has an inspiratory time limit, set by the clinician, which cannot be exceeded. If an airway leak is present, it may not be possible for breaths to be flow terminated.

Some ventilator designs have incorporated pressure support with a guaranteed minimum tidal volume. The terminology and algorithms for this capability vary; examples include volume-assured pressure support (VAPS, Viasys Healthcare, Yorba Linda, Calif.) and volume support (Servo-*i*, Maquet, Inc., Bridgewater, NJ). These variations in pressure support have been designed to improve patient safety by maintaining a minimum tidal volume while satisfying the patient's demand.

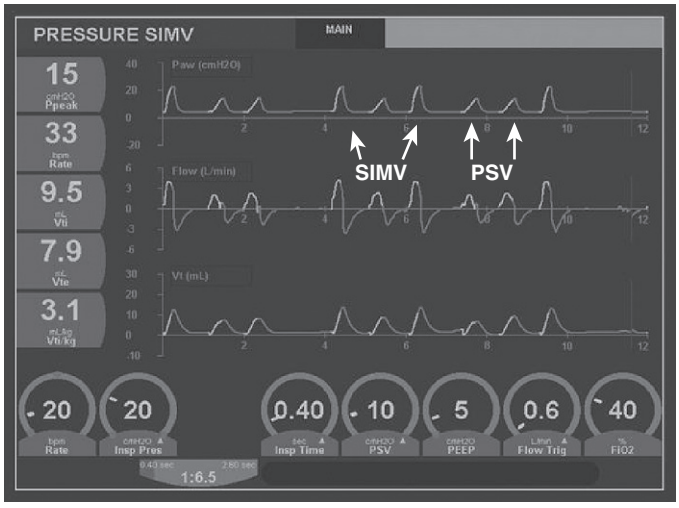

Figure 12-8 ■ Relationship of pressure-support ventilation (PSV) to synchronized intermittent mandatory ventilation (SIMV). In this example, the PSV breaths are supported by 10 cm H_2O pressure above baseline, whereas the SIMV breaths are supported with 20 cm H_2O above baseline. Pressure support is applied to spontaneous breaths occurring between the SIMV breaths.

Clinical Experience

Pressure support is attracting increased attention, not only as an alternative weaning mode but also as a primary modality in the treatment of patients with acute and chronic ventilatory failure.[28] PSV was introduced in the early 1980s to the European medical community. The Servo 900C was one of the first ventilators to incorporate this mode of ventilation. Clinical and technical research on PSV was reported somewhat later; the first case report of its use appeared in 1985. This study reported improved mixed venous blood oxygen saturation and decreased oxygen consumption in patients receiving SIMV with pressure support compared with those receiving only SIMV.[27] Other studies have reported reductions in spontaneous respiratory rates,[29] an increase in minute volumes,[30] a decrease in the time to extubation in postoperative thoracic surgery patients,[30] and patient preference for pressure support over SIMV (in communicative patients).[29] Decreased work of breathing with PSV is thought to be the reason for improvement. It has been reported that work of breathing through an artificial airway increases by 34% to 154% for each 1-mm reduction in internal diameter in the airway, depending on the minute ventilation.[31] PSV counteracts the effects of increased work of breathing imposed by artificial airways, ventilator circuits, and demand systems.[32-35] Furthermore, interest in system design has flourished. Two professional conferences, held in 1990 and 1991, focused exclusively on triggering and pressure-support delivery mechanisms.[36,37] As a result of improvement in ventilator design, many neonatologists are interested in the role PSV plays in the neonatal intensive

care unit. Neonatal specialists are applying pressure support to infants and achieving success, as well as trying to determine the best ways to use this mode.[38-42]

The application of PSV can accomplish one of two things: a patient may either (1) acquire a greater tidal volume with the same amount of effort or (2) achieve a similar tidal volume with less effort.[43] One physiologic advantage to this alternative ventilatory modality is that it more closely mimics a spontaneous breath. The patient initiates inspiration and has control of flow, volume, and inspiratory time. With SIMV, the patient may initiate inspiration, but flow, tidal volume, and inspiratory time are preset. Figure 12-9, shows the impact of PSV on respiratory waveforms. Figure 12-9, *A*, displays a series of breaths while the patient is receiving volume-targeted SIMV. Figure 12-9, *B*, shows visible improvement in flow and tidal volume delivery during spontaneous breaths with the addition of PSV. It is understandable that the breathing pattern may appear to be more comfortable when it more closely matches the patient's own ventilatory drive.

Tidal volumes that provide full support and require a minimum of work can be delivered, usually in the range from 4 to 8 mL/kg. Weaning is accomplished by progressively decreasing the level of pressure support. For endurance conditioning of the respiratory muscles without excessive work, tidal volumes of 3 to 5 mL/kg may be more appropriate. In the neonatal patient, it probably is not necessary to decrease pressure-support levels below 10 cm H_2O. At this point, the work of breathing caused by the highly resistive airway is considerably reduced, and the tidal volume that is generated is the result of patient effort rather than of pressure delivery.

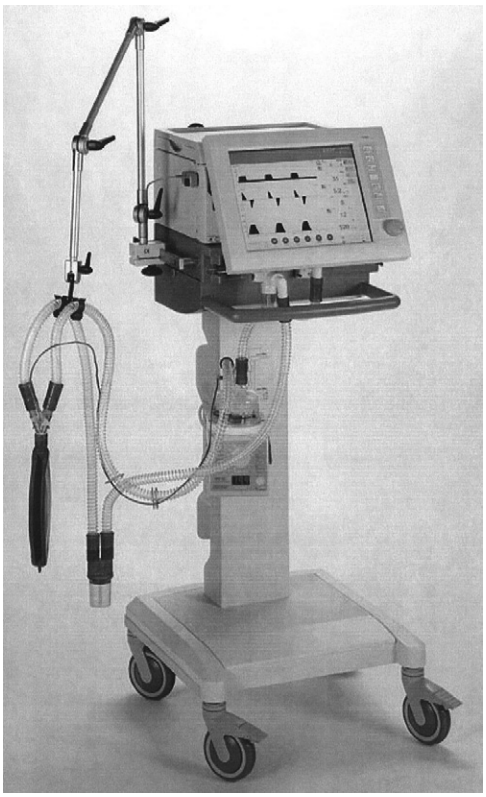

Figure 12-9 ■ Evita 4 ventilator. (Photo courtesy Dräger Medical.)

With the application of PSV to the newborn, several important factors must be observed, including triggering and synchrony, inspiratory time, and tidal volume. Reliable patient effort is very important, but of equal concern is the ability of the infant to consistently trigger the system and synchronize his or her breathing with the ventilator. Because of lower compliance and greater resistance, the breath may be prematurely terminated. This could result in an inspiratory time that is too short for adequate tidal volume delivery. Continuous breath-to-breath display of inspiratory time and tidal volume also are important. Tidal volume measurement is more accurate if it is done at the proximal airway. Also, pressure triggering may be more consistent if the pressure is measured at the proximal airway.

There are still limitations in neonatal PSV, usually because of triggering and the breath delivery algorithm. In most cases, pressure support is used as a weaning mode once volume-targeted SIMV has been initiated. A series of successful cases of neonatal volume-targeted ventilation followed by PSV has been reported. Patient profiles included birth weights from 2480 to 4300 g, gestational ages of 36 to 40 weeks, and diagnoses of respiratory distress syndrome, streptococcal (group B) sepsis, meconium aspiration syndrome, and persistent pulmonary hypertension of the newborn. Each infant required high ventilatory support (mean airway pressure greater than 12 cm H_2O; fraction of inspired oxygen [FIO_2] 0.7 to 1.0.) Initially, the indication for volume-targeted ventilation was a rescue approach; TCPL was not providing effective oxygenation. The oxygenation index was significantly reduced when patients were switched from TCPL (23.6) to volume-targeted ventilation (13.6) at virtually identical airway pressures. The infants were placed on volume-targeted SIMV with PSV as soon as the effects of elective paralytics were no longer evident and spontaneous respiratory effort was exhibited. Each patient was promptly weaned in this modality; none developed air leaks or radiographic signs of chronic lung changes.[44] PSV was also used during the weaning phases of a clinical trial that compared the efficacy of volume-targeted ventilation with pressure-limited ventilation in 50 infants with respiratory distress syndrome who weighed more than 1200 g. Infants assigned to volume-targeted A/C and weaned in volume-targeted SIMV and PSV met the success criteria significantly faster than infants kept in pressure-limited A/C, although it is not clear whether the difference is attributable to improvements in the acute phase, the chronic phase, or both.[45]

Other applications of PSV include the treatment of infants who are chronically ventilator dependent and the management of infants with bronchopulmonary dysplasia. As long as the infant has a reliable respiratory effort, this mode of ventilation seems to satisfy the greater flow demands imposed by these disease entities. The use of PSV in the newborn was extensively reviewed recently by Sarkar and Donn.[46]

Hybrid and Combined Modalities

The introduction of the microprocessor into the neonatal ventilator has created numerous permutations of the way

mechanical breaths can be delivered and the manner in which spontaneous breaths may be augmented. Some of these modalities blend the best advantages of both volume-targeted and pressure-targeted breaths, use sophisticated breath averaging technology, and offer the clinician the opportunity to optimize mechanical ventilation by customizing it to the specific needs of the individual patient.

Volume Bracketing

Volume bracketing is a term used to describe setting a minimum and a maximum volume delivery of a pressure control (PC) breath. It may be considered a form of hybrid ventilation because it combines a pressure control breath with a minimum volume target. Volume bracketing is an advanced feature of the AVEA ventilator that is available in the pressure-control ventilation modality. The ventilator begins by delivering a standard pressure-control breath. The machine volume (the amount of volume delivered from the ventilator) is measured. If the measured volume from the ventilator (referred to as *Vdel*) is greater than the minimal volume requirement, the breath continues as a standard pressure-control breath. If the Vdel is less than the minimal volume, the ventilator will automatically change (in mid-breath) from the pressure-targeted breath to a volume-targeted breath. The volume target is the minimum machine volume setting. This adjustment is intra-breath and does not involve breath averaging.

Two observations to be made are that the peak inspiratory pressure will increase slightly when volume becomes the target, and targeting the machine volume does not always guarantee the patient will get the desired minimal tidal volume. The clinician should remember that when more pressure is generated in the system, there will be more compressible loss of volume within the circuit and not delivered to the patient. The upper limit of the bracketing is the volume limit. The volume limit does not allow more than that set volume to be delivered to the patient. (This is the inspiratory volume that is measured at the proximal airway.) Pressure ventilation with both a minimum required machine volume and a maximum delivered volume limit result in the volume bracketing of the breath.

Volume-Assured Pressure Support

Volume-assured pressure support (VAPS) is a hybrid form of ventilation that combines features of PSV and volume-targeted ventilation. VAPS can be used alone or in conjunction with other mechanical modes. VAPS breaths begin as pressure-supported breaths. These breaths may be patient-initiated or mechanically initiated and have all the features of a PSV breath. When inspiratory flow decelerates to the set flow rate, delivered tidal volume is measured. If it matches or exceeds the minimal desired tidal volume, the breath will be terminated according to the usual pressure support algorithm. If the minimal desired tidal volume has not been met, however, the breath will transition to a volume-targeted breath by prolonging the inspiratory phase at a constant flow rate, creating the typical square wave flow pattern until the desired tidal volume is delivered (see Fig. 12-8). Pressure may also be ramped slightly. This technique enables full tidal volume delivery in the face of decreasing pulmonary compliance, patient effort, or patient fatigue. It holds great potential for use in weaning or in patients with irregular respiratory drive or rapidly changing compliance.[28]

Pressure-Regulated Volume Control

Pressure-regulated volume control (PRVC) is a modality that incorporates the features of both pressure and volume ventilation. PRVC is used fairly commonly in the pediatric and adult patient populations. It is also available in some ventilators for neonatal use. When PVRC is selected, the ventilator delivers a test volume controlled breath based on the selected volume. The test breath has a short pause during which the ventilator obtains an end-inspiratory pressure measurement. The ventilator then automatically sets the target pressure of the next breath, which is a pressure control breath, based on the end-inspiratory pressure of the test breath. All of the subsequent breaths are pressure control breaths with the inspiratory pressure automatically adjusted based on the previous breath to achieve the set volume. The maximum change in pressure between two consecutive breaths is 3 cm H_2O. Like PCV, PRVC delivers variable flow to meet the patient's inspiratory demand, while targeting a tidal volume. In PRVC, there will be more tidal volume variability than with volume-controlled ventilation, because of the maximum pressure change between two consecutive breaths and because it is determined by previously delivered breaths.

Mandatory Minute Ventilation

Mandatory minute ventilation (MMV) is another hybrid form of ventilation. It is available on the Evita ventilator (Dräger, Lübeck, Germany). With this technique, the clinician sets a target minute volume (the product of tidal volume and frequency). As long as the baby meets this goal, only pressure support of spontaneous breathing is provided. However, if the baby fails to meet the minimum minute ventilation, additional mechanical breaths are provided as SIMV breaths until the baby "catches up" to the desired level (i.e., minute volume). The ventilator averages the minute volume every 7.5 sec. A recent study by Guthrie, et al.[47] demonstrated the safety and feasibility of MMV in a cohort of ventilator-dependent infants with normal pulmonary function. Further study in infants with lung disease is warranted.

Adaptive Support Ventilation

Adaptive support ventilation (ASV) is a modification of MMV. It maintains a clinician-chosen minimum minute volume, which is independent of the patient's own activity. The target breathing pattern (tidal volume and rate) is calculated to produce the lowest possible work of breathing for the patient and results in the lowest inspiratory pressure when patient effort is minimal or absent. ASV has been used successfully in adults and is presently being investigated as a potential neonatal modality in the Galileo ventilator (Hamilton Medical, A.G., Rhazuns, Switzerland).

Proportional Assist Ventilation

Proportional assist ventilation (PAV) is a form of PTV in which the pressure applied to each spontaneous breath is

servocontrolled, increasing proportionally to the inspiratory flow and tidal volume generated by the patient. The patient controls the frequency, timing, and rate of lung inflation. In a recent small two-center study using a crossover design, Schulze, et al.[48] demonstrated that PAV safely maintained gas exchange at lower mean airway pressures than standard PTV.

Ventilators

The current trend in the ventilator market is designing and manufacturing ventilators that are capable of ventilating neonatal through adult patients. Technology has advanced greatly, such that ventilators are now capable of precisely ventilating and accurately monitoring the tiny neonate through the large adult patient in the same platform. The following text includes a discussion on four ventilators that have neonatal capabilities incorporated into a universal platform; the AVEA® (Viasys Healthcare), Evita 4® (Dräger Medical), Servo-*i*® (Maquet), and Galileo® (Hamilton Medical). The salient features and capabilities of these four ventilators are summarized in Table 12-2.

AVEA

The AVEA ventilator (Viasys Healthcare, Yorba Linda, Calif.) is an integrated life support system designed to meet the needs of neonatal, pediatric, and adult patients. It incorporates both pressure-targeted (PC/AC and PC/SIMV) and volume-targeted (VC/AC and VC/SIMV) ventilation, which gives the clinician flexibility in treating the various neonatal respiratory disorders. Weaning is facilitated with PSV in SIMV and PS/CPAP (continuous positive airway pressure). In addition, work of breathing through the endotracheal tube can be minimized with automatic airway compensation, which incorporates endotracheal tube diameter, length, and curvature into the algorithm.

The gas delivery system is very precise and capable of delivering volumes ranging from 2.0 mL to 2.5 L per breath. Flow rates as low as 0.4 L/min can be delivered accurately through the patented three-stage flow sensor and closed feedback loop algorithm. The AVEA has a low maintenance internal scroll pump compressor and an internal battery that will power the ventilator and compressor for 30 minutes. An extended battery for longer intra-hospital transports is optional. The internal blending system delivers the desired mixture of air and oxygen with accuracy and is the first ventilator to incorporate a safe, reliable system for delivering Heliox to patients with obstructive airway disease.

Volume and flow delivery to the neonate is accurately monitored with a proximal airway flow sensor incorporating hot wire anemometry. Proximal airway monitoring has been shown to be the most accurate method of assessing volume delivery in infants.[49] The proximal flow sensor provides rapid, responsive detection of all patient-initiated breaths (assisted and spontaneous) with an adjustable flow trigger sensitivity as low as 0.1 L/min. One other useful feature with volume monitoring is the ability to set a patient's ideal body weight and monitor all volume parameters corrected to that weight, for example, tidal volume per kilogram of weight (VT/kg).

Advanced functions include the ability to set a volume limit, controlled by the proximal flow sensor, to minimize the risk of overdistension when compliance increases. Additionally, a minimum volume can be set for pressure control breaths in the event that compliance suddenly decreases. Other advanced functions include the ability to sculpt the inspiratory slope of a pressure breath with an adjustable rise time function, and flow cycling of pressure breaths. The AVEA incorporates features to assist in patient care such as an "Increase O_2" button that can be configured between 21% and 100% and a "Suction" touchpad that silences alarms and increases F_{IO_2}.

The graphic user interface is a touch screen that allows the clinician to adjust the ventilator parameters using a "touch-turn-touch" approach. The color screen also displays monitored parameters and graphics, which can be almost infinitely configured by the user. The interface is very intuitive so that the clinician can rapidly access vital ventilation information. There are 35 monitored parameters from which the clinician may choose five to be displayed continuously; on this same screen pressure-flow-volume waveforms or pressure-volume and flow-volume loops, as well as set ventilator parameters, are shown. There is also a monitor screen that will continuously display 15 monitored values. Trended data are captured minute-by-minute for a running 24-hour period for the 35 monitored parameters.

The AVEA is a comprehensive ventilator that can accommodate technologic advances, allowing the user the ability to upgrade the platform, minimizing obsolescence. It incorporates many desirable features that promote safe and effective ventilation and accurate monitoring of the ventilated neonate.

Evita 4

The Evita 4 ventilator (Dräger Medical, Lübeck, Germany) is another state-of-the-art device that is capable of treating the entire population of patients from the smallest neonate to the largest adult (see Fig. 12-9). Its NeoFlow® is an optional feature that is required for neonatal ventilation. With NeoFlow, the Evita 4 is able to precisely monitor flows and volumes at the proximal airway and provide accurate, responsive triggering. In addition, NeoFlow incorporates automatic leak compensation, which allows for direct adjustment of tidal volumes as small as 3 mL.

Dräger uses a different nomenclature for its modes of ventilation. Pressure-control ventilation on the Dräger is called *BiPAP*, biphasic positive airway pressure or PCV⁺/BiPAP™. This mode of ventilation uses a concept that encourages spontaneous breathing. It is the standard mode for ventilation and weaning in pressure-control ventilation, and also allows the patient to breathe spontaneously at any time during the respiratory cycle, using active exhalation. Intermittent positive-pressure breathing (IPPB)–Autoflow and SIMV-Autoflow are used to refer to volume assist/control and volume SIMV, respectively. AutoFlow is a feature that makes spontaneous breathing easier in volume-targeted modes of ventilation. The ventilator automatically regulates inspiratory flow to the patient's effort. Spontaneous breathing can occur throughout the entire inspiratory and expiratory cycle because of an active expiratory valve. Even though the mode is volume targeted, flow is decelerating. One additional volume-targeted mode, MMV, was described above.

Pressure-support ventilation, called *assisted spontaneous breathing (ASB)* on the Dräger, refers to augmented pressure support. The Dräger also delivers airway pressure release ventilation (APRV),[50] sometimes called *bilevel* or *biphasic ventilation*. It is a relatively new modality of ventilation that has been used in adult patients and is now being tried with some success in neonatal and pediatric patients. It is a spontaneous breathing mode; the patient must breathe spontaneously for ventilation to be effective. Spontaneous breathing can occur during high or low pressures. Ventilators that offer APRV have active exhalation valves that allow spontaneous breathing anytime during the ventilatory cycle. The ventilator is set at two pressures (high CPAP, low CPAP), and both levels are time cycled. The high pressure is maintained for the majority of the breath and the low pressure is maintained for a very short duration to allow exhalation and gas exchange. This modality has the benefit of alveolar recruitment. Its disadvantage is that the tidal volume is variable. The clinician must be constantly aware of the patient's minute ventilation to prevent hypercapnia or hypocapnia.

The Evita 4 incorporates a comprehensive monitoring and graphics package, including waveforms, loops, and trends that are configurable by the clinician. With waveforms and loops, the horizontal and vertical axes can be modified to allow for different displays. Integrated pulse oximeter (Spo_2) and end tidal CO_2 ($ETCO_2$) monitoring are additional features that are available on the Evita 4. Automatic tube compensation (ATC), to reduce the work of breathing resulting from the endotracheal tube, is also an optional feature.

Galileo

The Galileo (Hamilton Medical, Bonaduz, Switzerland) is a technology-enhanced ventilator that is capable of ventilating neonatal, pediatric, and adult patients (Fig. 12-10). Not only does it cover the whole spectrum of patients, it offers a full range of ventilation capabilities. It incorporates an intuitive interface that is easy to use and monitors 26 parameters, loops, waveforms, and trends. The monitoring parameters can be configured to user specifications. A large color screen displays all of this information.

In the neonatal patient population, the Galileo uses a proximal flow sensor to deliver breaths and monitor the volumes. Tidal volumes delivered in pressure-based modes can be as small as 2 mL and in volume modes as small as 10 mL (the latter being a disadvantage in the neonatal population).

The modalities available to infants include, pressure-controlled mandatory ventilation and SIMV, pressure-support ventilation, DuoPAP (dual positive airway pressure ventilation; CPAP at two levels), airway pressure release ventilation (described above), adaptive pressure ventilation plus conventional mechanical ventilation (APV_{CMV}), and adaptive pressure ventilation plus SIMV (APV_{SIMV}). Adaptive pressure ventilation is similar to PRVC. It is a dual breath type that delivers a pressure breath type, but targets a volume. The ventilator monitors each breath and compares the delivered tidal volume to the set tidal volume. If the delivered volume is too low, it increases the inspiratory pressure on the next breath. If it is too high, it decreases the inspiratory pressure. This adjustment gives the patient the lowest peak inspiratory pressure needed to achieve a preset tidal volume. Tube resistance compensation (TRC) is also available to reduce the work of breathing resulting from the endotracheal tube.

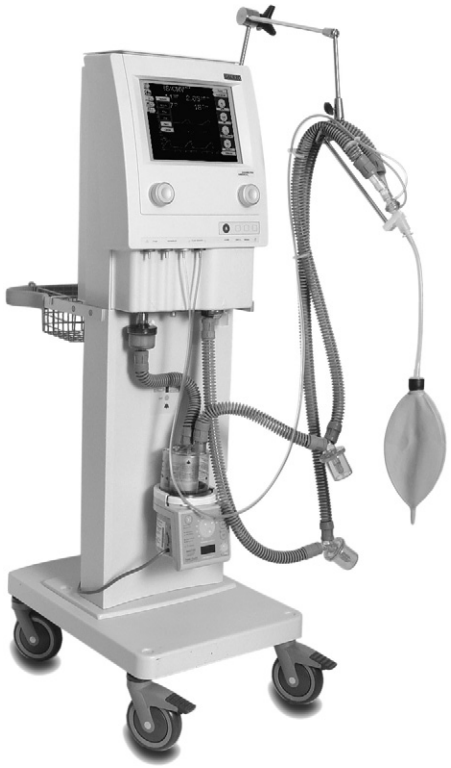

Figure 12-10 ■ Galileo ventilator. (Photo courtesy Hasmilton Medical.)

Servo-i

The Servo-*i* (Maquet Critical Care, Solna, Sweden) is another versatile ventilator that is used to provide support to all patient populations (Fig. 12-11). Some of the features of the Servo-*i* include the ability to patient trigger the ventilator by either a flow or pressure change. A proximal wye-sensor may be placed at the airway to monitor volumes. This is an optional feature; if a proximal flow sensor is not desired or malfunctions, the integrated monitoring system takes over. The system compensates for compressible volume loss in the tubing.

The Servo-*i* features an intuitive interface with large touch screen and easy-to-follow menus. Start-up settings such as positive end-expiratory pressure (PEEP), FIO_2, rate, and volume/pressure are directly accessible with push buttons and knobs, making initiation of ventilation relatively easy. The graphics interface has the ability to monitor four waveforms, including pressure, flow, volume, and the CO_2 capnogram. The *open lung tool* displays pulmonary graphics to assist the clinician in the interpretation of patient/ventilator interaction as well as ventilator data.

The Servo-*i* has a suction support button that pauses cycling during a suction procedure. Oxygen concentration can be manually set by the clinician for pre- and post-oxygenation phases to meet the patient's needs.

Another feature of the Servo-*i* is the ability to provide noninvasive ventilation (NIV) and nasal CPAP. There are

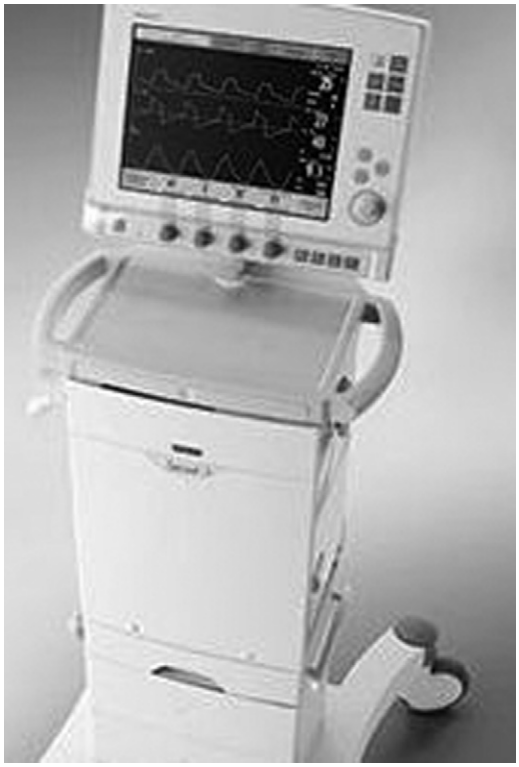

Figure 12-11 ■ Servo-*i* ventilator. (Photo courtesy Maquet Critical Care.)

also many options and a number of distinct modalities of ventilation available for a wide variety of patients and differing pulmonary pathology. The available ventilator modalities focus upon three basic mechanical strategies: pressure, flow/volume, and pressure/volume.

Pressure modalities of ventilation provide a consistent pressure delivery from breath to breath. These include pressure control and pressure support ventilation. In the face of changing pulmonary compliance, the tidal volume delivery will vary with the pressure being constant.

The flow/volume modality provides a constant inspiratory tidal volume and a constant inspiratory flow rate. In the face of changing pulmonary compliance, the inspiratory tidal volume delivery is constant and the pressure level will vary. The available modality is volume control.

Pressure/volume modalities of ventilation provide advantages of both pressure and volume ventilation by delivering a constant inspiratory tidal volume while making continuous adjustments in the pressure level. These include pressure-regulated volume support and volume support.

Another way the Servo-*i* categorizes modalities of ventilation is by describing them as *controlled*, *supported*, or *spontaneous*. Controlled modalities have a set mandatory ventilatory rate that will be delivered with or without patient effort. Supported modalities differ in that they only deliver ventilator breaths with patient effort. Spontaneous modalities, such as CPAP, require the patient's own spontaneous effort to generate tidal volume to facilitate ventilation.

All of the controlled modalities have the option of SIMV and PSV. With this option, the patient will receive the mandatory breath rate that is set by the user. Additional patient-triggered breaths will be augmented with pressure support.

In addition to these basic strategies, the Servo-*i* also has a combined feature named *automode*. Automode combines both controlled modes and support modes to provide improved interaction between the ventilator and the patient. The ventilator begins in a controlled modality and automatically switches to a corresponding support modality when the patient makes spontaneous efforts. If the patient ceases to make spontaneous effort, the ventilator will automatically switch back to a controlled modality. The corresponding modalities are as follows:

Pressure control ⇌ Pressure support
Volume control ⇌ Volume support
PRVC ⇌ Pressure support

Another interesting feature available with the Servo-*i* is bi-vent. Bi-vent is similar to APRV in providing the spontaneously breathing patient with two different levels of pressure. The time the ventilator delivers or holds each pressure is controlled by the user. The patient is allowed to breathe spontaneously throughout each phase (high-low or PEEP), because of the active expiratory system. The patient's spontaneous breaths may also be supported by a set pressure boost with pressure support.

The Servo-*i* has plug-in modules that allow for flexibility in choosing optional features, such as CO_2 monitoring, use of a wye flow sensor, nebulizer, or battery backup. Modules are interchangeable with all Servo-*i* ventilators.

Conclusion

With the advancement of ventilator technology, modes of ventilation that have been successful in the pediatric and adult populations for many years are now being applied to the neonatal population. Ventilators designed for neonatal use now offer various modalities, including volume-targeted ventilation and pressure support. These ventilators have incorporated some of the latest enhancements, which have resulted in increased triggering sensitivity, shortened response times, reduced flow acceleration, and improved breath termination parameters. These improvements are important when ventilating with small, uncuffed endotracheal tubes and in the management of patients with diseases in which compliance is low and resistance is high. Other refinements include guaranteed tidal volume delivery in different modes, adaptive ventilation, and availability of adequate alarms to meet the needs of the newborn. Another area that has improved dramatically since the inception of infant ventilation is monitoring.[51] In addition to mean airway pressure monitoring, which has provided valuable information since its introduction in the 1980s, tidal volume monitoring is becoming a standard practice, largely as a result of the accuracy of available monitors. It also enables calculation of minute ventilation (and modalities which incorporate it) and provides the clinician the ability to assess spontaneous breathing during mechanical ventilation (see also Chapter 18).[52,53] From 1970 to the early 1990s, neonatal ventilation did not change significantly. Now, the expansion of technology provides neonatal clinicians with exciting new opportunities for research

and application of these different modalities of infant ventilation.

Future Directions

Introduction of PTV, whether SIMV, assist/control, or PSV, has been an exciting breakthrough in the management of newborns with respiratory failure. Experience has demonstrated the benefits of synchronization in improving gas exchange and pulmonary mechanics and in shortening the duration of mechanical ventilation in some populations. With the addition of flow-cycling, mechanical ventilation of the newborn is coming increasingly closer to matching spontaneous breathing. Perhaps even more important, control of ventilation is now patient-driven rather than ventilator- or clinician-driven.

Numerous infant ventilators that offer synchronization options are commercially available. All of them have been demonstrated to be advantageous over conventional IMV. What still remains to be determined, however, is which ventilatory mode is best in different clinical circumstances. Although it may seem intuitive that assist/control ventilation should decrease the work of breathing when compared with SIMV, it is unclear what price an infant may ultimately have to pay. For instance, do spontaneous unsupported breaths interspersed with mechanical breaths result in lower mean thoracic pressures, thus promoting venous drainage, cardiac output, and cerebral blood flow? Alternatively, could assist/control ventilation speed resolution of respiratory disease states, thus decreasing chronic lung disease and its attendant respiratory and neurologic sequelae?

Although clinicians are experiencing a technologic revolution in the neonatal intensive care unit, they must not embrace the new techniques without close clinical scrutiny. Clearly, enthusiasm should be tempered by continued investigation and refinement. At the same time, the future of neonatal respiratory care has never been brighter.

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13 Special Ventilation Techniques II: Lung Protective Strategies

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Despite the many advances made in respiratory techniques for the neonate during the past several decades, lung injury remains a significant complication and an ongoing concern in the care of the critically ill neonate. Although many investigations in neonatal medicine have focused on the prevention of bronchopulmonary dysplasia (BPD) and lung and airway injury, BPD still affects many critically ill neonates (see Chapter 23). A recent survey of BPD at the U.S. Library of Medicine web site (www.PubMed.gov) revealed more than 3500 investigations on the subject of BPD. The incidence of the disease has not changed dramatically in recent years (Figure 13-1), although it has declined slightly. Managing pulmonary limitations in the chronically affected infant and preventing further injury remain challenges for the clinician.

As our understanding of the pathophysiology of neonatal lung disease progresses, so does our appreciation of the potential entry points of therapy. Because chronic lung disease is multifactorial in origin, virtually all aspects of neonatal care can be viewed as subjects for preventative strategies. There is little question that issues such as severe prematurity, infection, fluid management, patent ductus arteriosus, nutritional status, pulmonary air leaks, anemia, and several others all impact on pulmonary outcome. Consequently, prevention of chronic lung disease will only occur when a global approach, which includes attention to the prenatal and perinatal environment, neonatal nutrition, and thermoregulatory, antioxidant, inflammatory, and other health issues of the infant, is developed. For the purposes of this chapter, however, we focus on preventative pulmonary strategies, although the neurodevelopmental consequences of care are also described where appropriate.

Although preterm infants can have structural or developmental lung problems, the prematurely delivered infant typically has normally developing lungs (up to the time of delivery), but nevertheless, lungs with immature structure and function. This immaturity includes anatomic immaturity of the lung parenchyma and airways, surfactant deficiency with decreased lung compliance, immature lung fluid maintenance, and increased chest wall and airway compliance; both the airways and thoracic cage are very soft. Managing pulmonary needs therefore requires the provision of support to maintain adequate gas exchange while minimizing the risk for iatrogenic injury or intercurrent illness, especially infection. The preterm infant who progresses to chronic lung disease often does so because of ventilator-induced injury, which may be preventable, at least in part.

Some chronic lung injury is inescapable, even with current technology. It is clear from studies of preterm infants, however, that certain management techniques and styles appear to be associated with a decreased incidence of chronic lung disease, even when rigid statistical analysis for confounding factors is used.[1,2] The definition of BPD, however, also appears to be important in assessing the impact of lung injury.[3] This chapter assesses current strategic approaches in ventilatory management and how they might impact upon the outcome of care provided in the neonatal intensive care unit (NICU).

Initial Lung Protective Strategies for the Fetus

Effective pulmonary management of the infant with respiratory failure begins during prenatal care and in the delivery room. Evidence suggests that a majority of premature infant deliveries are the result of maternal chorioamnionitis, exposing the fetus to elevated cytokine production in utero.[4,5] Because tocolytic therapy is required frequently in premature labor and a conservative approach often is taken with premature rupture of membranes, the premature neonate may be exposed for a variable period to high levels of cytokines or other vasoactive substances. This exposure appears to initiate a fetal pulmonary vasculitis, which may make subsequent resuscitation and ventilatory management more difficult.[6] The obstetrician therefore has the complex and unenviable task of attempting to decide when a fetus will do better outside of the uterus than remaining inside.

To date, there are few data that can successfully answer this thorny question. Clearly, in the face of evolving infection and fever or with worsening preeclampsia, delivery of the fetus is essential. In the afebrile mother who has repeatedly threatened premature labor, however, there are no answers. Is the fetus better off with aggressive tocolysis at 25 to 26 weeks, or is the long-term risk actually less ex utero? What about the baby who is beyond 27 to 28 weeks? Where can the line to deliver be successfully drawn, and what are the resulting pulmonary and neurodevelopmental consequences? Although there is increasing belief that prolonged tocolysis may not be in the best clinical interest

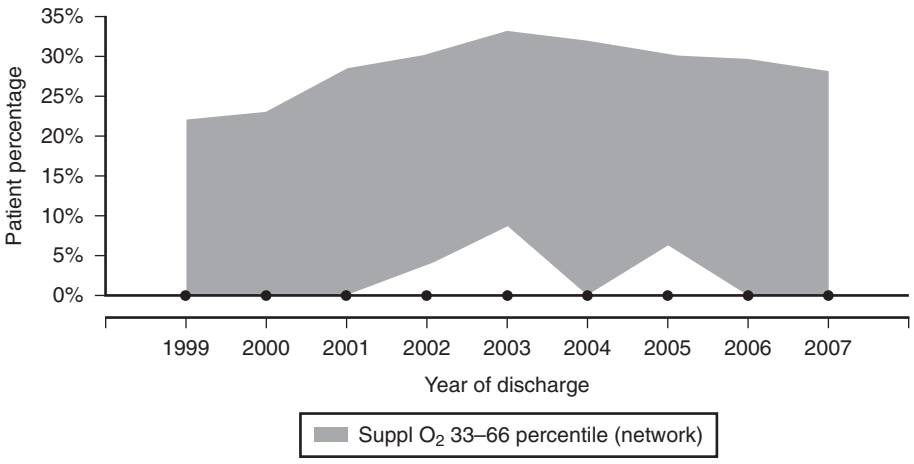

Figure 13-1 ■ The incidence of chronic lung disease in all Pediatrix Medical Group Neonatal Intensive Care Units (NICUs) between 2000 and 2007. The figure shows the results for all NICUs in the Pediatrix Medical Group Clinical data Warehouse. The shaded area represents the 33% to 66%, or middle third, of all NICUs. There was a slight upward trend prior to 2003, after which there has been a slow decline in the incidence of BPD. Clinical rates are nearly the same, regardless of NICU size. The decline since 2007 is thought to be the result of improved oxygen and respiratory management techniques. These data are based on information from more than 424,000 neonates in the Pediatrix Clinical Data Warehouse.

of the fetus in many cases, it is likely that this research issue will be aggressively pursued in the near future.[7,8] One of the most promising avenues of investigation appears to be the use of proteomic detection of intraamniotic infection before infection is clinically apparent, or as importantly, before subclinical infection begins.[9,10] Theoretically, if infection can be identified and treated before the initiation of the cytokine cascade, the outcome for that pregnancy may be dramatically altered.

Management of Ventilation in the Delivery Room

The development of adequate pulmonary blood flow, functional residual capacity (FRC), and ventilation-perfusion matching with uniform distribution of lung surfactant can be affected by the management in the first few minutes of life. Animal studies demonstrate that airway and lung parenchymal injury can occur with only a few large breaths at the time of birth.[11] This potential injury is exacerbated in the preterm infant in whom the immature airway structure can be easily disrupted by pressure deformation. The resulting loss in airway integrity can lead to an escalating cycle of airway collapse and distal atelectasis, the need for increased inflation pressures, and further airway injury. Bjorklund et al.[11] demonstrated in an animal model that manual ventilation with only six large tidal breaths after birth can alter lung function.

In addition to airway injury, tidal breathing in the delivery room can cause alterations in surfactant function.[12] These changes may be due to parenchymal disruption with protein leak and surfactant inactivation.[12,13] Hence, tidal breaths in the delivery room can reduce the efficacy of exogenous surfactant administration while simultaneously disrupting the integrity of the airway structure and the pulmonary parenchyma as a result of these pressure effects. The airway in a tiny premature infant is not designed to handle the stress of positive-pressure ventilation from a mechanical perspective. When combined with the damaging effects of ventilation upon surfactant, the difficulty in preventing BPD can be readily appreciated.

Early Surfactant Administration

As a result of the initial application of tidal breathing in the delivery room, from even shortly after birth, the physician attempting to reduce pulmonary trauma in the neonate may be fighting a losing battle. Early instillation of exogenous surfactant appears to reduce the lung injury and protein leak associated with preterm delivery.[14] This protection is diminished if therapy is delayed beyond 30 minutes.[15] Although distribution of exogenous surfactant is improved with instillation during the first few minutes of life, the outcome of very-low-birth-weight infants probably is improved if instillation is delayed until adequate respiration is established. Our ability to predict which infants will develop respiratory distress syndrome (RDS) is limited in later-gestation (greater than 32 weeks) preterm infants, so most practices limit the use of early or prophylactic exogenous surfactant administration to the most immature low-birth-weight infants. The instillation of exogenous surfactant can be given cautiously as soon as the infant has been stabilized.

A recent adjunct to surfactant administration as a lung protective strategy is the transient intubation of the infant solely for the purpose of administering surfactant. The endotracheal (ET) tube is soon withdrawn and the infant is placed on nasal continuous positive airway pressure (CPAP) (**IN**tubation, **SUR**factant administration, **E**xtubation—INSURE protocol).[16] In that trial, Curosurf was the surfactant selected and infants were also pretreated with theophylline to reduce the likelihood of

apnea. The weakness of this study is that it was performed as a historical evaluation of patients, rather than a prospective randomized trial. It did, however, appear to reduce the need for mechanical ventilation by 50%, although the incidence of BPD and air leaks was not altered by this approach. The administration of surfactant in this trial did require intubation, but an aerosolized form of surfactant is currently in development and may be of greater value in combination with the use of early nasal CPAP and will thus avoid the need for intubation (see Chapter 22).

Early CPAP Use in the Delivery Room

The optimal delivery room management of the preterm neonate would include the gentle establishment of an FRC and matched pulmonary blood flow, with even distribution of pulmonary surfactant. These events might be accomplished by either the early institution of continuous positive airway pressure (CPAP) or by delivery room initiation of mechanical ventilation (MV) with low tidal volumes. In recent years, it has been suggested that nasal CPAP might have the advantage of a significantly lowered risk of later lung injury than even low tidal-volume mechanical ventilation.[17] The result of a recent, large scale multicenter trial, however, led to somewhat inconclusive results. The COIN (CPAP Or early INtubation) Trial failed to demonstrate any difference in death or BPD with early CPAP, but fewer infants needed oxygen at 28 days of life and there was a reduced need for mechanical ventilation in the CPAP group, which also had a reduced need for surfactant. Somewhat surprisingly, the CPAP group had a higher incidence of pneumothorax. Because the study also excluded infants who were felt to need immediate intubation, there were some limitations that may have affected the outcomes that would have better defined the overall benefits or risks of early nasal CPAP. It appears likely that further investigations may help define the benefits of early nasal CPAP. Again, as is often the case in respiratory studies in neonates, the numbers of potential confounding variables may ultimately prevent precise assessment of the merits of early CPAP use (see Chapter 8).

Room Air Resuscitation in the Delivery Room

The other novel approach to lung protection in the delivery room is the increasing evidence for the beneficial effects of room air or low inspired oxygen resuscitation. Championed initially by Saugstad[18] and Vento et al.,[19] this approach has rapidly been gaining favor,[20] and recent studies suggest that there may be value in limiting oxygen use below the 100% level previously recommended by the Neonatal Resuscitation Program. A recent controlled trial, however, from the San Diego group was somewhat less optimistic, in that all neonates initially randomized to room air resuscitation ultimately needed additional oxygen administration (Fig. 13-2).[21] In addition, there were significant oxygen saturation differences between the room air group and the 100% oxygen group during the first 10 minutes of life, sufficient to cause some concern, because the room air group demonstrated mean saturation levels of 55% during this period. It appears likely that further work in this area will be forthcoming, however, given the controversy that is emerging.

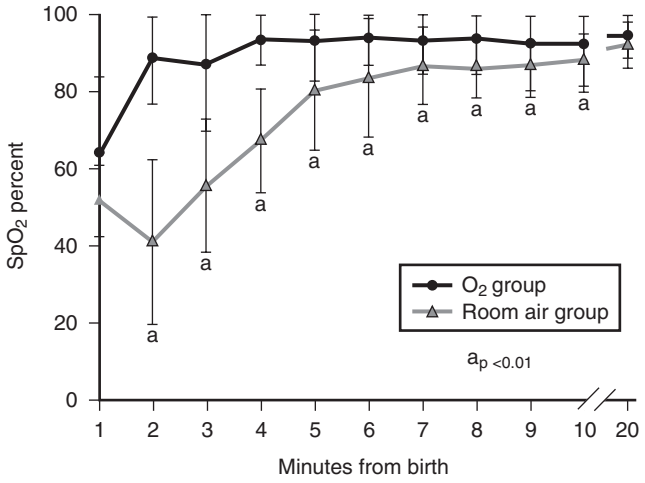

Figure 13-2 ■ Differences in oxygen saturation during neonatal resuscitation, comparing 100% oxygen versus room air resuscitation. (From Wang CL, Anderson C, Leone TA, et al: Pediatrics 121:1083-1089, 2008.)

Managing Mechanical Ventilation to Optimize Lung Protective Strategies

The management of neonatal respiratory failure has changed dramatically during the past several decades. Some therapies, such as the use of endogenous surfactant and inhaled nitric oxide (iNO), have been shown to decrease mortality or the need for more intense therapy such as high frequency ventilation (HFV) or extracorporeal membrane oxygenation (ECMO) life support.[22] Defining specific management strategies to improve outcomes, especially for the extremely low-birth-weight infant, has been more difficult to elucidate. It is clear that slightly different pulmonary approaches, even when using similar medications and ventilators, can result in different outcomes. These results would suggest that controlling for other variables in respiratory studies may not be entirely possible. In addition, the incidence of chronic lung disease varies among different intensive care nurseries, even some of the more notable units in the United States.[23]

Because there are many variables that affect the pulmonary outcome of an infant, determining which factors primarily contribute to these differences is exceedingly difficult, as seen in the numbers of publications attempting to understand the pathogenesis of neonatal lung injury. The multivariate analyses of Van Marter et al.[24] suggested that most of the increased risk for chronic lung disease among very-low-birth-weight infants was explained simply by the decision to initiate mechanical ventilation. Similarly, using regression analysis, Graziani et al.[25] also showed that the decision to initiate mechanical ventilation had significant neurologic implications for the very-low-birth-weight infant. The Vermont-Oxford Group has encouragingly demonstrated, however, that strategies could be effectively introduced through a multidisciplinary collaborative quality improvement program, with resultant diminished chronic lung disease.[26,27]

Optimal neonatal management should theoretically reduce ventilator-induced lung injury (VILI). Which specific ventilator variable induces the greatest injury remains a controversial question. As can be seen from the earlier discussion on the various ventilator approaches to positive-pressure ventilation (see Chapter 9), the attempt to completely eliminate lung injury in the neonate has been less than successful. Because it is possible to achieve the same tidal volume, minute ventilation, and gas exchange with different ventilator settings, it becomes important to try to determine which variable achieves adequate gas exchange with the least potential iatrogenic injury. Animal studies suggest that tidal breathing (volutrauma), as well as ventilating the atelectatic lung (atelectotrauma), causes injury.[28-31] The size of the breath, therefore, may be more important than the inflating pressure in determining the risk for chronic lung disease. In the atelectatic lung, adequate minute ventilation is sometimes achieved by overinflating already expanded lung regions, thereby causing damage to those ventilated regions. Using an adequate amount of end-expiratory pressure or mean airway pressure to optimize alveolar volume recruitment may diminish lung injury.

Although less information is available on other ventilator controls, for conventional ventilators used to support infants with restrictive lung disease, shorter inspiratory times with more rapid rates and low flow rates (to prevent turbulent gas flow in the airways) appears to be preferable in trying to minimize lung injury.[32] In addition, the use of a disease-specific ventilator approach that changes as the lung mechanics change may be most beneficial. The availability of volume-guarantee ventilation, which essentially "autoweans" peak inspiratory pressure (PIP) as compliance improves, is an example of such a management strategy. Hence, the concept of patient-triggered ventilation, especially synchronized intermittent mandatory ventilation (SIMV) and assist/control ventilation in association with volume guarantee, have proved increasingly useful in this respect.[33]

Recent advances in technology have allowed the introduction of patient-triggered ventilation and online lung mechanics using conventional ventilators. These new technologies allow more accurate monitoring of the infant's status and permit a wide array of new ventilator modalities, such as synchronized IMV, pressure-support, assist/control, proportional assist, volume-controlled, volume guarantee, and mandatory minute ventilation. In addition, the clinician can use the graphics information from several new ventilators to make more rapid changes, thereby reducing injury (see Chapter 18). These techniques may improve outcomes of infants, although further work on these techniques needs to be pursued.

Once an infant is being treated with mechanical ventilation and is stabilized, weaning the infant from the ventilator is always challenging. As noted previously, mechanical breaths, even at low ventilator settings, can induce lung injury. When the infant finally begins to wean progressively, the decision to ultimately remove the mechanical ventilator and move the infant to CPAP, oxygen, or nasal flow cannula is difficult. The wealth of current ventilators available provides a variety of options, however, to assist in this regard.

Approaches to Neonatal Ventilation

Some general and specific strategies for mechanical ventilation of the neonate are discussed in Chapter 9 and will not be repeated here. These suggestions, however, represent but a few of the many approaches to respiratory support of the newborn infant. Numerous other methods that work equally well in the hands of experienced clinicians have been described in the literature. In recent years, the number of different strategies has seemingly expanded exponentially, although the evidence supporting one approach compared to another is relatively modest at the present time. All such techniques are guided by certain basic physiologic principles and consistency of management in an individual nursery (Fig. 13-3). Table 13-1 lists some alternative styles of mechanical ventilation of the newborn and the basic principles on which the techniques are based. These techniques of neonatal ventilation are discussed briefly. For more extensive reviews of HFV and patient-triggered ventilation, the reader is referred to Chapters 11 and 12.

Slow-Rate Ventilation

The first systematic approach to neonatal mechanical ventilation was devised by Reynolds and Tagizadeh during the early 1970s.[34] Although lung protection was not a specific goal of this strategy, the intent of approving oxygenation at the most modest pressure was part of the design. This technique, commonly referred to as *slow-rate ventilation*, used a ventilator rate of 20 to 30 breaths/min and a reversed inspiratory-to-expiratory (I:E) ratio (2:1 to 4:1) to improve oxygenation. This method improved oxygenation by increasing mean airway pressure, but it had associated problems. Air trapping and elevated $Paco_2$ levels were common, and the observed incidence of intraventricular hemorrhage was much higher than that reported by other investigators. Consequently, this approach fell out of favor and is rarely used today, except for rare instances of oxygenation difficulty.

Rapid-Rate Ventilation

In the mid-1970s, Bland et al.[35] reported on a series of infants treated with a more rapid rate of ventilation, in whom hand ventilation was often used to improve gas exchange. Bland used lower pressures but rates over 100 breaths/min in an attempt to decrease the risk of chronic lung disease. This approach was one of the first to emphasize the potential of higher rates and lower pressures in reducing lung injury in neonates. The results, although favorable, were likely due to the creation of inadvertent positive end-expiratory pressure (PEEP), and the inconsistency of hand ventilation was unsatisfactory for many nurseries. It did suggest, however, that rapid rates could be used successfully in some infants.

Hyperventilation

Several years later, Peckham and Fox[36] explored the possibility of using higher rates and pressures to lower $Paco_2$ and decrease pulmonary vascular resistance intentionally. This hyperventilation technique is today used only rarely for treatment of persistent pulmonary hypertension of the

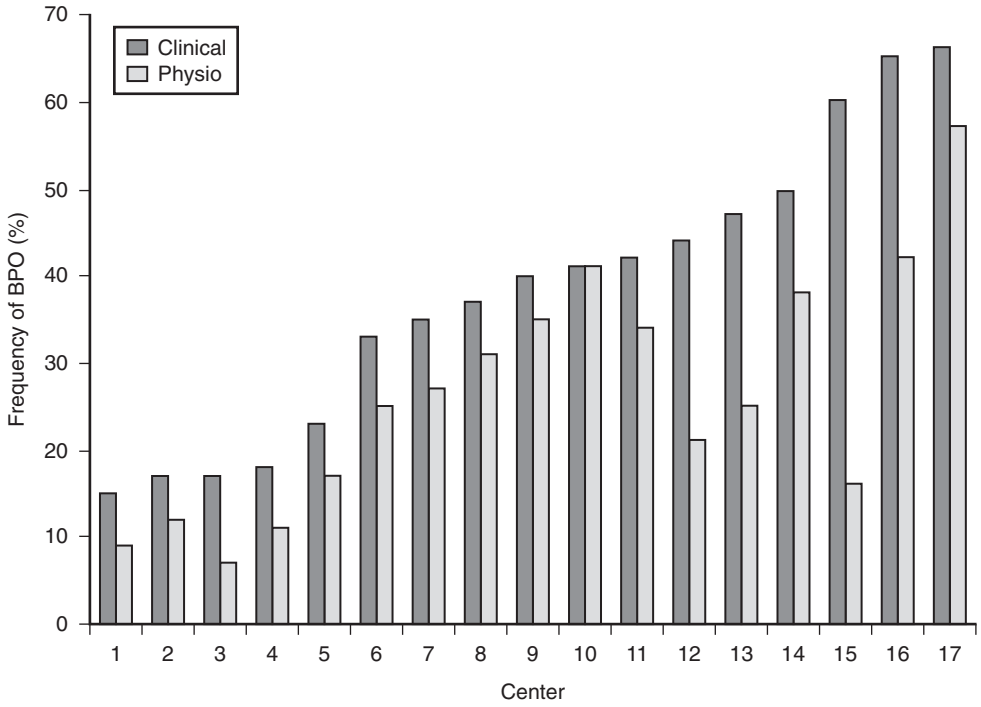

Figure 13-3 ■ Comparison of bronchopulmonary dysplasia (BPD) rate by the clinical definition and physiologic definition of BPD at each National Institute of Child Health and Human Development (NICHHD) Neonatal Network center. The overall reduction in mean BPD rate ($P < .0001$) and the reduction in variation ($P < .01$) between centers are both significant. (From Walsh MC, Yao Q, Gettner P, et al: Pediatrics 114:1305-1311, 2004.)

neonate (PPHN). Initially, the authors advocated rates as high as 150 breaths/min, but they subsequently suggested that some of the complications of hyperventilation could be prevented through the use of slower rates (60 breaths/min) and sufficient peak inspiratory pressure (PIP) to lower the $PaCO_2$ to the point at which oxygenation improves. This technique has been criticized as being "overly aggressive" by some clinicians, many of whom fail to understand the goals of therapy. This treatment is designed to ventilate an infant only to the highest $PaCO_2$ at which adequate oxygenation is seen (the "critical $PaCO_2$"). Many physicians mistakenly believe that simply "cranking up the ventilator" to achieve the lowest $PaCO_2$ is the primary goal, but this approach results in needless barotrauma. Accumulated evidence has indicated, however, that neurologic injury, especially cerebral palsy and hearing loss, may be more common in infants who are hyperventilated.[37] Because of these risks, the use of hyperventilation has become less frequent, both from a lung and a neurological perspective. It cannot be stressed enough that continued use of high pressures for prolonged periods of ventilatory support are associated with pulmonary and central nervous system injury and should be avoided whenever possible. It may be preferable in many instances, for example, to refer an infant who is large enough (i.e., 2 kg or larger) for ECMO rather than continue high-pressure ventilation.

If hyperventilation is used at all, it should be initiated cautiously in PPHN. Once the rate of 60 breaths/min is set, the PIP should be increased until the $PaCO_2$ begins to fall. At some point, oxygenation suddenly improves. This level is the critical $PaCO_2$. The PaO_2 should be kept at approximately 100 to 120 mm Hg to assist in pulmonary vasodilatation. PEEP usually is maintained at 2 to 5 cm H_2O unless the patient also has pneumonitis and volume recruitment within the lung is necessary to sustain oxygenation. Paralysis is sometimes necessary during this phase of illness, although it should be used judiciously. Paralysis removes the work of breathing contributed by the patient and may result in sudden deterioration of blood gases. If patients appear to be "fighting the ventilator," it usually is the result of hypoxemia or hypercarbia. Improvement in gas exchange through an alternative ventilatory approach will often reduce the agitation of the baby while avoiding paralysis. In addition, external stimulation should be kept to a minimum. Vasopressor agents (dopamine or dobutamine) often are beneficial, and intravenous administration of sodium bicarbonate may help in alkalinization.

Once the child has been stable for 12 to 24 hours, it is appropriate to challenge the infant by allowing $PaCO_2$ to increase slightly (3 to 5 mm Hg) by decreasing PIP by 1 to 2 cm H_2O. Excessively large decreases in PIP in the early phases of this disease can often result in sudden marked deterioration ("flip-flop") from which recovery is difficult. If oxygenation remains adequate, it is likely that the child has entered the transitional phase of PPHN, and slow, cautious weaning can proceed. Weans of PIP and FIO_2 should always be small (1 cm H_2O or 2% FIO_2) and infrequent to avoid flip-flop. The goal should be to have the child receive below 50% O_2 and a PIP of 25 cm H_2O within 48 hours. Once these levels are reached, management usually poses few difficulties.

TABLE 13-1 Historical and New Approaches to Neonatal Mechanical Ventilation

Approach	Rationale	Technique
Slow rate ventilation (Reynolds)	Improve oxygenation; decrease barotrauma.	Rate at 20-30 bpm. Increase MAP with longer T_I, or reversal of I:E ratio.
"Gentle ventilation" or permissive hypercapnia (Wung)	Accept higher $PaCO_2$ and lower pH to reduce airway and lung injury. Focus on adequate oxygenation.	Rate of 20-40 bpm, but increase rate preferentially to PIP. Keep PIP low; accept $PaCO_2$ up to 60 torr, occasionally higher. pH can be as low as 7.15-7.20 for brief periods.
Rapid-rate ventilation (Bland)	Use rapid rate and hand ventilation to achieve oxygenation at lower PIP. Reduce barotrauma; accept some inadvertent PEEP.	Rate of 60-80 bpm, higher at times, to maximum of 120-150. Keep low PIP; use shortened T_I.
Hyperventilation (Fox and Peckham)	Use rapid rate and PIP as necessary to reduce $PaCO_2$ to the *highest* level at which oxygenation occurs. Reduce right-to-left shunting by decreasing pulmonary artery pressure. In general, used to treat PPHN. Should be used cautiously in other diseases because of risk of air leak.	Rate of 60-150 bpm. Use PIP to reduce $PaCO_2$ to 35 torr or less. Achieve the *highest* $PaCO_2$ that allows oxygenation. Periodically challenge infant by decreasing support to see if PPHN has resolved or transition phase has begun.
High-frequency jet ventilation (Spitzer)	Use rate of 400-500 bpm at reduced pressure in the treatment of severe lung disease or pulmonary air leak. Extremely low tidal volume. Background sigh used to improve oxygenation.	Rate of 400-500 bpm. T_I of 0.02. Background sigh rate by conventional ventilator of 5-10 bpm with T_I of 0.5 sec. Avoid excessively low $PaCO_2$, common in HFJV. Maintain alveolar volume with PEEP.
High-frequency oscillatory ventilation—high-volume strategy (Friese, Bryan, deLemos)	Use rate of 600-900 bpm with alveolar recruitment technique to increase lung volume. Allows use of HFOV with decreased tidal volume and reduces lung injury.	Rate of 600-900 bpm. Give prolonged inflation periodically with bag and mask or ventilator control to recruit volume in lung. Wean by decreasing oscillatory pressure.
Patient-triggered ventilation: SIMV and A/C (Donn)	Allow patient to trigger and self-regulate (to some extent) level of ventilatory support that is required, thereby reducing barotrauma. With SIMV, patient breaths and ventilator breaths are synchronized to avoid "stacking" of pressures and simultaneous patient and ventilator breath. With A/C, patient triggers ventilator to deliver all breaths. Both forms have backup rate if patient becomes apneic.	SIMV: set ventilator rate at about 40-45 to start. Use approach similar to conventional IMV, keeping pressures at a minimum to exchange gas adequately, while reducing barotrauma. With A/C ventilation, set PIP and PEEP for adequate gas exchange; allow patient to increase rate of breathing to blow off CO_2. In both cases give adequate FIO_2 to keep PaO_2 at 60-80 mm Hg.
Tidal volume-guided ventilation or volume-guarantee ventilation	Consistent delivery of a uniform minimum V_T while maintaining the ability to set pressure limits.	Clinician sets upper limit of pressure and desired V_T. Ventilator attempts to deliver guaranteed V_T with lowest possible pressure. If pressure is inadequate to deliver volume, unit alarms to alert physician to increase pressure limit or lower V_T.
PAV and RMU (Schulze, Bancalari)	Microprocessor-controlled feedback loop to assist mechanical ventilation. Process allows clinician to provide support throughout the ventilatory cycle to ease work of breathing for the infant. Ventilator senses flows throughout respiratory cycle.	With PAV, desired assist flow above baseline is generated during inspiration to overcome airway and ventilator resistance. During RMU, the reverse occurs as circuit pressure falls below baseline and respiratory muscles are unloaded, further easing work of breathing.
Tracheal gas insufflation	Provision of fresh gas into the distal endotracheal tube reduces anatomic dead space and lowers V_T and pressure requirements.	Small continuous gas injection into the distal endotracheal tube is given at 0.5 L/min with another form of ventilation simultaneously being used, or with spontaneous breathing on CPAP.

A/C, Assist/control; *bpm,* breaths per minute; *CPAP,* continuous positive airway pressure; *I:E,* inspiratory-to-expiratory; *HFJV,* high-frequency jet ventilation; *HFOV,* high-frequency oscillatory ventilation; *MAP,* mean airway pressure; *PAV,* proportional assist ventilation; *PEEP,* positive end-expiratory pressure; *PIP,* peak inspiratory pressure; *PPHN,* persistent pulmonary hypertension of the neonate; *RMU,* respiratory muscle unloading; *SIMV,* synchronized intermittent mandatory ventilation; T_I, inspiratory time; V_T, tidal volume.

High-Frequency Ventilation

The concept of minimizing volutrauma and atelectotrauma is best seen in the use of *high-frequency ventilation,* which often reduces $PaCO_2$ with less barotrauma to the airways and lungs. *High-frequency jet ventilation (HFJV)* has been well established as an effective rescue tool for infants with RDS who require high levels of respiratory support or infants with pulmonary air leaks.[38,39] It has been our approach since 1985 to use this ventilatory strategy rather

than conventional ventilation with hyperventilation because of the reduced barotrauma and the improved outcomes in air leak syndromes. *High-frequency oscillatory ventilation (HFOV)*, however, does not appear to be as successful as HFJV in either treatment or prevention of air leaks.[40] Both HFJV and HFOV, however, often will improve oxygenation at lower pressures than conventional ventilation. Unfortunately, studies to date have not demonstrated significant prophylactic value for HFV when infants are randomized to HFV early during their hospital course, a very disappointing finding. However, it appears that HFV is an ideal rescue technique for patients who have encountered a variety of ventilatory difficulties, either with oxygenation or air leaks.

Inhalational Nitric Oxide

Inhaled nitric oxide (iNO) has emerged as the first significant pharmacologic agent used for lung protection. With the introduction of iNO as an adjunct to therapy in PPHN, there was a significant change in the management of the term or late preterm infant with pulmonary hypertension. Although there are still many neonates treated each year in the United States with ECMO, the number has fallen significantly compared to the peak era of ECMO during the early 1990s (see Chapter 16).[41] This change has been due to improved conventional ventilator approaches, the widespread use of HFV, and iNO. More recently, iNO has also been used to treat the premature infant as well, although results have been very inconsistent to date, with some studies revealing benefits, whereas others have shown no overt lung protective effects.[42-45] It appears that additional work will need to be done to define the precise value of iNO in the premature infant. Barrington and Finer[46] have recently written a superb review of the current situation.

Nitric oxide acts as a direct pulmonary vasodilator when it is given through a separate circuit to the patient on a ventilator. It appears to work most effectively in PPHN syndromes where there is little debris in the airway. Meconium aspiration syndrome with PPHN seems to respond less well than the "pure" forms of pulmonary hypertension. Approximately 30% to 40% of infants with PPHN will respond to this therapy, and ECMO may be avoided in a number of situations.[47] Arterial oxygenation appears to improve rapidly, even at nitric oxide concentrations as low as 1 to 2 ppm, although starting dose is usually 20 ppm. One must be cautious, however, to not use nitric oxide to the potential detriment of the lung. The excessively prolonged use of iNO in an attempt to avoid ECMO in the most severely affected larger patients may actually increase exposure to high ventilator pressures, prolong the ultimate length of stay, increase the risk of BPD, and be associated with a higher likelihood of neurologic injury. Infants should respond rapidly to iNO or they should be referred to an experienced ECMO center to prevent these injuries (see Chapter 14).

Gentle Ventilation

In contrast to hyperventilation, Wung et al.[48] at Babies Hospital in New York introduced the concept of *gentle ventilation* in the mid-1980s as a lung protective strategy. They advocated the use of ventilator rates of 20 to 40 breaths/min and sufficient pressures to allow adequate oxygenation while tolerating a $PaCO_2$ that was as high as 60 to 70 mm Hg rather than injure the lung by using higher pressures. If $PaCO_2$ could not be controlled, they recommended the use of more rapid rates (120 to 140 breaths/min) in an attempt to decrease $PaCO_2$. If this attempt failed, they suggested returning to the previous lower rates. The pH in this system was accepted at low levels (to 7.15) for periods of time as long as 24 hours. Weaning was accomplished with reduction in pressures as the infant's status improved. The results appear to be comparable with those from hyperventilation but with the added benefit of less chronic lung injury in the patient with PPHN. The use of this technique in premature infants with respiratory distress syndrome (RDS) has been reported, with a very low incidence of BPD (approximately 5%).[49] Furthermore, Wung and colleagues have suggested that the use of this approach may decrease the need for ECMO in PPHN.

The number of infants described in the medical literature to date who were managed with this approach has been small, and follow-up data on the results of this approach are limited. In certain nurseries, however, it appears that "gentle ventilation" is a valuable tool for some infants with severe respiratory disease. What Wung and colleagues have demonstrated is that the lungs of a critically ill neonate are fragile and need to be treated as such. In addition, their approach has shown neonatologists that tolerance of slightly higher CO_2 levels is preferable to continued battering of the lung with high-pressure ventilation.

The concept of "gentle ventilation" illustrates one of the most confusing aspects of managing respiratory distress in the newborn, namely, when and to what degree to intervene. The introduction of mechanical ventilation is potentially detrimental, and deciding to place an infant on mechanical ventilator support remains a difficult decision. In addition, determining what measurements (blood gases, graphics monitoring) should guide ventilator changes remains unclear. Permissive hypercapnia in preterm infants seems safe and may reduce the duration of assisted ventilation.[50] This strategy has particular appeal in that hypocarbia may be related to brain injury.[51] Severe hypercapnia may cause brain injury, however, which strongly suggests that there are excellent physiologic reasons why nature has seen fit to establish eucapnic ventilation as the normal range.[52] When using a strategy of permissive hypercapnia, it is important to minimize atelectasis because the recruitment and de-recruitment of lung regions are not optimal. In addition, although the data look promising when this strategy is implemented, long-term follow-up of infants managed with high levels of carbon dioxide has not been explored.

Patient-Triggered Ventilation

Patient-triggered ventilation, as previously indicated, has now become a standard part of the repertoire of neonatologists. In general, patient-triggered ventilation consists of two forms of mechanical ventilation: SIMV and A/C ventilation. As part of recent ventilator enhancements, these capabilities have been combined with pressure support ventilation or volume guarantee (VG), permitting a wide variety of approaches to minimize lung injury.

These techniques of ventilation are also discussed in Chapter 12.

With SIMV, the ventilator is synchronized to the infant's breathing pattern. If the patient triggering threshold is met within a specific time window (depending on the preset ventilator rate), a ventilator breath is not delivered and the infant breathes spontaneously. On the other hand, a ventilator breath is delivered if the infant fails to breathe. Examination of the baby's breathing pattern with SIMV will reveal both spontaneous breaths and ventilator breaths. The value of this form of support is that pressures within the airway are not stacked, so airway and lung injury theoretically is reduced and gas is not inadvertently "dumped" from the ventilator because airway pressures are reached prematurely. Although many neonatologists will use SIMV as their primary mode of ventilator support for neonates, it appears to have greater benefit as a weaning tool or if overdistension is present with A/C ventilation, particularly in the extremely low-birth-weight infant with either RDS or pulmonary insufficiency of prematurity.

A/C ventilation is another form of patient-triggered support. With A/C ventilation, each infant breath that reaches the trigger threshold will initiate a full ventilator breath. If the infant is apneic or the effort is inadequate to trigger a ventilator breath, the ventilator will deliver a preset backup rate to the baby. All breaths in this form of ventilation appear similar and are entirely ventilator derived. No spontaneous infant breaths ever occur on A/C support, unless the generated pressure is so low that it fails to trigger the ventilator. With A/C ventilation, the infant is fully synchronized to the ventilator. With the use of termination sensitivity as an adjunct, inspiratory time will be limited to a percentage of maximum flow, and air trapping usually can be reduced or eliminated (Fig. 13-4).

A/C ventilation is an effective form of initial treatment for many babies with a variety of neonatal lung diseases in the early stages of their illness. It has been our experience that the use of A/C ventilation will limit pressure exposure for the infant, and the infant often will spontaneously select a rate that is optimal for gas exchange, with a lower pressure than would usually be set on SIMV. Minute ventilation is usually higher on A/C ventilation than on SIMV.[53] It is more difficult, however, to wean babies who are on A/C ventilation. Occasionally some overdistension will occur if there is excessive neural drive to breathe, and prolonged use of A/C may lead to some diaphragmatic muscle atrophy and further weaning difficulty. Consequently, it is helpful to move an infant from A/C ventilation to SIMV when he or she begins to show signs of recovery from the lung disease.

With A/C ventilation, one must also be cautious of "autocycling" of the ventilator. This problem can occur when there is erroneous triggering of the ventilator from leaks in the system, buildup of humidity in the circuit, or sensing of cardiac pulsations as breaths. Frequent breaths are delivered unnecessarily to the baby. We have also seen an occasional infant on A/C support who does well while he or she is awake, with good gas exchange, but who has inadequate blood gases while sleeping or sedated. In such cases, it would be helpful to have the capability of using two separate ventilator settings, one for waking periods and one during apneic support when slightly more pressure may be necessary for gas exchange. Therefore most clinicians will use volume guarantee ventilation in conjunction with SIMV or A/C to avoid this situation.

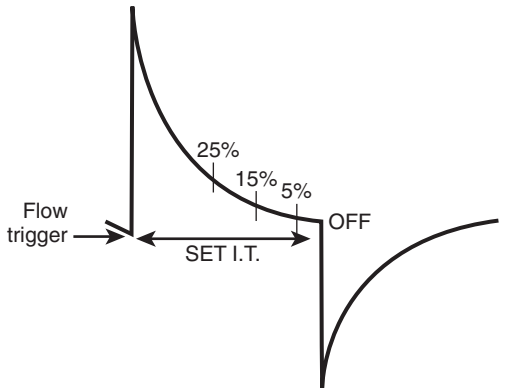

Figure 13-4 ■ Termination sensitivity or expiratory trigger. Inspiration is initiated by a change of flow at the airway. When the lungs have inflated, flow decreases at the proximal airway, resulting in breath termination. The point of termination can be adjusted by the clinician, and represents a percentage of peak inspiratory flow. For example, a 10% termination sensitivity will end the breath when flow is 10% of peak flow. (From Becker MA, Donn SM, Bird VIP Gold Ventilator. In Donn SM and Sinha SK (eds). Manual of Neonatal Respiratory Care, 2nd ed, Mosby, Elsevier, 2006, p. 251)

Pressure-Support Ventilation

An adjunctive therapy during patient-triggered ventilation is *pressure-support ventilation,* in which spontaneous infant breaths are partially or fully augmented by an inspiratory pressure assist above baseline PEEP. This modification eases the work of breathing for the infant by allowing additional pressure delivery to overcome the various sources of resistance encountered by the infant, such as the endotracheal tube, circuitry, and valves. This form of therapy can be used alone or, more commonly, in association with SIMV. It is not necessary when A/C ventilation is employed, because the ventilator will provide the necessary inhalational assist. Because it is fully synchronized with the infant's ventilation, it can be used to treat babies who are becoming fatigued from work of breathing, for sedated infants, and for infants who are in a weaning phase of ventilation who are first beginning to reuse their respiratory musculature. When used in conjunction with SIMV, it is important that the SIMV rate not be set too high, which may reduce the baby's impetus to breathe and would nullify one of the primary purposes of pressure support. Typical starting levels for pressure support are approximately 6 to 10 cm H_2O, and adjusted as necessary, based on blood gases and the infant's perceived work of breathing, as guided by graphics monitoring.

Volume-Guarantee Ventilation

Tidal volume–guided ventilation or *volume-guarantee ventilation* is a more recent approach to therapy in which the clinician sets a mean tidal volume to be delivered by the ventilator while still allowing management of ventilator pressures. In essence it is a variation of pressure-support ventilation in which volume, not pressure, guides the delivery of an augmented breath. The goal in this form of ventilation is to minimize variation in delivery of tidal

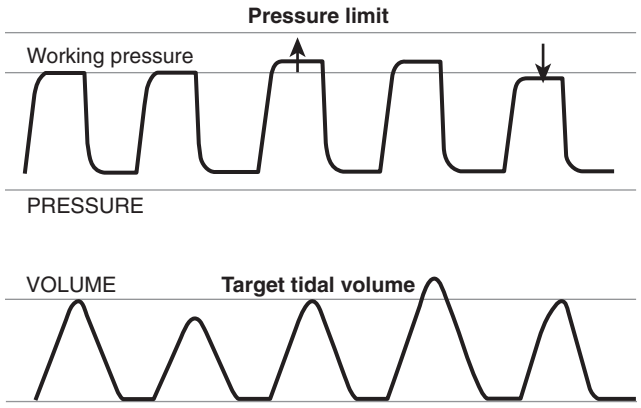

Figure 13-5 ■ Principles of operation of volume guarantee. The device automatically adjusts the inspiratory pressure, based on exhaled tidal volume of the previous breath, to deliver the tidal volume (VT) that is set by the user. As illustrated, the VT of the first breath is on target, thus no adjustment is made. The second breath falls short of the target VT, leading to an increase in working pressure of the next breath. The third breath is on target, thus there is no change in working pressure. The fourth breath is above the target, leading to a drop in the working pressure for the fifth breath, bringing the VT back to the target value. (Modified from Keszler M: Early Hum Dev 82:811-818, 2006; with permission.)

volume, which is thought to be the cause of pulmonary trauma in many infants (Fig. 13-5). Volume guarantee is available on the Dräeger Babylog 8000 ventilator, as well as a number of other units, and is often used in conjunction with patient-triggered modalities. When the physician sets the upper limit of PIP during patient-triggered support, the ventilator attempts to deliver the set guaranteed tidal volume using the lowest airway pressure possible. When the expired tidal volume exceeds the upper limit PIP, the ventilator will use a lower PIP on the next breath. If the set tidal volume cannot be delivered within the PIP set by the clinician, an alarm alerts the operator to reset the PIP to a higher level or adjust the guaranteed tidal volume to a lower level. The effects of volume guarantee on gas delivery can be seen in Figure 13-6.

The standard starting tidal volume (VT) for most infants is approximately 4 to 6 mL/kg, although occasionally, levels as high as 8 to 10 mL/kg may be needed. PIP maximum should initially be set at a level of about 15 to 20 cm H_2O, and adjusted as necessary. Although data to date are not substantial, it appears that volume guarantee can achieve similar levels of gas exchange with slightly lower mean levels of PIP.[54] One of the most valuable aspects of volume guarantee is the automatic reduction of PIP delivered to the infant as lung compliance improves. It appears that volume guarantee will reduce ventilator support more rapidly than other patient triggered approaches, but there have been no definitive studies that have established a clear long-term reduction in chronic lung disease with this strategy of lung protection.

A variant of the volume guarantee for each breath is guaranteed *minute* ventilation, in which a desired minute ventilation is designated, with the ventilator providing a mix of guaranteed tidal volume and frequency to provide the desired minute ventilation. This approach to guaranteed volume ventilation is used less often, however, than the volume guarantee method described above.

Proportional Assist Ventilation

Proportional assist ventilation (PAV) and *respiratory muscle unloading (RMU)* require even more sophisticated computer assistance to achieve their effects. These innovative approaches servocontrol ventilator pressure throughout inspiration (in the case of PAV) or throughout the entire respiratory cycle (during RMU). With both forms of ventilator support, the infant's respiratory effort is continuously monitored. During inspiration, as with pressure-support ventilation, pressure rises above baseline to produce the desired inspiratory resistive unloading, thereby easing work of breathing. During exhalation, circuit pressure falls below baseline end-distending pressure, facilitating elastic and resistive unloading throughout that phase of the

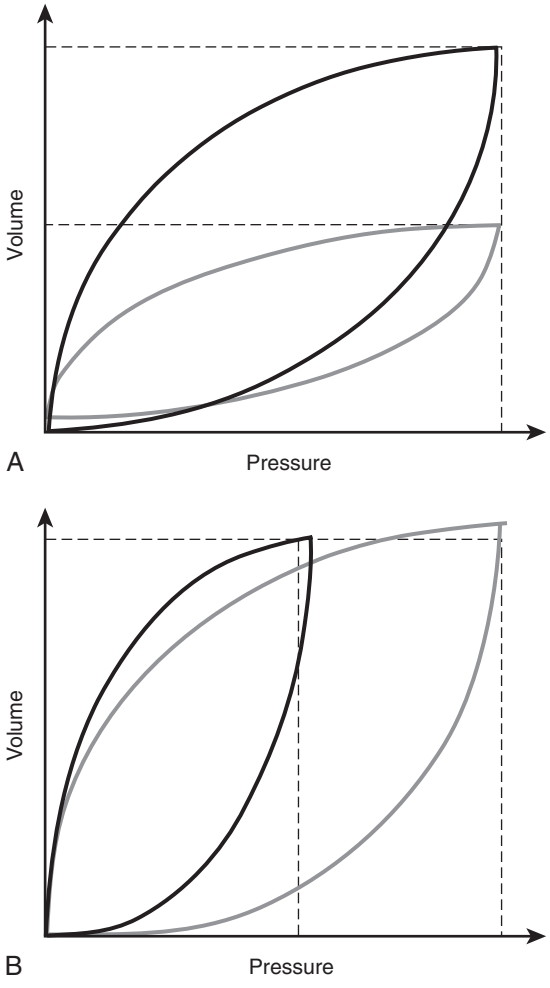

Figure 13-6 ■ The diagram in *A* demonstrates pressure-volume loops in pressure-limited ventilation. Pressure is plotted on the horizontal axis and volume is plotted on the vertical axis. In a low compliance lung (*dotted line*), less volume is delivered to the lung than in a higher compliance situation (*solid line*).The pressure used is the same in both situations. In *B*, the pressure volume loops for both the low compliance lung (*dotted line*) and the higher compliance lung (*solid line*) reveal consistent volume delivery. The low compliance situation, however, requires a higher pressure to deliver the same gas volume. (From Singh J, Sinha SK, Donn SM. Volume-Targeted Ventilation of Newborns. Clin Perinatol. 2007;34:96)

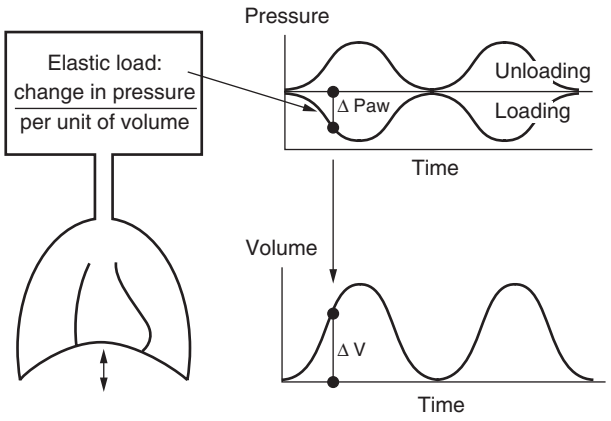

Figure 13-7 ■ Mechanical model of respiratory elastic loading and unloading during the respiratory cycle. Air flow increases during inspiratory to augment the breath and reduce the work of breathing for the infant. (From Schulze A, Bancalari E: Clin Perinatol, 28:561-578, 2001.)

respiratory cycle (Figs. 13-7 and 13-8). With this form of support, the resulting airway pressure is a moving variable that changes with the needs of the infant at any point during the respiratory cycle and is a weighted summation of a combination of air flow and tidal volume above the baseline (usually PEEP) level. Although human infant studies with PAV/RMU are somewhat limited at the present time, results of work by Schulze et al.[55] appear very encouraging. In that trial, PAV safely maintained gas exchange at lower mean airway pressures compared with PTV without adverse effects in this population. Backup conventional ventilation breaths must be provided, however, to prevent apnea-related desaturations. There may also be additional overall cardiovascular stability as an added benefit to infants treated with this form of support. Few centers are using this form of ventilatory support yet, although the concepts appear promising. Additional larger-scale trials will unquestionably be seen in the near future.

Tracheal Gas Insufflation

The added space of the ventilator adapter and the endotracheal tube result in a significant amount of anatomic dead space during mechanical ventilation, particularly to the airway of an extremely low-birth-weight (less than 1000 g) infant. Through a mechanism of tracheal gas insufflation, fresh gas is delivered to the more distal part of the endotracheal tube and aids in washing out CO_2 from the airway. PIP and tidal volume usually can be decreased.[56] These factors may reduce barotrauma and volutrauma in these infants, and results of early studies appear promising. The technique, however, has not been used widely as yet in infants.

Commentary

Respiratory insufficiency remains a frequently occurring and challenging complication of birth. Managing the pulmonary status of a sick neonate is a great responsibility. The decision to place an infant on respiratory support and the selection of appropriate ventilator settings should be made with an understanding of the ramifications of those decisions. When many breaths are imposed on an infant each minute, even small deviations from perfection can be significant and potentially catastrophic in terms of lung injury and long-term neurologic impairment. Evidence suggests that, despite recent advances in technology, length of hospital stay for the preterm population has begun to increase, and BPD remains a significant complication in every nursery.

As is evident from much of this discussion, the technologic innovations in positive-pressure ventilation during the past several years have been substantial and, no doubt, confusing to many neonatologists. There is likely to be even more innovation in the future, as computer technology becomes even faster in execution speed. Many of these techniques may offer theoretical benefits to infants, but actual demonstration of substantial clinical value has been sparse to date. Moreover, some approaches are so recent that they have been limited to small scale trials. The clinician should always keep in mind that the large majority of infants with lung disease can be successfully ventilated with standard positive-pressure ventilators. The use of SIMV with pressure support or volume guarantee will care for the overwhelming majority of neonates with acceptable outcomes.

When one is caring for an extremely premature infant whose lungs are never supposed to be subject to positive-pressure ventilation (or even air breathing) at such an early stage of development, it simply may not be possible to

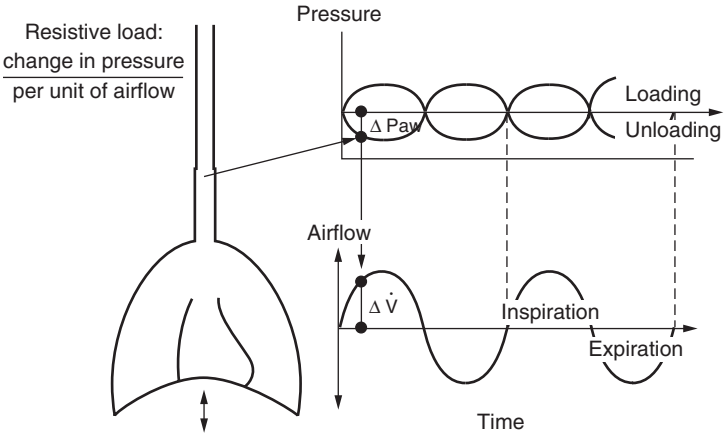

Figure 13-8 ■ Mechanical model of resistive loading and unloading during the respiratory cycle. (From Schulze A, Bancalari E: Clin Perinatol 28:561-578, 2001.)

limit entirely the pulmonary injury that occurs in many babies. In addition, no approach to ventilatory support should ever be used unless the physician is well aware of the potential risks, both acute and long term, especially with respect to neurologic injury and neurodevelopmental handicap (see Chapter 28). In our own work over many years, the follow-up of our patients over time has been instrumental in allowing us to work to improve outcomes. Although this information occasionally was disappointing to us at first, the obligation to publish this work and consider alternatives has been important in our own education and, we hope, to other clinicians. We believe that all neonatologists have an obligation to examine their infants carefully and publish their findings so that others can benefit from their accomplishments, as well as from their errors. No approach to respiratory support is complete without such information.

Although studies ultimately will help frame a preferred sequence of ventilators, modalities, and therapies that provide optimal lung protection for a general population of infants, the care will always need to be individualized. No neonate is supposed to have gas forced into the lung under positive pressure; therefore, all ventilators are two-edged swords. Ventilators keep babies alive, but at some cost to the infant. As we continue to undertake the care of ever tinier and more fragile babies, as well as larger infants with pulmonary insufficiency, we will continue to see infants who manifest many long-term problems. Ultimately, optimal pulmonary outcomes can be achieved only when we can guarantee that neurodevelopmental outcomes will also be as good as possible.

Addendum: Liquid Ventilation

In the last edition of this textbook, the use of liquid ventilation appeared to be on the verge of emerging as a major part of the armamentarium of the neonatologist. Unfortunately, work in this area has essentially stopped, and there appears to be little likelihood of a reappearance of this therapy in the near future. In general, the manufacturers of perfluorocarbons have been unwilling to assume the risk of adverse long-term effects that might occur with the instillation of perfluorocarbons into the lung. As a result, the perfluorochemicals that appeared most promising have been withdrawn from research trials and none have been submitted for FDA approval for the application of neonatal ventilation.

Respiratory morbidity is caused, in part, by tidal lung inflation and ventilation of the atelectatic lung. With liquid instillation of the lung, alveolar volumes can be gently recruited and the air-fluid interface eliminated, thereby reducing the high surface forces that are present in the air-filled, surfactant-deficient lung. In addition to reduced surface forces, however, a liquid solution must be able to hold sufficient oxygen to permit adequate gas delivery within the air spaces. Saline solubility for O_2 is only 3 mL per 100 mL of fluid at 1 atm, or about 5% of that needed by the infant. As a result, if liquid breathing is contemplated, an alternative solution capable of dissolving and exchanging far greater concentrations of O_2 must be used.

Solutions for Liquid Ventilation

The first reports of mammalian survival during breathing of oxygenated perfluorocarbon (PFC) liquids came from Clark and Gollan in 1966.[57] Additional work has demonstrated that mammals can successfully breathe these liquids and subsequently return to air-breathing conditions.[58] Much of the work in liquid ventilation has, therefore, focused on PFCs. PFCs have a high solubility for respiratory gases and are formed by the replacement of all carbon-bound hydrogen atoms on organic compounds with fluorine. Oxygen dissolves in PFCs approximately 20 times more readily than in saline. Carbon dioxide (CO_2) solubility also is high, although more variable depending on the specific perfluorochemical. In addition to demonstrating excellent solubility of O_2 and CO_2, these liquids are odorless and colorless, have low surface tension properties, and are generally immiscible in lipids, alcohol, and water. They generally are biologically inert and are absorbed systemically in low concentrations. They typically evaporate rapidly in room air.

Although their attributes tend to make PFCs an ideal respiratory medium for gas exchange, these substances have high density, viscosity, and diffusion coefficients, which make the work of breathing during spontaneous respiration with them significantly greater than that needed for gas breathing.[59] In particular, the higher viscosity markedly increases resistance to flow, prolonging both inspiratory and expiratory time constants. In addition, the diffusion coefficient is prolonged so that the inspiratory time requirement is further increased. Because expiratory flow rates are reduced markedly in the PFC-filled lung compared with the gas-filled lung and because they are inversely proportional to lung volume, expiratory time is substantially greater than that seen during gas breathing. One can, therefore, conceive of PFC breathing as a process in which respiratory rate is reduced, inspiratory and expiratory times are more prolonged, and an exchange period or "dwell" time is required for adequate gas exchange to occur.

In animal trials, these liquids have been used for periods as long as 30 hours with no apparent ill effects. At the present time, there do not appear to be any physiologic limitations to the duration of exposure of mammals to PFCs in liquid breathing. The long-term toxicities remain unknown. Histologic evaluation of prematurely delivered animals ventilated with PFCs and recovered to air respiration demonstrates decreased hyaline membrane formation, reduced injury to airway epithelium and distal air spaces, and clearance of alveolar debris.[60]

Systemically, PFCs appear to be eliminated almost entirely through the lungs, with small amounts excreted through the skin. Little PFC is absorbed by the pulmonary circulation during therapy, although small amounts may remain stored in fat cells for years after liquid breathing.[61,62] PFCs appear to be biologically inert and do not undergo transformation; therefore, toxicity seems unlikely. Elimination in these conditions appears to be dependent on subsequent reentry into the circulation, with ultimate excretion occurring through the usual routes of the lungs and skin. Perflubron, a brominated perfluorochemical used during magnetic resonance imaging, has been shown

to be safe when it is administered intratracheally. PFCs can also be used for removal of airway debris, as seen in meconium aspiration syndrome; drug delivery (antibiotics, bronchodilators, cancer chemotherapeutics, surfactants, vasopressors, vasodilators) to the lung; and radiologic applications. The PFC-filled organ has low acoustic attenuation; thus PFCs are ideal for ultrasound applications, and the presence of fluorine is valuable in magnetic resonance imaging. Furthermore, perfluorochemicals are radiopaque and consequently of value in standard radiographic applications.

Techniques and Results of Liquid Breathing

Human studies with perfluorochemicals were initially quite promising. Liquid ventilation seemed most applicable in assisting the surfactant and structural deficiencies of the preterm lung. Surface tension forces were reduced or eliminated and lung recruitment could be optimized and atelectasis gently reexpanded, while the fluid environment of the developing fetal lung can be reproduced.[63,64] Application to the term infant with structural lung disease (e.g., congenital diaphragmatic hernia [CDH]) or lung disease associated with airway or lung parenchymal debris (e.g., aspiration syndromes, pneumonia) has also been supported by animal data. Investigation of a lamb preparation of CDH supported with partial liquid ventilation (PLV), either prophylactically at birth or rescued after a period of gas ventilation, showed improved gas exchange and compliance compared to conventional gas ventilation.[65] Perfluorochemicals also had apparent value in a variety of imaging applications and in debris removal from the lung and also appeared to have antiinflammatory properties.

The initial liquid ventilation study enrolled premature human infants who were near death at the time of treatment.[53,54] A gravity-assisted approach was used and tidal volumes of liquid were given in brief cycles. The infants tolerated the procedure, showed improvement in several physiologic parameters including lung compliance and gas exchange, and maintained some improvement after liquid ventilation was discontinued. The protocol used a form of total liquid ventilation, but it also reported on the sustained benefit of gas ventilating the liquid-filled lung: PLV. Subsequent protocols have used a PLV technique.

Greenspan et al.[66] reported on six term infants with respiratory failure whose status was not improving while they were receiving ECMO. The infants were treated with PLV using LiquiVent for up to 96 hours, with hourly dosing. Dynamic pulmonary compliance increased significantly and lung volume was recruited. The authors concluded that the technique appeared to be safe and improved lung function in these critically ill term infants.

These clinical reports have described few adverse effects. Filling and subsequent ventilation have generally been well tolerated, even in these unstable populations. One noteworthy phenomenon has been the appearance during treatment of tenacious debris, which causes endotracheal tube occlusion and interferes with gas exchange. It has not been determined whether this represents alveolar and deep pulmonary secretions that otherwise would not be mobilized or an exudative response to the liquid.

Future of Liquid Breathing

Although the results of initial studies of perfluorochemical respiration appeared encouraging, many questions remain. The long-term efficacy and safety of these substances need to be defined in further trials. While animal work has continued, human trials have been essentially stopped. Only occasional rescue attempts have been undertaken.[67] The optimal PFC for specific clinical situations is uncertain, and much work still is required for the establishment of an optimal delivery system for therapy of the human infant. The spectrum of drugs that can be effectively delivered by perfluorochemicals must be determined, as well as the efficacy of combination therapies. Safety issues remain to be resolved, and there have been reports of prolonged retention of perfluorochemicals years after therapy.[68] Liquid breathing appears to be an important therapy, however, and the work that is currently in progress may reawaken this lung protective strategy for use in the neonate, if safety issues can be resolved.

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14 Special Ventilation Techniques III: Inhaled Nitric Oxide Therapy*

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Inhaled nitric oxide (iNO) therapy causes potent, selective, sustained pulmonary vasodilation and improves oxygenation in term newborns with severe hypoxemic respiratory failure and persistent pulmonary hypertension.[1-6] Multicenter randomized clinical studies have demonstrated that iNO therapy reduces the need for extracorporeal membrane oxygenation (ECMO) treatment in term neonates with hypoxemic respiratory failure.[7,8]

The role of iNO therapy has been extensively studied, leading to regulatory approval in 1999 by the United States Food and Drug Administration of the treatment of near-term and term newborns with hypoxemic respiratory failure and evidence of persistent pulmonary hypertension of the newborn (PPHN). Since the last edition of this textbook, considerably more has been learned about the potential role of iNO in the premature newborn, indicating possible benefits in both bronchopulmonary dysplasia (BPD) prevention and neuroprotection. In this chapter, we review an approach to the initial evaluation of the hypoxemic newborn for treatment with iNO, summarize the clinical experience with iNO in near-term and term newborns, and propose guidelines for the use of iNO in this population. We also review the current evidence for the use of iNO in the premature newborn, although its use remains investigational in this population.[9]

Background

The physiologic rationale for iNO therapy in the treatment of neonatal hypoxemic respiratory failure is based upon its ability to achieve potent and sustained pulmonary vasodilation without decreasing systemic vascular tone (Fig. 14-1).[10] Persistent pulmonary hypertension of the newborn (PPHN)[11] is a syndrome associated with diverse neonatal cardiac and pulmonary disorders that are characterized by high pulmonary vascular resistance (PVR) causing extrapulmonary right-to-left shunting of blood across the ductus arteriosus and/or foramen ovale (see Chapter 26) (Fig. 14-2).[12,13] Extrapulmonary shunting due to high PVR in severe PPHN can cause critical hypoxemia that is poorly responsive to inspired oxygen or pharmacologic vasodilation. Vasodilator drugs administered intravenously, such as tolazoline and sodium nitroprusside, often are unsuccessful because of systemic hypotension and an inability to achieve or sustain pulmonary vasodilation.[14,15] Thus the ability of iNO therapy to selectively lower PVR and decrease extrapulmonary venoarterial admixture without affecting blood pressure accounts for the acute improvement in oxygenation observed in newborns with PPHN.[16]

As described in children[17] and adults with severe respiratory failure,[18] oxygenation can improve during iNO therapy in some newborns who do not have extrapulmonary right-to-left shunting. Hypoxemia in these cases is primarily due to intrapulmonary shunting caused by continued perfusion of lung units that lack ventilation (e.g., atelectasis), with variable contributions from ventilation-perfusion ($\dot{V}/\dot{Q}$) inequality. Distinct from its ability to decrease extrapulmonary right-to-left shunting by reducing PVR, low-dose iNO therapy can improve oxygenation by redirecting blood from poorly aerated or diseased lung regions to better aerated distal air spaces ("microselective effect").[19]

In addition to its effects on vascular tone and reactivity, other physiologic targets for iNO therapy in hypoxemic respiratory failure may include direct effects of NO on lung inflammation, vascular permeability, and thrombosis in situ. Although some laboratory studies have suggested that NO can potentiate lung injury by promoting oxidative or nitrosative stress,[20] inactivating surfactant, and stimulating inflammation,[21] other studies have demonstrated striking antioxidant and antiinflammatory effects in models of lung injury.[22-24] Thus clinical benefits of low-dose iNO therapy may include reduced lung inflammation and edema, as well as potential protective effects on surfactant function,[25] but these effects remain clinically unproven (Box 14-1).

Finally, the diagnostic value of iNO therapy is important because failure to respond to iNO raises important questions about the specific mechanism of hypoxemia. Poor responses to iNO should lead to further diagnostic evaluation for "unsuspected" anatomic cardiovascular or pulmonary disease (see Chapter 26).

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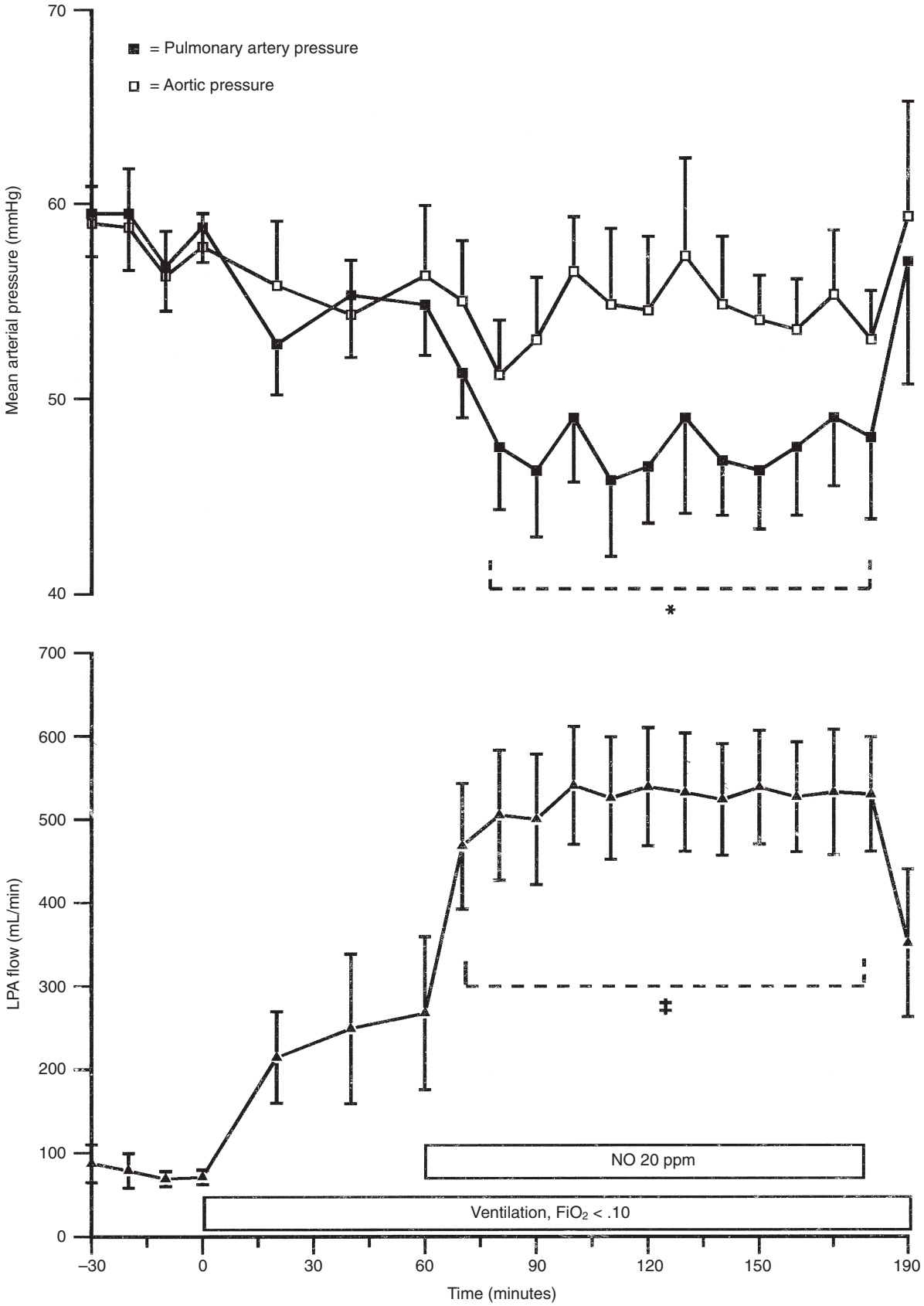

Figure 14-1 ■ Inhaled nitric oxide causes selective and sustained pulmonary vasodilation. (From Kinsella JP, Abman SH: J Pediatr 136:717-726, 2000.)

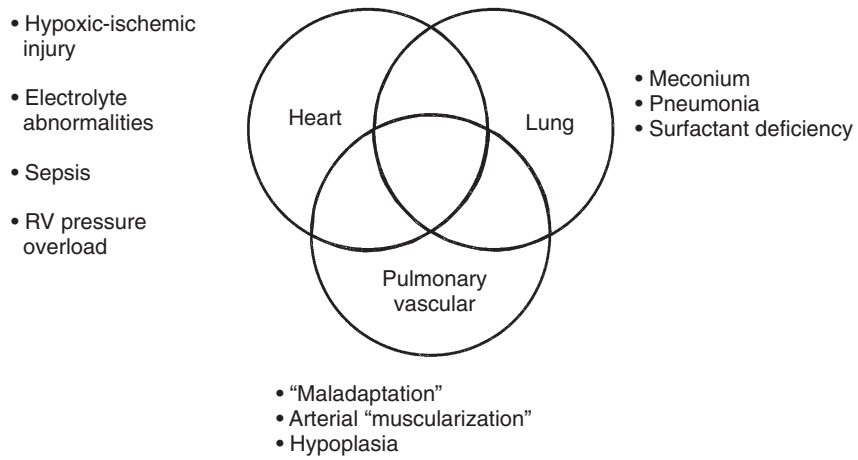

Figure 14-2 ■ Disorders associated with persistent pulmonary hypertension in the newborn (PPHN).

Box 14-1 POTENTIAL BENEFICIAL EFFECTS OF LOW-DOSE INHALED NITRIC OXIDE IN HYPOXEMIC RESPIRATORY FAILURE

1. Pulmonary vasodilation → decreased extrapulmonary right-to-left shunting
2. Enhanced matching of alveolar ventilation with perfusion
3. ↓ Inflammation (↓ lung neutrophil accumulation)
4. ↓ Vascular leak and lung edema
5. Preservation of surfactant function
6. ↓ Oxidant injury (inhibition of lipid oxidation)
7. Preservation of vascular endothelial growth factor expression
8. Altered proinflammatory gene expression

Physiology of Nitric Oxide in the Pulmonary Circulation

The fetal circulation is characterized by high PVR. Pulmonary blood flow accounts for less than 10% of combined ventricular output in the late-gestation ovine fetus.[26] Mechanisms responsible for maintaining high fetal PVR and causing sustained pulmonary vasodilation at birth are incompletely understood; however, studies in fetal and transitional pulmonary vasoregulation have led to increased understanding of the normal physiologic control of PVR. Fetal and neonatal pulmonary vascular tone is modulated through a balance between vasoconstrictor and vasodilator stimuli, including mechanical factors (e.g., lung volume) and endogenous mediators.

The pharmacologic activity of nitrovasodilators derives from the release of NO, which was recognized as a potent vascular smooth muscle relaxant as early as 1979.[27] In 1987 investigators from two separate laboratories reported that the endothelium-derived relaxing factor (EDRF) was NO or an NO-containing substance.[28,29] NO modulates basal pulmonary vascular tone in the late-gestation fetus; pharmacologic NO blockade inhibits endothelium-dependent pulmonary vasodilation and attenuates the rise in pulmonary blood flow at delivery, implicating endogenous NO formation in postnatal adaptation after birth.[30] Increased fetal oxygen tension augments endogenous NO release,[31,32] and the increases in pulmonary blood flow in response to rhythmic distension of the lung and high inspired oxygen concentrations are mediated in part by endogenous NO release.[33] However, in these studies the pulmonary circulation was structurally normal. Studies using a model of PPHN in which marked structural pulmonary vascular changes are induced by prolonged fetal ductus arteriosus compression demonstrated that the structurally abnormal pulmonary circulation also was functionally abnormal.[34,35] Despite the progressive loss of endothelium-dependent (acetylcholine) vasodilation with prolonged ductus compression in this model, the response to endothelium-independent (atrial natriuretic peptide, NO) vasodilation was intact.

Exogenous (inhaled) NO causes potent, sustained, selective pulmonary vasodilation in the late-gestation ovine fetus.[36] Based on the chronic ambient levels considered to be safe for adults by regulatory agencies in the United States,[37] studies were performed in near-term lambs using inhaled NO at doses of 5, 10, and 20 ppm. Inhaled NO caused a dose-dependent increase in pulmonary blood flow in mechanically ventilated newborn lambs.[38] Inhaled NO at 20 ppm did not decrease coronary arterial or cerebral blood flow in this model.

Roberts et al.[39] studied the effects of inhaled NO on pulmonary hemodynamics in mechanically ventilated newborn lambs. Inhaled NO reversed hypoxic pulmonary vasoconstriction, and maximum vasodilation occurred at doses greater than 80 ppm. They also found that the vasodilation caused by inhaled NO during hypoxia was not attenuated by respiratory acidosis in this model. Berger et al.[40] investigated the effects of inhaled NO on pulmonary vasodilation during group B streptococcal sepsis in piglets. Inhaled NO at 150 ppm for 30 minutes caused marked pulmonary vasodilation but was associated with physiologically significant increases in methemoglobin concentrations. Corroborating studies in other animal models support the observations that inhaled NO is a selective pulmonary vasodilator at low doses (less than 20 ppm).[41-43]

Initial Evaluation of the Term Newborn for Inhaled Nitric Oxide Therapy

Although extensive reference material is available to the clinician when a specific diagnosis has been determined for the hypoxemic term newborn, an approach to the initial evaluation of the cyanotic newborn has received less attention. In this section, we propose an approach to the evaluation of the hypoxemic newborn that may be useful in clarifying the etiology of hypoxemia and in assessing the need for iNO treatment (Fig. 14-3).

History

Evaluation of the newborn with cyanosis begins with an approach designed to assess the primary cause of hypoxemia. Marked hypoxemia in the newborn can be caused by parenchymal lung disease with $\dot{V}/\dot{Q}$ mismatch or intrapulmonary shunting, pulmonary vascular disease causing extrapulmonary right-to-left shunting (PPHN), or

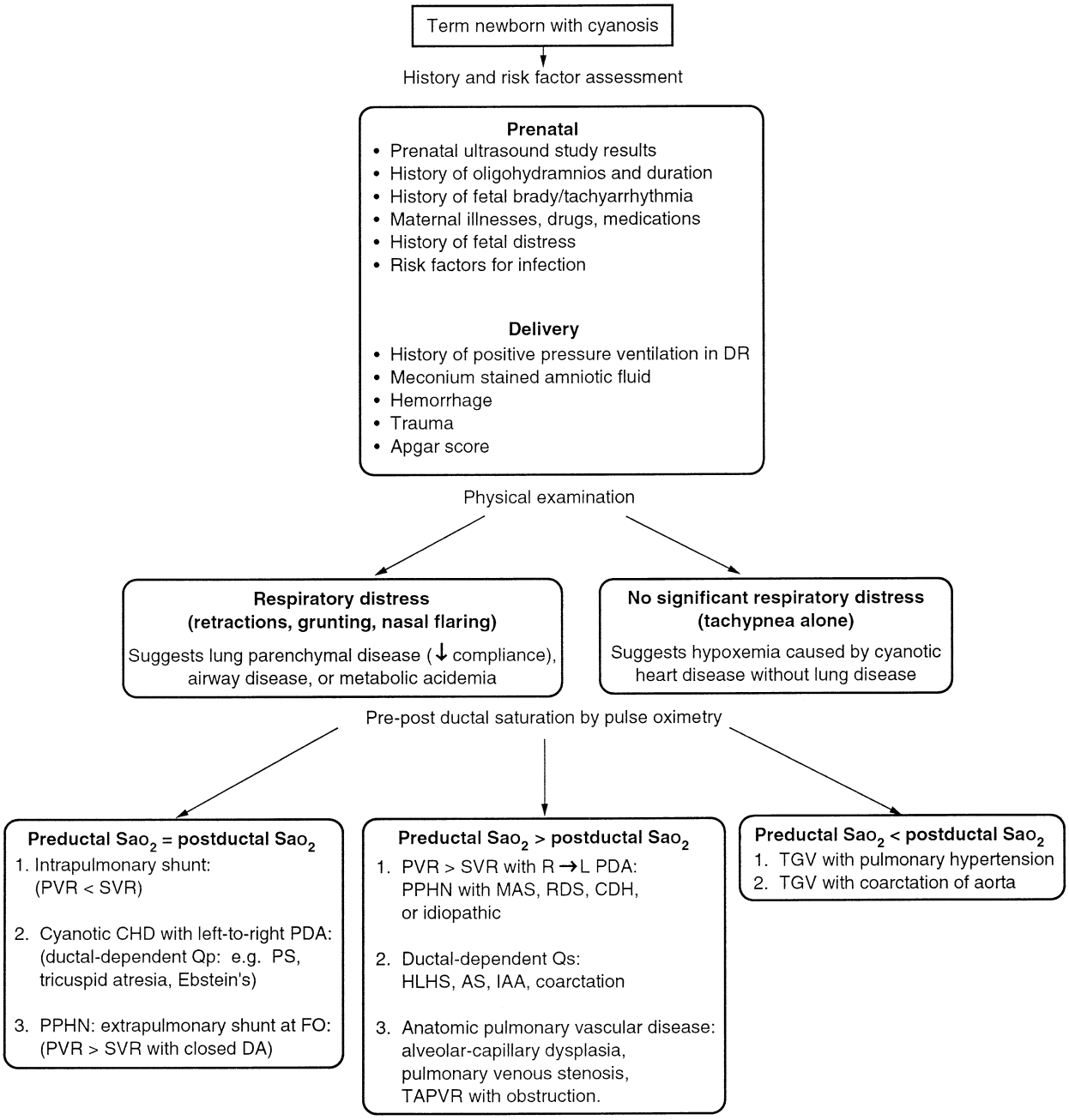

Figure 14-3 ■ An approach to evaluation for inhaled nitric oxide therapy in the cyanotic newborn. *AS,* Aortic stenosis; *CDH,* congenital diaphragmatic hernia; *DA,* ductus arteriosus; *DR,* delivery room; *FO,* foramen ovale; *HLHS,* hypoplastic left heart syndrome; *IAA,* interrupted aortic arch; *MAS,* meconium aspiration syndrome; *PDA,* patent ductus arteriosus; *PPHN,* persistent pulmonary hypertension of the newborn; *PVR,* pulmonary vascular resistance; *RDS,* respiratory distress syndrome; *SVR,* systemic vascular resistance; *TAPVR,* total anomalous pulmonary venous return; *TGV,* transposition of the great vessels.

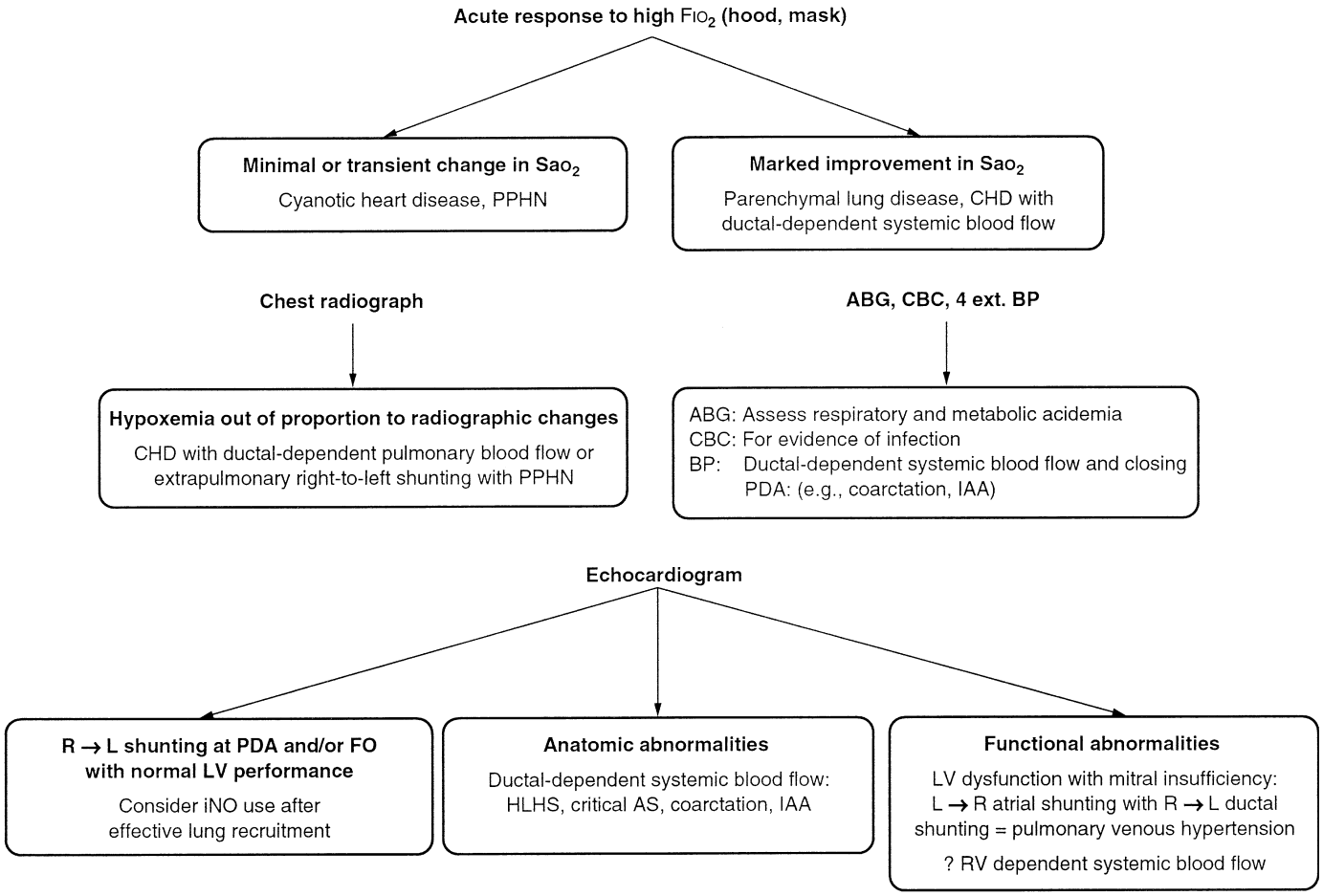

Figure 14-3 ■ *continued*

anatomic right-to-left shunting associated with congenital heart disease. Evaluation should begin with the history and assessment of risk factors for hypoxemic respiratory failure. Relevant history may include the results of prenatal ultrasound studies. Lesions such as congenital diaphragmatic hernia (CDH) and congenital cystic adenomatoid malformation are diagnosed prenatally with increasing frequency. Although many anatomic congenital heart diseases can be diagnosed prenatally, vascular abnormalities (e.g., coarctation of the aorta, total anomalous pulmonary venous return) are more difficult to diagnose with prenatal ultrasound. A history of a structurally normal heart by fetal ultrasonography should be confirmed by echocardiography in the newborn with cyanosis (see Chapter 26).

Other historical information that may be important in the evaluation of the cyanotic newborn includes a history of severe and prolonged oligohydramnios causing pulmonary hypoplasia. Absent or a marked decrease in fetal movement over several days and a nonreactive fetal heart rate from time of admission may be indicators of chronic fetal hypoxia and acidosis. Prolonged fetal bradyarrhythmia and/or tachyarrhythmia and marked anemia (caused by hemolysis, twin-twin transfusion, or chronic hemorrhage) may cause congestive heart failure, pulmonary edema, and respiratory distress. Maternal illness (e.g., diabetes mellitus), medication use (e.g., aspirin or medications containing nonsteroidal antiinflammatory drugs causing premature constriction of the ductus arteriosus, association of Ebstein malformation with maternal lithium use), and drug use may contribute to acute cardiopulmonary distress in the newborn. Risk factors for infection that cause sepsis/pneumonia should be considered, including premature or prolonged rupture of membranes, fetal tachycardia, maternal leukocytosis, uterine tenderness, and other signs of intraamniotic infection.

Events at delivery may provide clues to the etiology of hypoxemic respiratory failure in the newborn. For example, if positive-pressure ventilation is required in the delivery room, the risk of pneumothorax increases. A history of meconium-stained amniotic fluid, particularly if meconium is present below the cords, is the *sine qua non* of meconium aspiration syndrome. Birth trauma (e.g., clavicular fracture, phrenic nerve injury) or acute fetomaternal or fetoplacental hemorrhage may cause respiratory distress in the newborn.

Physical Examination

The initial physical examination provides important clues to the etiology of cyanosis. Marked respiratory distress in the newborn (retractions, grunting, nasal flaring) suggests the presence of pulmonary parenchymal disease with

decreased lung compliance. However, it is important to recognize that upper airway obstruction (e.g., Pierre Robin sequence or choanal atresia) and metabolic acidemia also can cause severe respiratory distress. In contrast, the newborn with cyanosis alone or cyanosis plus tachypnea ("nondistressed tachypnea") typically has cyanotic congenital heart disease, most commonly transposition of the great vessels (TGV) or idiopathic PPHN.

The presence of a heart murmur in the first hours of life is an important sign in the newborn with cyanosis or respiratory distress. In that setting, it is unusual for the common left-to-right shunt lesions (patent ductus arteriosus, atrial septal defect, ventricular septal defect) to produce an audible murmur because PVR remains high and little turbulence is created across the defect. A murmur that sounds like a ventricular septal defect in the first hours of life is most commonly caused by tricuspid regurgitation (associated with PPHN or asphyxiated myocardium).

Interpretation of Pulse Oximetry Measurements

The interpretation of preductal (right hand) and postductal (lower extremity) saturation by pulse oximetry provides important clues to the etiology of hypoxemia in the newborn. Right-to-left shunting across the ductus arteriosus (but not the patent foramen ovale) causes postductal desaturation (i.e., greater than 5% difference). However, it is important to recognize that variability in oximetry readings may be related to differences in available devices and affected by local perfusion. If the measurements of preductal and postductal Sa_{O_2} are equivalent, this suggests either that the ductus arteriosus is patent and PVR is subsystemic (i.e., the hypoxemia is caused by parenchymal lung disease with intrapulmonary shunting or cyanotic heart disease with ductal-dependent pulmonary blood flow) or that the ductus arteriosus is closed (precluding any interpretation of pulmonary artery pressure without echocardiography). It is uncommon for the ductus arteriosus to close in the first hours of life in the presence of systemic or suprasystemic pulmonary artery pressures.

The most common cause of preductal-postductal gradients in oxygenation is suprasystemic PVR in PPHN causing right-to-left shunting across the ductus arteriosus (associated with meconium aspiration syndrome, surfactant deficiency/dysfunction, CDH, non-CDH pulmonary hypoplasia, or idiopathic). However, ductal-dependent systemic blood flow lesions (hypoplastic left heart syndrome, critical aortic stenosis, interrupted aortic arch, coarctation) may also present with postductal desaturation. Moreover, anatomic pulmonary vascular disease (alveolar-capillary dysplasia, pulmonary venous stenosis, anomalous venous return with obstruction) can cause suprasystemic PVR with right-to-left shunting across the ductus arteriosus and postductal desaturation.

Finally, the unusual occurrence of markedly lower preductal Sa_{O_2} compared to postductal measurements suggests one of two diagnoses: TGV with pulmonary hypertension or TGV with coarctation of the aorta.

Laboratory and Radiologic Evaluation

One of the most important tests to perform in the evaluation of the newborn with cyanosis is the chest radiograph (CXR). The CXR can demonstrate the classic findings of respiratory distress syndrome (air bronchograms, diffuse granularity, underinflation), diffuse parenchymal lung disease in pneumonia, meconium aspiration syndrome, and CDH. Perhaps the most important question to ask when viewing the CXR is whether the severity of hypoxemia is out of proportion to the radiographic changes (Table 14-1). In other words, marked hypoxemia despite supplemental oxygen in the absence of severe pulmonary parenchymal disease radiographically suggests the presence of an extrapulmonary right-to-left shunt (idiopathic PPHN or cyanotic heart disease). The diagnosis of PPHN without CXR evidence of pulmonary parenchymal disease is sometimes called *black lung PPHN*.

Other essential measurements include an arterial blood gas to determine the blood gas tensions and pH, a complete blood count to evaluate for signs of infection, and blood pressure measurements in the right arm and a lower extremity to determine aortic obstruction (interrupted aortic arch, coarctation).

Response to Supplemental Oxygen

Marked improvement in Sa_{O_2} (increase to 100%) with supplemental oxygen (100% oxygen by hood, mask, or endotracheal tube) suggests the presence of intrapulmonary shunt or $\dot{V}/\dot{Q}$ mismatch resulting from lung disease or reactive PPHN. The response to mask continuous positive airway pressure is also a useful discriminator between severe lung disease and other causes of hypoxemia. Most patients with PPHN have at least a transient improvement in oxygenation in response to interventions such as high inspired oxygen and/or mechanical ventilation. If the preductal Sa_{O_2} never reaches 100%, the likelihood of cyanotic heart disease is high.

TABLE 14-1 Mechanisms of Hypoxemia in the Term Newborn with Respiratory Failure

Mechanism	Associated Conditions	Response to 100% Oxygen
Ventilation-perfusion ($\dot{V}/\dot{Q}$) disturbances (high $\dot{V}/\dot{Q}$ ratios = increased dead space; low $\dot{V}/\dot{Q}$ ratios = alveolar underventilation)	Meconium aspiration, retained lung fluid, pulmonary interstitial emphysema, effects of positioning on gas exchange (i.e., decreased ventilation in dependent lung)	Pa_{O_2} ↑↑
Intrapulmonary right-to-left shunt ($\dot{V}/\dot{Q}$ = 0, blood that passes through nonventilated segments of lung)	Atelectasis, alveolar filling (meconium, blood), bronchial collateral circulation	Little change in Pa_{O_2}
Extrapulmonary right-to-left shunt	PPHN (right-to-left shunting at FO and DA), cyanotic heart disease	Little change in Pa_{O_2}

DA, Ductus arteriosus; *FO,* foramen ovale; *PPHN,* persistent pulmonary hypertension of the newborn.

Echocardiography

Echocardiography has become a vital tool in the clinical management of newborns with hypoxemic respiratory failure. The initial echocardiographic evaluation is important to rule out structural heart disease causing hypoxemia (e.g., coarctation of the aorta, total anomalous pulmonary venous return). Moreover, it is critically important to diagnose congenital heart lesions for which iNO treatment would be contraindicated. In addition to the lesions mentioned earlier, congenital heart diseases that can present with hypoxemia unresponsive to high inspired oxygen concentrations (i.e., dependent on right-to-left shunting across the ductus arteriosus) include critical aortic stenosis, interrupted aortic arch, and hypoplastic left heart syndrome. Decreasing PVR with iNO in these conditions could lead to systemic hypoperfusion, worsening the clinical course and delaying definitive diagnosis.

Echocardiographic evaluation is an essential component in the initial evaluation and ongoing management of the hypoxemic newborn. Not all hypoxemic term newborns have echocardiographic signs of PPHN. As noted earlier, hypoxemia can be caused by intrapulmonary right-to-left shunting or $\dot{V}/\dot{Q}$ disturbances associated with severe lung disease. In unusual circumstances, right-to-left shunting can occur across pulmonary-to-systemic collaterals. However, extrapulmonary right-to-left shunting at the foramen ovale and/or ductus arteriosus (PPHN) also complicates hypoxemic respiratory failure and must be assessed to determine initial treatments and evaluate the response to those therapies.

PPHN is defined by the echocardiographic determination of extrapulmonary venoarterial admixture (right-to-left shunting at the foramen ovale and/or ductus arteriosus), not simply evidence of increased PVR (i.e., elevated PVR without extrapulmonary shunting does not directly cause hypoxemia). Echocardiographic signs suggestive of pulmonary hypertension (e.g., increased right ventricular systolic time intervals, septal flattening) are less helpful (Table 14-2).

Doppler measurements of atrial and ductal level shunts provide essential information when managing a newborn with hypoxemic respiratory failure. For example, left-to-right shunting at the foramen ovale and ductus arteriosus with marked hypoxemia suggests predominant intrapulmonary shunting, and interventions should be directed at optimizing lung inflation.

Finally, the measurements made with echocardiography can be used to predict or interpret the response or lack of response to various treatments. For example, in the presence of severe left ventricular dysfunction with pulmonary hypertension, pulmonary vasodilation alone may be ineffective in improving oxygenation. The echocardiographic findings in this setting include right-to-left ductal shunting (caused by suprasystemic PVR) and mitral insufficiency with left-to-right atrial shunting. In this setting, efforts to reduce PVR should be accompanied by targeted therapies to increase cardiac performance and decrease left ventricular afterload.

This constellation of findings suggests that left ventricular dysfunction may contribute to pulmonary venous hypertension, such as occurs in congestive heart failure. In this setting, pulmonary vasodilation alone (without improving cardiac performance) will not cause sustained improvement in oxygenation. Careful echocardiographic assessment will provide invaluable information about the underlying pathophysiology and help guide the course of treatment.

The initial echocardiographic evaluation determines both structural and functional (i.e., extrapulmonary right-to-left shunting in PPHN, left ventricular performance) causes of hypoxemia. Serial echocardiography is important to determine the response to interventions (e.g., pulmonary vasodilators) and to reevaluate cases where specific interventions have not resulted in improvement or have resulted in progressive clinical deterioration. For example, in a patient with extrapulmonary right-to-left shunting and severe lung disease, pulmonary vasodilation might reverse the right-to-left venous admixture with little improvement in systemic oxygenation. These observations unmask the critically important contribution of intrapulmonary shunting to hypoxemia (see also the discussion in Chapter 26).

TABLE 14-2 Echocardiographic Findings in Persistent Pulmonary Hypertension of the Newborn

Measurement	Findings in PPHN
Estimate of PA pressure using Doppler estimate of tricuspid regurgitation jet: 4 (V^2) + CVP, where V = peak velocity of tricuspid regurgitation jet (in m/sec), and CVP = central venous pressure	Elevated PA pressure reliably estimated (mm Hg); compare with simultaneous systemic pressure
Direction of PDA shunt (by pulsed and color Doppler)	Right-to-left or bidirectional PDA shunting
Direction of atrial shunt (by pulsed and color Doppler)	Right-to-left or bidirectional shunting through PFO

PA, Pulmonary artery; *PDA,* patent ductus arteriosus; *PFO,* patent foramen ovale; *PPHN,* persistent pulmonary hypertension of the newborn.

Whom to Treat

Guidelines for the use of iNO therapy are given in Box 14-2.

Diseases

Due to its selective pulmonary vasodilator effects, iNO therapy is an important adjunct to available treatments for term newborns with hypoxemic respiratory failure. However, hypoxemic respiratory failure in the term newborn represents a heterogeneous group of disorders, and disease-specific responses have clearly been described.[3]

Several pathophysiologic disturbances contribute to hypoxemia in the newborn infant, including cardiac dysfunction, airway and pulmonary parenchymal abnormalities, and pulmonary vascular disorders. In some newborns with hypoxemic respiratory failure a single mechanism predominates (e.g., extrapulmonary right-to-left shunting in idiopathic PPHN), but more commonly several of these mechanisms contribute to hypoxemia. For example, in a newborn with meconium aspiration syndrome, meconium may obstruct some airways, decreasing $\dot{V}/\dot{Q}$ ratios and

Box 14-2	GUIDELINES FOR USE OF INHALED NITRIC OXIDE THERAPY
Patient profile	Near-term/term newborn 34 weeks' or greater gestation in the first week of life with echocardiographic evidence of extrapulmonary right-to-left shunting and OI greater than 25 after effective lung recruitment
Starting dose	20 ppm (decrease to less than 10 ppm by 4 hours)
Monitoring for methemoglobinemia	Monitor percentage methemoglobin by co-oximetry within 4 hours of starting iNO and at 24-hour intervals
Duration of treatment	Typically less than 5 days
Discontinuation	F_{IO_2} less than 0.60 with increase in F_{IO_2} less than 0.15 after discontinuation
ECMO availability	If used in a non-ECMO center, arrangements should be in place to continue iNO during transport

ECMO, Extracorporeal membrane oxygenation; *iNO,* inhaled nitric oxide; *OI,* oxygenation index.

increasing intrapulmonary shunting. Other lung segments may be overventilated relative to perfusion and increase physiologic dead space. Moreover, the same patient may have severe pulmonary hypertension with extrapulmonary right-to-left shunting at the ductus arteriosus and foramen ovale. Not only does the overlap of these mechanisms complicate clinical management, but time-dependent changes in the relative contribution of each mechanism to hypoxemia requires continued vigilance as the disease progresses. Therefore, understanding the relative contribution of these different causes of hypoxemia becomes critically important as the inventory of therapeutic options expands.

Considering the important role of parenchymal lung disease in many cases of PPHN, pharmacologic pulmonary vasodilation alone would not be expected to cause sustained clinical improvement. The effects of inhaled NO may be suboptimal when lung volume is decreased in association with pulmonary parenchymal disease.[44] Atelectasis and air space disease (e.g., pneumonia, pulmonary edema) will decrease effective delivery of iNO to its site of action in terminal lung units, and PVR increases at lung volumes above and below functional residual capacity. In PPHN associated with heterogeneous ("patchy") parenchymal lung disease, inhaled NO may be effective in optimizing $\dot{V}/\dot{Q}$ matching by preferentially causing vasodilation within lung units that are well ventilated. The effects of inhaled NO on $\dot{V}/\dot{Q}$ matching appear to be optimal at low doses (less than 20 ppm).[17,45] However, in cases complicated by homogeneous (diffuse) parenchymal lung disease and underinflation, pulmonary hypertension may be exacerbated because of the adverse mechanical effects of underinflation on PVR. In this setting, effective treatment of the underlying lung disease is essential (and sometimes sufficient) to resolve the accompanying pulmonary hypertension (Fig. 14-4).

Clinical Criteria

Gestational and Postnatal Age

Available evidence from clinical trials supports the use of iNO in near-term (greater than 34 weeks' gestation) and term newborns.[7,8] The use of iNO in infants less than 34 weeks' gestation remains investigational. Clinical trials of iNO in the newborn have incorporated ECMO treatment as an endpoint. Most patients were enrolled in the first few days of life. Although one of the pivotal studies used to support the new drug application for iNO therapy included as an entry criterion a postnatal age up to 14 days, the average age at enrollment in that study was 1.7 days.[7] Currently, clinical trials support the use of iNO before treatment with ECMO, usually within the first week of life. However, clinical experience suggests that iNO may be of benefit as an adjuvant treatment after ECMO therapy in patients with sustained pulmonary hypertension (e.g., CDH). Thus postnatal age alone should not define the duration of therapy in cases where prolonged treatment could be beneficial.

Severity of Illness

Studies support the use of iNO in infants who have hypoxemic respiratory failure with evidence of PPHN and require mechanical ventilation and high inspired oxygen concentrations. The most common criterion used has been the oxygenation index (OI). Although clinical trials commonly allowed for enrollment of patients with OI levels greater than 25, the mean OI at study entry in multicenter trials was approximately 40.[3,7] It is unclear whether infants with less severe hypoxemia would benefit from iNO therapy. Davidson et al.[6] reported a controlled clinical trial in which the average OI at study entry was 49. Unlike other trials, however, iNO treatment in this study did not reduce ECMO use. In addition, although entry criteria for this trial included echocardiographic evidence of pulmonary hypertension, only 9% of the patients had clinical evidence of right-to-left ductal shunting. Because of the mechanism of action of iNO as a selective pulmonary vasodilator, it is likely that acute improvement in oxygenation caused by decreased PVR and reduced extrapulmonary right-to-left shunting would be most predictive of clinical improvement.[7] Current multicenter studies suggest that indications for treatment with iNO may include an OI greater than 25 with echocardiographic evidence of extrapulmonary right-to-left shunting.

Treatment Strategies

Delivery of Nitric Oxide During Mechanical Ventilation

Early studies of NO treatment in newborns used simple two-stage regulators with low-flow meters that were manually adjusted to deliver finely regulated flow rates of NO gas into the circuit of continuous-flow neonatal ventilators. Monitoring of NO/NO_2 was performed using chemiluminescence analyzers.[2] This configuration was inexpensive and reliable but lacked an alarm system to detect high/low delivered gas errors. Currently, gas for NO therapy in the United States is provided by a single

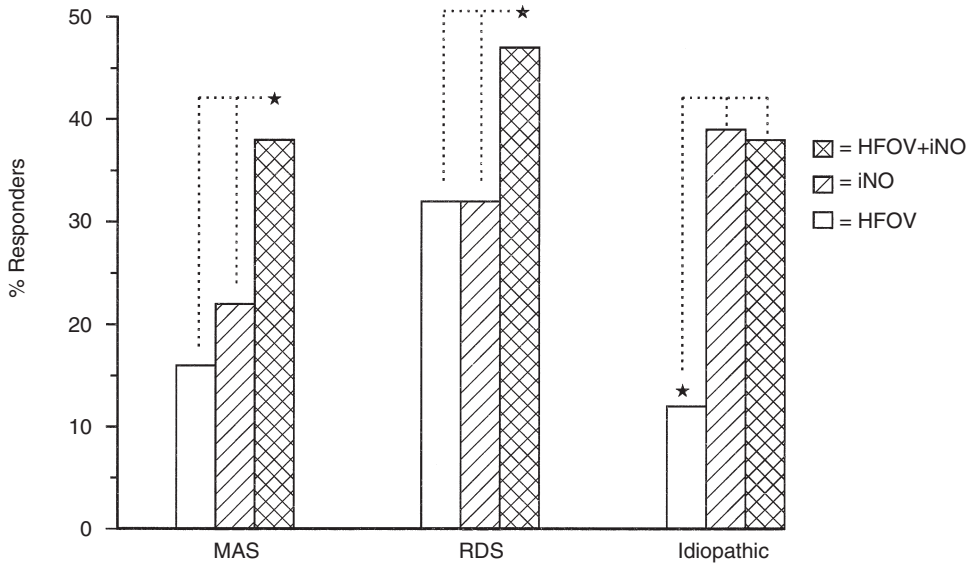

Figure 14-4 ■ Effects of combined therapy with high-frequency oscillatory ventilation (HFOV) and inhaled nitric oxide (iNO) in term newborns with persistent pulmonary hypertension of the newborn (PPHN). HFOV augments the response to iNO in newborns with PPHN and parenchymal lung disease.

manufacturer (Ikaria, Clinton, NJ, USA) and is linked to a single delivery system (INOvent, Datex-Ohmeda).

The INOvent delivery system uses an inline sensor to detect flow rates of gas through the ventilator circuit and a mass-flow controller for delivery of NO gas to yield the desired NO concentration. This device allows for stable NO delivery in ventilator systems that do not use continuous flow throughout the inspiratory/expiratory cycle. The range of NO delivery is 0 to 80 ppm, and the system includes NO/NO_2 alarms that use electrochemical sensors. This device also has a manual NO delivery unit for use during bag ventilation; it delivers 20 ppm NO when set at 15 L/min with an 800 ppm NO source tank.

Dose

The first studies of iNO treatment in term newborns reported initial doses that ranged from 80 ppm[1] to 6 to 20 ppm.[2] The rationale for doses used in these clinical trials was based on concentrations that previously had been found to be effective in animal experiments by the same investigators.[10,46] Roberts et al.[1] reported that brief (30 minutes) inhalation of NO at 80 ppm improved oxygenation in patients with PPHN, but this response was sustained in only one patient after NO was discontinued. In the second report, rapid improvement in oxygenation in neonates with severe PPHN also was demonstrated, but this was achieved at lower doses (20 ppm) for 4 hours.[2] This study also reported that decreasing the iNO dose to 6 ppm for the duration of treatment provided sustained improvement in oxygenation. The relative effectiveness of low-dose iNO in improving oxygenation in patients with severe PPHN was corroborated in a study by Finer et al.[47] Acute improvement in oxygenation during treatment was not different with doses of iNO ranging from 5 to 80 ppm.

These laboratory and clinical studies established the boundaries of iNO dosing protocols for subsequent randomized clinical trials in newborns.[3-5] Increasing the dose to 40 ppm does not generally improve oxygenation in patients who do not respond to the lower dose of 20 ppm.[3] The initial dose in the Neonatal Inhaled Nitric Oxide Study (NINOS) trial was 20 ppm, but the dose was increased to 80 ppm if the improvement in PaO_2 was less than 20 torr.[7] In this study, only 3 (6%) of 53 infants who had little response to 20 ppm had an increase in PaO_2 greater than 20 torr when treated with 80 ppm iNO. Whether a progressive increase in PaO_2 would have occurred with continued exposure to 20 ppm could not be determined with this study design. Roberts et al.[4] initiated treatment with 80 ppm NO and subsequently weaned the iNO concentration if oxygenation improved; thus the effects of lower initial iNO doses could not be evaluated and the effects on ECMO use were not evaluated.

The effects of sustained exposure to different doses of iNO in separate treatment groups of newborns were evaluated by Davidson et al.[6] These investigators reported the results of a randomized, controlled, dose-response trial in term newborns with hypoxemic respiratory failure. In this study, patients were randomized to treatment with 0 (placebo), 5, 20, or 80 ppm NO. Each iNO dose improved oxygenation compared to placebo, but there was no difference in responses among groups. However, at 80 ppm, methemoglobinemia (blood levels greater than 7%) occurred in 13 (35%) of 37 patients and high inspired NO_2 concentrations (greater than 3 ppm) were reported in 7 (19%) of 37 patients. Thus iNO at a dose of 80 ppm was not more effective in improving oxygenation than 5 or 20 ppm and was associated with adverse effects.

The available evidence supports the use of doses of iNO beginning at 20 ppm in term newborns with PPHN, because this strategy decreased ECMO use without an increased incidence of adverse effects. Although brief exposures to higher doses (40 to 80 ppm) appear to be safe, sustained treatment with 80 ppm NO increases the risk of methemoglobinemia.

Duration of Treatment

In multicenter clinical trials of iNO therapy, the typical duration of iNO treatment has been less than 5 days, which parallels the clinical resolution of PPHN. However, individual exceptions occur, particularly in cases of pulmonary hypoplasia.[48] If iNO is required for more than 5 days, investigations into other causes of pulmonary hypertension should be considered (e.g., alveolar capillary dysplasia), particularly if discontinuation of iNO results in suprasystemic elevations of pulmonary artery pressure noted by echocardiography. In our practice, we discontinue iNO if F_{IO_2} is less than 0.60 and Pa_{O_2} is greater than 60 without evidence of rebound pulmonary hypertension or an increase in F_{IO_2} greater than 15% after iNO withdrawal.

In the pre-iNO era, concerns were raised about delaying ECMO therapy if conventional treatment was prolonged. However, these retrospective data do not account for recent changes in management strategies, which include newer ventilator devices and exogenous surfactant therapy. Moreover, decreased ECMO use with iNO treatment in recent multicenter controlled trials has not been associated with an increased incidence of chronic lung disease.[7] In the most recent trial, iNO treatment was associated with improved pulmonary outcomes.[8] No controlled data are available to determine the maximal safe duration of iNO therapy.

Weaning

After improvement in oxygenation occurs with the onset of iNO therapy, strategies for weaning the iNO dose become important. Numerous approaches have been used, and little differences have been noted until final discontinuation of iNO treatment. In one study, iNO was reduced from 20 to 6 ppm after 4 hours of treatment without acute changes in oxygenation. In another trial, iNO was reduced in a stepwise fashion to as low as 1 ppm without changes in oxygenation.[49] Weaning iNO has different physiologic consequences than discontinuation of iNO therapy (see discussion below).

Discontinuation of Inhaled Nitric Oxide Therapy

Early clinical studies reported rapid and sometimes dramatic decreases in oxygenation and increases in PVR after abrupt withdrawal of iNO during prolonged therapy.[14] These responses often are mild and transient, and many patients with decreased oxygenation after iNO withdrawal will respond to brief elevations of F_{IO_2} and careful observation. In patients with a persistent need for treatment with higher inspired oxygen concentrations or increased pulmonary hypertension after iNO withdrawal, restarting iNO treatment will generally cause rapid clinical improvement. Clinical experience with postoperative cardiac patients suggests that children with higher pulmonary artery pressure at the time of iNO withdrawal may be at greatest risk for adverse hemodynamic effects. In general, this so-called "rebound" response appears to decrease over time after more prolonged therapy. However, iNO withdrawal can be associated with life-threatening elevations of PVR, profound desaturation, and systemic hypotension due to decreased cardiac output.

Mechanisms that contribute to these "rebound" effects are uncertain but include several factors. First, exogenous NO may down-regulate endogenous NO production, which contributes directly to the severity of vasospasm after iNO withdrawal. For example, exposure of normal adult rats to iNO (40 ppm) for 2 days potentiated the pressor response to angiotensin II and hypoxia and selectively impaired endothelium-dependent vasodilation.[50] This response also occurred at low doses of iNO (1 ppm) and reversed after discontinuation of iNO for 8 hours. Because lung endothelial NO synthase (NOS) protein content was unchanged, these authors speculated that iNO decreased NOS activity by an alternate mechanism. Second, decreased vascular sensitivity to NO due to alterations in other components of the NO-cyclic guanosine monophosphate (cGMP) pathway, such as decreased soluble guanylate cyclase (sGC) or enhanced phosphodiesterase (PDE5) activities, may contribute to vasospasm after NO withdrawal. For example, in a prospective study of postoperative cardiac patients with marked hemodynamic changes after iNO withdrawal, dipyridamole (a cGMP-specific PDE type V inhibitor) inhibited the adverse effects of acute iNO withdrawal.[51] These findings led to the speculation that dipyridamole may sustain smooth muscle cGMP content and that persistent PDE5 activity may contribute to rebound pulmonary hypertension after iNO withdrawal.

Alternatively, the rise in PVR and drop in oxygenation after iNO withdrawal may simply represent the presence of more severe underlying pulmonary vascular disease with loss of treatment effect of iNO. Increasing pulmonary blood flow into a hypertensive vascular bed with decreased NOS activity may augment myogenic responses or stimulate vasoconstrictor products (such as endothelin) that increase vascular tone.[52] The sudden increase in pulmonary artery pressure after rapid withdrawal of vasodilator therapy is not unique to iNO; it has been observed in other clinical settings, such as prostacyclin withdrawal in adults with primary pulmonary hypertension and in postoperative cardiac patients.

Monitoring

Early experience suggested that careful monitoring of NO and NO_2 levels should be done with chemiluminescence devices. It now has become clear that NO_2 levels remain low at delivered iNO doses within the recommended ranges and that electrochemical devices are reliable. The currently available systems use electrochemical cells and appear to be reliable when they are used appropriately. However, the response time of electrochemical sensors is relatively slow, and these devices are not accurate when measurement of acute changes in NO concentrations is desired.

Methemoglobinemia occurs after exposure to high concentrations of iNO (80 ppm).[6] This complication has not been reported at lower doses of iNO (less than 20 ppm). Because methemoglobin reductase deficiency may occur unpredictably, it is reasonable to measure methemoglobin levels by co-oximetry within 4 hours of starting iNO therapy and subsequently at 24-hour intervals.

Ventilator Management

Along with iNO treatment, other therapeutic strategies have emerged for the management of the term infant with hypoxemic respiratory failure. Considering the important role of parenchymal lung disease in specific disorders included in the syndrome of PPHN, pharmacologic pulmonary vasodilation alone should not be expected to cause sustained clinical improvement in many cases.[53] Moreover, patients who do not respond to iNO can show marked improvement in oxygenation with adequate lung inflation alone.[22] High success rates in early studies were achieved by withholding iNO treatment until aggressive attempts were made to optimize ventilation and lung inflation with mechanical ventilation. These early studies demonstrated that the effects of iNO may be suboptimal when lung volume is decreased in association with pulmonary parenchymal disease, for several reasons. First, atelectasis and air space disease (pneumonia, pulmonary edema) may decrease the effective delivery of iNO to its site of action in terminal lung units. Second, in cases complicated by severe lung disease and underinflation, pulmonary hypertension may be exacerbated because of the adverse mechanical effects of underinflation on PVR. Third, attention must be given to minimize overinflation to avoid inadvertent positive end-expiratory pressure and gas trapping that may elevate PVR from vascular compression. This commonly complicates the management of infants with asymmetric lung disease or airways obstruction as observed in meconium aspiration syndrome.

In newborns with severe lung disease, high-frequency oscillatory ventilation (HFOV) frequently is used to optimize lung inflation and minimize lung injury (see Chapter 11).[54] In clinical pilot studies using iNO, we found that the combination of HFOV and iNO resulted in the greatest improvement in oxygenation in some newborns who had severe PPHN complicated by diffuse parenchymal lung disease and underinflation (e.g., respiratory distress syndrome, pneumonia).[55,56] A randomized multicenter trial demonstrated that treatment with HFOV + iNO often was successful in patients who failed to respond to HFOV alone or iNO with conventional mechanical ventilation in severe PPHN, and differences in responses were related to the specific disease associated with the complex disorders of PPHN[3] (see Fig. 14-4). For patients with PPHN complicated by severe lung disease, response rates for HFOV + iNO were better than with HFOV alone or iNO with conventional ventilation. In contrast, for patients without significant parenchymal lung disease, both iNO and HFOV + iNO were more effective than HFOV alone. This response to combined treatment with HFOV + iNO likely reflects both improvement in intrapulmonary shunting in patients with severe lung disease and PPHN (using a strategy designed to recruit and sustain lung volume rather than to hyperventilate) and augmented NO delivery to its site of action. Although iNO may be an effective treatment for PPHN, it should be considered as only part of an overall clinical strategy that cautiously manages parenchymal lung disease, cardiac performance, and systemic hemodynamics.

Use in Non–Extracorporeal Membrane Oxygenation Centers and Transport with Inhaled Nitric Oxide

Published reports on the use of iNO in ECMO centers have not substantiated early concerns that iNO would adversely affect outcome by delaying ECMO use. In one study, the median time from randomization to treatment with ECMO was 4.4 hours for the control group and 6.7 hours for the iNO group.[17] Although this difference was statistically significant, there were no apparent adverse consequences caused by the delay. Indeed, iNO treatment may play an important role in stabilizing patients before ECMO is initiated, thus improving the chances that ECMO cannulation can proceed without progressive clinical deterioration.[5] In support of this concept of stabilization prior to cannulation for ECMO, Fliman et al.[60] recently reviewed Extracorporeal Life Support Organization (ELSO) data on 7017 neonates cannulated for respiratory reasons between 1996 and 2003 and found that mortality for NO-treated patients was lower than for infants not treated with NO.

The dissemination of iNO therapy to non-ECMO centers warrants a cautious approach. Whether the use of iNO for PPHN in non-ECMO centers will cause undue delays in initiation of transport to an ECMO center, increase the risks of transport, or significantly delay ECMO cannot be determined from the currently available evidence from clinical trials. It is likely that promising new therapies for severe hypoxemic respiratory failure will not be limited to centers that provide all modes of rescue treatment. Although marked improvement in oxygenation occurs in many term newborns with severe PPHN, sustained improvement may be compromised in some patients by the nature of the underlying disease leading to progressive changes in lung compliance or cardiovascular dysfunction.[57] When the clinical course is complicated by progression in severity of the cardiopulmonary disease, withdrawal of iNO during transport to an ECMO center may lead to acute deterioration. In such cases, iNO provides an important therapeutic bridge ensuring stability during transport. When progressive deterioration in oxygenation occurs during iNO treatment in institutions that cannot offer more advanced rescue therapy, provisions must be in place to accomplish transport to the ECMO center without interruption of iNO treatment.[58] Hospitals that are not ECMO centers and cannot guarantee uninterrupted iNO delivery during transport to an ECMO center should not begin an iNO therapy program.

Three systems are available for administration of iNO during transport. The two-stage regulator/low-flow meter and INOvent systems were described earlier. A third system is the Aeronox device (Pulmonox Medical Inc., Tofield, Alberta, Canada). This is a portable system (5 kg) that monitors NO/NO_2 using electrochemical cells and is appropriate for use with continuous-flow ventilator devices.

Based on our clinical experience with iNO in emergency medical transport, we have developed local guidelines for the transport use of iNO that may be applicable to other regions.[59] These guidelines include at least five points. First, it is important that communications between referral hospitals and ECMO centers be established prior to initiating

iNO therapy. Non-ECMO centers should have an iNO transport system available and be prepared to initiate early referral in the event of a suboptimal response to iNO therapy. Second, prior to initiation of iNO therapy at a non-ECMO center, attention should be given to optimizing hemodynamic stability and lung inflation using conventional mechanical ventilation strategies, as previously described.[9] Moreover, for infants who require emergency medical transport and have not been treated with iNO, the use of iNO should be considered only after careful echocardiographic examination to rule out structural and functional contraindications (anatomic defects with ductal-dependent systemic blood flow or severely diminished left ventricular performance). Third, for near-term and term newborns who have been treated with iNO at a non-ECMO center and subsequently require transport to an ECMO center, iNO should be continued on transport unless withdrawal of iNO can be safely accomplished for at least 1 hour prior to transport. Fourth, newborns treated with HFOV (Sensormedics 3100A) who require transport pose a uniquely difficult challenge. This ventilator has not been configured for use in fixed-wing or helicopter transport, and it is cumbersome in ground transport; thus conversion to conventional mechanical ventilation often is necessary prior to initiation of transport. The use of iNO may blunt pulmonary vasoreactivity and pulmonary hypertensive episodes, potentially reducing the risk of transport for these infants.

The Federal Aviation Administration (FAA) has not developed a uniform policy to guide the use of iNO on fixed-wing or rotary flights. Currently, recommendations must be based upon policies determined by each of nine FAA regions within the United States. In the Rocky Mountain region, requirements for the use of iNO in transport include the following: (1) the carrier must have approval to handle iNO under a hazardous materials program; (2) proper storage is required and is guided by rules for transported compressed gas; (3) a material safety data sheet (MSDS) must be carried aboard the aircraft; and (4) the pilot must be aware that NO is being carried aboard the aircraft.

Continuing iNO delivery during transport sustains acute improvements in oxygenation and diminishes the oxygenation lability characteristic of PPHN. Several delivery systems are available to provide iNO during transport and can be easily incorporated into transport modules. Considering the proliferation of iNO use in non-ECMO centers, prudent integration of functional iNO transport systems within the catchment area of an ECMO center should be a priority. Finally, the use of HFOV and iNO in non-ECMO centers may pose undue risk for infants who subsequently need to be transported. However, iNO may facilitate these transport missions by decreasing vasolability and stabilizing oxygenation en route.

Role of Inhaled NO in Newborns with Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) is a complex syndrome that causes severe hypoxemic respiratory failure and is associated with a high mortality rate.[61] In the most severely affected subset of newborns, CDH is characterized by pulmonary hypoplasia, pulmonary hypertension with structural and functional pulmonary vascular abnormalities, and disturbances in cardiac performance.

Inhaled NO was considered a promising therapy for the treatment of acute pulmonary hypertension in CDH, and the first report of the use of iNO in newborns with CDH suggested that early, acute improvement in oxygenation was possible when adequate lung inflation was first achieved.[62] However, the largest randomized, controlled trial of early iNO treatment in patients with CDH found no difference in the combined endpoint of death and/or ECMO use between iNO treated and control infants.[63] Moreover, in this trial, ECMO use was higher in the iNO-treated group. In retrospect, this observation was perhaps predictable, because an often unrecognized physiologic perturbation caused by CDH is severe left ventricular (LV) systolic and diastolic dysfunction early in the course of treatment. In this setting, pulmonary vasodilation with inhaled NO might not be beneficial. Indeed, decreasing pulmonary vascular resistance and increasing preload to the LV that is incapable of responding with increased stroke volume could be detrimental by worsening pulmonary venous hypertension. Moreover, some patients with CDH and severe LV dysfunction actually benefit from pulmonary hypertension by allowing the right ventricle to serve as a systemic pump through the contribution of right-to-left ductal shunting (in the most extreme cases, similar to hypoplastic left heart syndrome). Thus patients with severe CDH are poor responders as a group. Available evidence suggests that iNO therapy in patients with CDH should not be routinely used; rather, its use should be limited to patients with suprasystemic PVR after establishing optimal lung inflation and demonstrating adequate LV performance (i.e., without ductal-dependent systemic blood flow).

However, there is clearly a role for inhaled NO therapy in the treatment of late pulmonary hypertension (LPH) in patients with CDH. Often clinically evident protracted or late pulmonary hypertension leads to prolonged mechanical ventilation, a second course of ECMO, or death.[64-68] Late pulmonary hypertension in newborns with CDH is clinically evident when PVR becomes suprasystemic with right-to-left venoarterial admixture of blood across the foramen ovale and/or the ductus arteriosus causing hypoxemia. However, suprasystemic levels of PVR may be masked during treatment with ECMO or iNO, and subsystemic levels of PVR can be determined only by direct pulmonary artery measurements or echocardiography. Moreover, some newborns with CDH may have persistent pulmonary vascular abnormalities despite marked improvements in respiratory function, necessitating pulmonary vasodilator therapy to reduce PVR even when mechanical ventilation is no longer required. Thus targeting LPH may be an effective approach to reducing mortality in a subset of newborns with CDH.[69]

The Premature Newborn

Early reports of iNO therapy in a premature newborn with pulmonary hypertension demonstrated marked improvement in oxygenation caused by effective treatment of severe pulmonary hypertension and resolution of

extrapulmonary right-to-left shunting;[70] improvement was also noted in other preterm infants with severe respiratory failure.[71,72] Subsequently, several randomized, controlled trials (RCTs) have confirmed the acute improvement in oxygenation caused by iNO treatment. However, in contrast to the direct pulmonary vasodilator effects of iNO, the focus of the most recently published studies was on the potential beneficial effects of prolonged iNO administration on lung parenchymal and vascular development.[73]

In a small, unmasked, randomized trial of iNO (20 ppm) and dexamethasone treatment, Subhedar et al.[74] reported no differences in survival, chronic lung disease, or intracranial hemorrhage (ICH) between iNO-treated infants and controls. In a randomized, masked, multicenter clinical trial of low-dose iNO therapy (5 ppm) in severely ill premature newborns with RDS who had marked hypoxemia despite surfactant therapy (a/A O_2 ratio less than 0.10), iNO acutely improved PaO_2, but did not reduce the incidence of mortality or BPD.[75] Notably, there was no increase in the incidence or severity of ICH in this trial, and the incidence of the most severe ICH (grade 4) was 19% for the iNO group and 29% for the control group. The Franco-Belgium study group reported the results of an acute iNO response study (2-hour oxygenation endpoint); however, the brief duration of therapy and a high rate of crossover before the 2-hour trial endpoint compromised the interpretation of late outcome measures.[76] Hascoet et al.[77] reported the results of an unmasked, randomized trial of iNO in 145 premature newborns with hypoxemic respiratory failure. They found no difference between the iNO and control groups in the primary outcome measure (intact survival at 28 days), and no differences in adverse events. As noted by Finer[78] in an accompanying editorial, interpretation of the findings is limited by a relatively high rate of "open-label" iNO use and the lack of important outcomes such as death before discharge and BPD incidence at 36 weeks.[79] However, these investigators also studied the effect of low-dose iNO on serum markers of oxidative stress, and found that iNO treatment apparently reduced signs of oxidative stress in these patients. Field et al.[80] described the findings of the UK INNOVO trial. In this unblinded study, 108 premature infants with severe hypoxemic respiratory failure were randomized to receive or not receive iNO. There was no difference between the iNO and control group in the main outcome measure (death or severe disability at 1-year corrected age), and no difference in adverse events. Limitations of the study included an 8% crossover to iNO treatment, and treatment with other pulmonary vasodilators in 30% of the control group. Moreover, Field[81] described a lack of equipoise among investigators demonstrated by the observation that 75 infants eligible for enrollment were treated with iNO outside of the trial, leaving only infants with very severe lung disease enrolled in the study.

The largest trials of iNO therapy in premature newborns reported to date include the single center study of Schreiber et al.[82] and the multicenter trials of Van Meurs et al.,[83] Ballard et al.,[84] and Kinsella et al.[85] All of these studies were randomized, controlled, and masked, but have key differences in patient population, disease severity, dose and duration of therapy, and other factors.

Schreiber et al.[82] randomized 207 infants to treatment with iNO or placebo. The main finding of the trial was a reduction in the incidence of BPD and death by 24% in the iNO group. These benefits appeared to accrue predominantly from the subset of newborns with relatively mild respiratory failure (OI less than 6.94). However, in addition to apparent pulmonary benefit caused by low-dose iNO, these authors also reported a 47% decrease in the incidence of severe ICH and periventricular leukomalacia (PVL). Moreover, in a subsequent report, the same group showed that the early decrease in ICH/PVL associated with iNO treatment manifested in improved neurodevelopmental outcome on follow-up examinations of this population.[86] In this follow-up study, 138 children (82% of survivors of the RCT) were evaluated for neurodevelopmental outcome at 2 years of age. In the group treated with iNO in the newborn period, 24% had abnormal outcomes (defined as cerebral palsy, blindness, hearing loss, or one score of less than 70 on the Bayley Scales of Infant Development II), in contrast to 46% in the control group.

Van Meurs et al.[83] enrolled 420 newborns (401-1500 g birth weight) in a multicenter RCT. Although the focus of this study was on premature newborns and the major outcome measure was BPD, the design of the trial was similar to the previous NINOS trial in which term newborns were enrolled and acute changes in oxygenation determined continued treatment with study gas. That is, an acute dose-response study was performed and only patients who showed significant improvement in PaO_2 were continued on study gas. In striking contrast to other studies, the average duration of iNO treatment was only 76 hours. Overall, they found no difference in the incidence of death/BPD between the iNO and control groups. However, in post hoc analyses, infants with birth weight greater than 1000 g showed a reduction in death/BPD after treatment with iNO (50% iNO vs. 69% control). But a worrisome outcome was suggested in a post hoc analysis of newborns weighing less than 1000 g. This analysis showed an increased risk of ICH/PVL (43% iNO vs. 33% control). However, as noted in an editorial by Martin and Walsh,[87] baseline ultrasound examinations were not performed, and it cannot be determined whether these very severely ill infants had ICH before iNO was initiated. Indeed, the severity of illness of infants in this trial of Van Meurs et al.[83] was also markedly different from the study of Schreiber et al.[82] In the Van Meurs trial, the mean oxygenation index (OI) at enrollment for the iNO group was 23, compared to the median OI of 7.3 in the Schreiber study. This suggests that the degree of illness based upon the severity of respiratory failure may be related to iNO safety and efficacy in this population; however, an increased risk of ICH/PVL was not observed in a previous trial of iNO in premature newborns with severe hypoxemic respiratory failure (OI = 30).[88] Other differences between these two trials may offer insights into the disparate outcomes, including the duration of iNO treatment (3 days vs. 7 days), birth weight (839 g vs. 992 g), and gestational age (26 weeks vs. 27.4 weeks). Thus Van Meurs et al.[83] enrolled smaller, more immature infants with severe respiratory failure who were treated relatively briefly with iNO, making direct comparisons between these two trials problematic.

The results of the two largest randomized, controlled, and masked trials of iNO treatment in premature newborns were recently reported. Ballard et al.[84] randomized 582 premature newborns with birth weights of 500 to 1250 g who required ventilatory support between 7 and 21 days of age. Infants were treated with study gas for a minimum of 24 days, and had an estimated OI of 7. They found that the incidence of survival without BPD was increased in the iNO treatment group (43.9%) compared to controls (36.8%) ($P = 0.042$). A major finding of this trial was that the benefit of BPD reduction derived almost entirely from the subset of patients enrolled between 7 and 14 days, suggesting that early treatment is important to prevent BPD. There were no differences between the iNO and control groups in adverse events, including medical or surgical treatment of patent ductus arteriosus (PDA). There also were no differences between the groups in ICH incidence; however, infants were enrolled after the first week of life. Thus this trial does not help inform the debate about iNO effects on brain injury in the premature newborn.

In the second trial, 793 premature newborns with birth weights of 500 to 1250 g and requiring mechanical ventilation in the first 48 hours of life were randomized to treatment with 5 ppm iNO or placebo gas and treated for 21 days or until extubated.[85] Overall, there was no difference in the incidence of death or BPD between groups; however, iNO therapy reduced the incidence of BPD for infants with birth weight greater than 1000 g by 50% ($p = 0.001$). Low-dose iNO therapy reduced the incidence of PVL ($p = 0.048$), as well as the combined endpoints of ICH, PVL, and ventriculomegaly for the entire study population ($p = 0.032$). iNO therapy did not increase the incidence of adverse events, including mortality, ICH, PVL, pulmonary hemorrhage, and PDA treatment in any subgroup. In this trial there was no relationship between OI and brain injury risk, in contrast to the findings of Van Meurs et al.[83] Mechanisms through which iNO therapy might provide neuroprotection in the premature newborn are uncertain, and warrant further study. Based on laboratory studies, several possibilities exist that include modulation of circulating cells (including neutrophils, monocytes, and platelets) that may occur during NO exposure as they transit the pulmonary circulation. Alternatively, iNO-induced downregulation of lung-derived cytokines may also reduce distant organ injury.[88-90] Another possible mechanism may relate to distal delivery of NO or NO-related metabolites through the systemic circulation through red blood cell or protein mediated pathways.[91,92]

The effects of iNO in the premature newborn may depend on the timing, dose, and duration of therapy, and the nature of the underlying disease. The available evidence from clinical trials suggests that low-dose iNO may be safe and effective in reducing the risk of death/BPD for a subset of premature newborns, in particular infants with birth weights greater than 1000 g. A neuroprotective effect of iNO has been demonstrated in large RCTs, but the relationship of disease severity and ICH/PVL risk is uncertain. Treatment of premature newborns with respiratory failure between 7 and 14 days after birth appears to be safe and effective in reducing the incidence of BPD. Meta-analysis of these clinical trials will follow, but should be limited to studies that were properly masked and designed to effectively measure relevant outcomes. Finally, early concerns about the potential adverse effects of iNO on surfactant function and PDA risk have been effectively eliminated with the cumulative results of clinical trials; however, routine use of iNO in premature newborns should await the results of follow-up studies from the largest clinical trials.

Summary

Inhaled NO improves oxygenation and decreases ECMO use in term newborns with PPHN. From the available information, a reasonable recommendation for starting dose of iNO in the term infant is 20 ppm, with reductions in dose over time. Toxicity is apparent at a dose of 80 ppm, which causes increases in methemoglobinemia and inspired NO_2. High doses (greater than 20 ppm) of iNO may prolong bleeding time, but clinically significant increases in bleeding complications have not been reported in term newborns. The use of iNO in non-ECMO centers must be done cautiously, with arrangements in place for transport to an ECMO center without interruption of iNO delivery in patients with suboptimal acute responses. Finally, there is increasing evidence for the potential role of low-dose iNO (5 ppm) in premature newborns with hypoxemic respiratory failure. Low-dose iNO causes acute improvement in oxygenation and may prove to be useful as a lung-specific antiinflammatory therapy; however, clinical application currently should be limited to controlled trials that target outcomes of both safety and efficacy.

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15 Ventilation Strategies

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Less than three decades ago, survival of extremely premature infants was rare. Smaller, more immature neonates do survive today, in part, because of improved mechanical ventilation. Even in the most immature and smallest weight subgroups (e.g., 501-750 g) survival exceeds 50%.[1] The increased survival of these vulnerable newborns results in more infants at risk for various morbidities associated with mechanical ventilation, including bronchopulmonary dysplasia (BPD) and air leak syndromes (see Chapter 23).[2] Improved ventilatory strategies may result in decreased respiratory morbidities in these vulnerable infants.

Infants who receive assisted ventilation are at risk for acute and chronic lung injury. Pneumothorax and pulmonary interstitial emphysema are common manifestations of acute lung injury in infants with respiratory distress syndrome (RDS). Air leaks occur in about 10% of critically ill infants who receive mechanical ventilation. Chronic lung disease (CLD), sometimes used interchangeably with BPD, occurs on average in about one third of the very-low-birth-weight babies (1500 g or less)[2] and is a major cause of mortality and long-term morbidity.[3] However, the variability among over 600 institutions reporting to the Vermont-Oxford Network ranges from 5% to 60% for this condition at 36 weeks postmenstrual age. The smallest and most immature neonates are at highest risk for BPD after treatment for RDS, although BPD also has been described in neonates requiring ventilatory assistance for other causes of respiratory distress. The risk of BPD increases with decreasing birth weight and gestational age.[2]

Recent evidence suggests that lung injury is partially dependent on the ventilatory strategies used. There is an emerging consensus that mechanical ventilation leads to lung injury.[4,5] Various ventilation strategies have been evaluated with the aim of reducing lung injury in neonates. Ventilatory strategies that reduce volutrauma caused by high tidal volumes,[6-9] atelectotrauma caused by repeated collapse and recruitment of alveoli,[13,17] gas trapping and alveolar overdistension,[14] and oxidant exposure may prevent lung injury. Blood gas targets can be modified to accept higher than "normal" $Paco_2$ values,[10-12,15,16] and lower than "normal" Pao_2 target values are being evaluated as a means of reducing oxidant injury. These ventilatory strategies are considered "gentle ventilation."[10-12]

Optimal ventilatory strategies should promote adequate gas exchange with minimum lung injury and other adverse effects. Every patient requires an individualized ventilatory approach based on the underlying lung pathophysiology. Objective measures of lung function, such as flow volume relationships and blood gas data coupled with the chest radiograph and physical examination findings, should identify the disease state and guide decisions regarding ventilator mode and the magnitude of support. The goal of mechanical ventilation is to provide gas exchange while preventing or decreasing ventilator-associated lung injury. This chapter reviews assisted ventilation strategies of the newborn with an emphasis on the prevention of lung injury.

Components of Conventional Positive Pressure Ventilation

A discussion of six components of positive pressure ventilation and their physiologic impact follows. The reader is also referred to Chapter 2 on Physiologic Principles.

Positive End-Expiratory Pressure

Adequate positive end-expiratory pressure (PEEP) prevents alveolar collapse and improves functional residual capacity (FRC) and ventilation-perfusion ($\dot{V}/\dot{Q}$) matching.[17] Increasing PEEP raises the mean airway pressure and increases oxygenation by improving $\dot{V}/\dot{Q}$ matching. PEEP levels during conventional mechanical ventilation in excess of 6 to 7 cm H_2O may overdistend the lung and decrease pulmonary compliance. Overdistension of the lung reduces venous return and cardiac output leading to decreased oxygen transport. Principles used to select strategies to optimize PEEP adjustment are included in Box 15-1.

Although raising PEEP levels increases FRC, a concomitant reduction in tidal volume also occurs. Unless peak inspiratory pressure (PIP) is increased or tidal volume is maintained through other manipulations of the ventilator, alveolar hypoventilation may result. Furthermore, elevated FRC alters pulmonary mechanoreceptor-mediated prolongation of expiratory time and may decrease the infant's spontaneous respiratory rate. A decrease in the patient's respiratory rate reduces the contribution of spontaneous ventilation to total gas exchange and may lead to hypoventilation. Another potential hazard of high PEEP is air leak. Optimal PEEP prevents alveolar collapse without overdistension of the lung. For many infants, PEEP levels between 3 and 6 cm H_2O improve oxygenation and are

Box 15-1 VENTILATORY STRATEGIES FOR PEEP ADJUSTMENT

- Level of PEEP should be optimized to improve functional residual capacity and ventilation-perfusion matching and to prevent both overdistension and recurrent atelectasis (atelectotrauma).
- PEEP should be at or above the inflection point.
- High PEEP may decrease venous return and preload of the left ventricle, and thus decrease cardiac output.

PEEP, Positive end-expiratory pressure.

TABLE 15-1 Factors Considered in Selection of PIP

Yes	No
• Blood gas derangement	• Weight
• Chest rise	• Resistance
• Breath sounds	• Time constant
• Lung compliance	• PEEP
• Others	• Others

PEEP, Positive end-expiratory pressure; *PIP,* peak inspiratory pressure.

well-tolerated; however, using higher levels of PEEP, particularly in the tiniest infants, may lead to overdistension of the lung.

Peak Inspiratory Pressure

Peak inspiratory pressure (PIP) affects the pressure gradient (ΔP), which determines the tidal volume delivered to the infant. Tidal volume is proportional to the pressure gradient. Therefore, tidal volume, alveolar ventilation, and carbon dioxide elimination are strongly dependent on PIP. An increase in PIP normally increases oxygenation (Pa_{O_2}) and carbon dioxide elimination. Changes in PIP affect oxygenation by altering mean airway pressure and $\dot{V}/\dot{Q}$ matching. However, high levels of PIP increase tidal volume and increase the risk of "volutrauma," air leak syndromes, and lung injury. Very high PIP may result in overdistension and lower lung perfusion and cardiac output, leading to a decrease in oxygen transport despite an adequate Pa_{O_2}. Using the lowest level of PIP is one of the strategies for reducing volutrauma (Box 15-2).

The level of PIP required to deliver the desired tidal volume depends mainly on the compliance of the respiratory system. The compliance in turn depends on the pathophysiology of the underlying disease process. A useful clinical indicator of adequate PIP is gentle chest rise with every ventilator-delivered breath. Chest rise of ventilator-delivered breaths should be similar to the chest expansion seen with unlabored, spontaneous breathing. The degree of observed chest wall movement during the ventilator-delivered breaths indicates the compliance with fair accuracy.[18] The quality of breath sounds on auscultation is not very helpful in determining optimal PIP; however, the absence of breath sounds may indicate inadequate PIP, displacement or obstruction of the endotracheal tube, or ventilator malfunction. It is advisable to use the lowest effective PIP that maintains adequate gas exchange but minimizes volutrauma.

Although estimation of the airway resistance and time constant are useful in identifying whether pressure equilibration is occurring, they are more important in adjusting inspiratory and expiratory times and ventilatory rates and are not directly involved in the adjustment of the PIP. An increase in PIP and tidal volume when airway resistance is increased and time constant is prolonged may result in volutrauma and gas trapping. Factors that should or should not be considered in the selection of the PIP are listed in Table 15-1.

Box 15-2 VENTILATORY STRATEGIES FOR PIP ADJUSTMENT

- Overdistension should be avoided by:
  - Prevention of low C_{20}/C
  - Ventilation at the steep portion of the pressure volume curve.
- Tidal volume as low as 4 mL/kg may be effective
- Use of low PIP is generally preferred.

PIP, Peak inspiratory pressure.

Ventilator Rate

The ventilator rate (frequency) and tidal volume determine alveolar minute ventilation according to the following relationship:

$$\text{Alveolar minute ventilation} = \text{frequency} \times (\text{tidal volume} - \text{dead space})$$

Changes in ventilator rate alter alveolar minute ventilation and thereby affect Pa_{CO_2}. Increases in rate usually improve CO_2 elimination. However, as the ventilator rate is increased higher than physiologic rates and inspiratory time (T_I) decreases below three time constants, tidal volume delivery is impaired. Similarly, with high ventilator rates and short expiratory times (T_E), gas trapping occurs and tidal volume is further impaired. With ventilator rates above certain levels, minute ventilation plateaus and later falls.[19] The threshold frequency at which tidal volume decreases with increasing rate depends on the time constant of the respiratory system and varies with disease state and individual ventilators.

The time constant of the respiratory system is a measure of the time (expressed in seconds) necessary for the alveolar pressure or volume to reach 63% of the change in airway pressure (or maximum possible tidal volume if inspiration was complete).[20,21] Time constant is defined as the product of resistance and compliance, as follows:

$$\text{Time constant} = \text{resistance} \times \text{compliance}$$

Lungs with longer time constants will achieve the threshold frequency at lower ventilator rates, and tidal volume with each breath delivered will be reduced. In disease states with short pulmonary time constants, higher

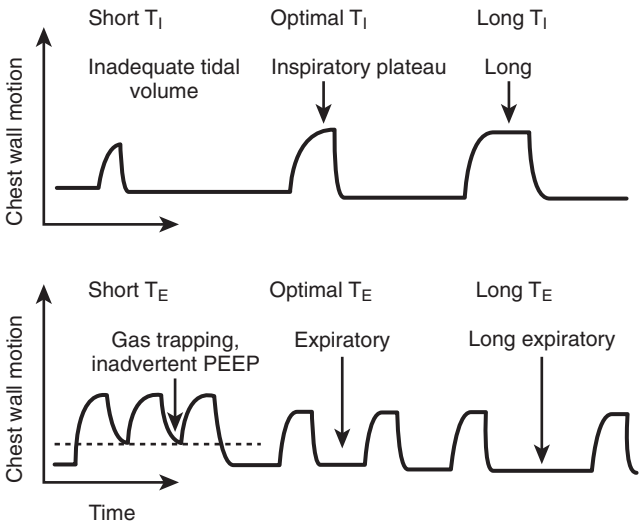

Figure 15-1 ■ Estimation of optimal inspiratory and expiratory times based on chest wall motion. The pattern of changes in chest wall motion can be used to identify whether inspiratory and expiratory times are short, optimal, or long. The figures show the consequences of short inspiratory and expiratory times.

respiratory rates can be tolerated without compromising tidal volume delivered.[22] This problem rarely occurs with rates less than 60 per minute in preterm infants. Indeed, studies using models that simulate the mechanical properties of the respiratory system suggest that frequencies of higher than 60 per minute are usually acceptable in infants.[22]

Very rapid rates may lead to inadvertent PEEP and gas trapping resulting from inadequate time for exhalation, and over time this may lead to CO_2 retention, elevation of mean airway pressure, and impaired cardiac output. Analysis of chest wall movement may help detect the adequacy of inspiratory and expiratory times (Figure 15-1). The absence of a brief pause in chest wall movement at end-inspiration or at end-expiration may indicate an inadequate TI (with decreased tidal volume delivery) or an inadequate expiratory time (with gas trapping), respectively (Figure 15-1). Maneuvers that increase expiratory time, such as reducing the ventilator frequency or shortening the T_I, may be necessary to allow adequate time for exhalation and to avoid inadvertent PEEP. Because compliance is low and resistance is typically not elevated in infants with RDS, higher rates (60 or more/min) can be used in the acute and resolving phases of RDS.[23] In infants with BPD or obstructive airway disease, the time constant is prolonged. With a prolonged time constant, rapid ventilatory rates may cause gas trapping, decreased tidal volume, and carbon dioxide retention. Because compliance is not corrected for lung size in the calculation of time constant, larger infants have a longer time constant than do smaller infants. Thus gas trapping is also more common in larger infants. Principles used to select strategies to optimize rate and inspiratory and expiratory times and inspiratory-expiratory (I:E) ratios are included in Box 15-3.

Box 15-3 VENTILATORY STRATEGIES FOR ADJUSTMENT OF VENTILATOR RATE, I AND E TIMES, AND I:E RATIOS

- Rate is adjusted to achieve target CO_2 at the lowest effective tidal volume.
- Inspiratory and expiratory time constants should be considered in the selection of rate, I and E times (T_I and T_E), and inspiration-expiration (I:E) ratios.
- Insufficient inspiratory durations can reduce tidal volume during delivery and should be avoided.
- Insufficient expiratory durations can cause gas trapping and should be avoided.
- Mean airway pressure should be adjusted to optimize oxygenation without reducing cardiac output.

Mechanical ventilation supplements spontaneous respiratory effort, when present, and does not replace it completely. Sedated infants require increased ventilatory support. Pharmacologically paralyzed infants who do not breathe at all require full ventilatory support. In spontaneously breathing infants, adjustments to the ventilator may not impact arterial blood gases to the degree anticipated, in view of the variable respiratory contribution by the neonate. Infants with minimal lung disease who are mechanically ventilated for recurrent apnea do not seem to benefit from higher mechanical ventilatory rates for reducing energy expenditure,[24] and hence, low rates (about 10 breaths/min) may be sufficient.

Inspiratory Time, Expiratory Time, or Inspiratory-Expiratory Ratio

The respiratory system time constant determines optimal inspiratory time (T_I) and expiratory time (T_E.) The ventilator T_I and T_E must be at least 3 to 5 times longer than the inspiratory and expiratory time constants of the respiratory system for adequate inhalation and exhalation. Inspiratory and expiratory time constants are not necessarily equal. The time constant may be longer during exhalation because expiratory airway resistance frequently is higher than inspiratory airway resistance. Normally, once the ventilatory rate and T_I are set, the other dependent variables (T_E and inspiratory-expiratory [I:E] ratio) are automatically determined. It is preferable to avoid extremes in T_I (less than 0.2 sec or greater than 0.7 sec). T_I of 0.3 to 0.5 sec suffices for most neonates. Infants with BPD often have a prolonged time constant and may need longer inspiratory and expiratory times, whereas infants with acute RDS may do better with short T_I and T_E and rapid rates.[7,8]

The main effect of changes in the I:E ratio is on mean airway pressure, but the effect on oxygenation is generally small.[25] When corrected for mean airway pressure, changes in the I:E ratio are not as effective in improving oxygenation as changes in PIP or PEEP.[25] Reversed I:E ratios (with inspiration longer than expiration) may improve $\dot{V}/\dot{Q}$ matching and oxygenation, but may cause impaired venous return, decreased cardiac output, gas trapping, and/or air leaks. Low ventilator rates (30-40/min) with reversed I:E ratios (I:E 1:1 or greater) were once suggested as a means to avoid high PIP and reduce the incidence of BPD, but subsequent studies have shown that reversed I:E ratios do

not reduce mortality or morbidity.[26] The cumulative evidence to date suggests that treatment of RDS with higher ventilatory rates combined with a short T_I decreases air leaks and BPD.[6-9]

Inspired Oxygen Concentration

Changes in inspired oxygen concentration (F_{IO_2}) alter oxygenation directly by changing the alveolar partial pressure of oxygen. Because both F_{IO_2} and mean airway pressure affect oxygenation, it is important to balance their relative contributions. Although there are insufficient data to compare the roles of oxygen-induced versus pressure-associated (or volume-associated) lung injury in the neonate, it is generally believed that the risk of oxygen toxicity is less than that of volutrauma when the F_{IO_2} is less than 0.6 to 0.7. The F_{IO_2} should be weaned on pulse oximetry or transcutaneous oximetry values rather than Pa_{O_2} values obtained during intermittent blood gas sampling, because frequent changes in F_{IO_2} are often required. A change in the anticipated trend of F_{IO_2} should prompt a reevaluation of the clinical situation. Target oxygen saturations are controversial. See the discussion of this in Chapters 7 and 17.

Flow Rate

An adequate flow rate is required for the ventilator to deliver the desired PIP and waveform. As long as a sufficient flow is used, there is minimal effect of flow rate on gas exchange. A higher flow leads to a more "square wave" pressure waveform, increasing PIP to the desired value in a shorter period of time. Shortening the time to peak pressure with high flow may cause a small increase in mean airway pressure. However, with higher flow rates, more turbulent flow is created, especially with small endotracheal tubes. High flows may be required when T_Is are short, in order to maintain tidal volume delivery. A minimum flow rate of about three times the infant's minute ventilation is usually required, and flows of 6 to 10 L/min are sufficient for most neonates when using most standard conventional ventilators.

Ventilatory Strategies in Neonates with Respiratory Distress Syndrome

The premature infant is at risk for respiratory failure because of surfactant deficiency and/or inactivation as well as structural immaturity of the lungs. Relative surfactant deficiency leads to alveolar collapse, decreased pulmonary compliance, and low FRC. The time constants of the respiratory system in neonates with RDS in the first several days of life are characteristically short (0.05-0.1 sec).[27] Surfactant deficiency, altered lung mechanics, and structural immaturity increases the risk of lung injury and air leak syndromes. Lung injury, accentuated in infants with RDS, may predispose to the subsequent development of BPD.

Initiating Positive Pressure Ventilation

The most common indications for assisted ventilation in the newborn infant are respiratory distress, cyanosis unresponsive to supplemental oxygen therapy, and apnea of prematurity that is refractory to medical management (Table 15-2). Clinical presentation of neonatal pulmonary insufficiency is variable. Some neonates present in the immediate newborn period with severe distress or inadequate respiratory effort and require intubation and assisted ventilation. Neonates with RDS may show rapid deterioration with increasing oxygen requirement and need for continuous positive airway pressure (CPAP) or assisted ventilation within the first few hours of life. Other neonates may require little or no respiratory support in the first postnatal days but subsequently develop respiratory failure because of severe apnea, intracranial hemorrhage, sepsis, or necrotizing enterocolitis.

Intubation and assisted ventilation may be indicated for many infants with respiratory failure. Indications for intubation include respiratory or mixed acidosis with a pH less than 7.20, Pa_{CO_2} higher than 55 to 60 mm Hg and hypoxemia (Pa_{O_2} less than 40-50 mm Hg) despite treatment with high supplemental oxygen (higher than 40%-70% F_{IO_2}) by hood or CPAP. However, decisions to provide assisted ventilation for critically ill neonates frequently must be made only on clinical assessment, particularly in the most preterm infants who may benefit from prophylactic or early surfactant treatment. Signs of respiratory failure include cyanosis, deep intercostal and sternal retractions, or apnea and require prompt immediate evaluation and intervention. The initial ventilatory settings and strategies are dependent on the pulmonary diagnosis and the mechanical properties of the respiratory system (Table 15-3).

Although assisted ventilation may be life-saving for infants with established respiratory failure, not all extremely premature infants require mechanical ventilation. Unnecessary use of mechanical ventilation may lead to a higher incidence of BPD.[28] Reducing the frequency of intubation and assisted ventilation of very-low-birth-weight (VLBW) neonates may decrease the incidence of BPD.[28] Furthermore, individualized airway management in the delivery

TABLE 15-2 Indications for Neonatal Mechanical Ventilation

Clinical Criteria	Laboratory Criteria
Respiratory distress: • Severe retractions: intercostal, subcostal, and suprasternal • Tachypnea (respiratory rate of more than 60-70/min)	Severe hypercapnia: • Pa_{CO_2} greater than 55-60 mm Hg and pH less than 7.2
Central cyanosis: • Cyanosis of oral mucosa on O_2 by hood (head box) or continuous positive airway pressure (CPAP) at a F_{IO_2} greater than 0.40-0.70	Severe hypoxemia: • Pa_{O_2} less than 40-50 mm Hg or oxygen saturation less than 85% Hg on O_2 by hood (head box) or CPAP at a F_{IO_2} of more than 40%-70%
Refractory apnea: • Apnea unresponsive to medical management (e.g., theophylline, caffeine, or CPAP)	Adequate methylxanthine levels

TABLE 15-3 Suggested Initial Ventilatory Strategies for Common Neonatal Respiratory Disorders

Disease	Initial Strategy	Blood Gas Targets
Respiratory distress syndrome (RDS)	1. Rapid rates (≥ 60/min) 2. Moderate PEEP (4-5 cm H_2O) 3. Low PIP (10-20 cm H_2O) 4. T_I of 0.3-0.4 sec 5. Tidal volume 4-6 mL/kg body weight	pH 7.25-7.35 PaO_2 50-70 mm Hg $PaCO_2$ 45-55 mm Hg
Bronchopulmonary dysplasia (BPD)	1. Slow rates (20-40/min) 2. Moderate PEEP (4-5 cm H_2O) 3. Lowest PIP required (10-20 cm H_2O) 4. T_I of 0.4-0.7 sec 5. Tidal volume 5-8 mL/kg body weight	pH 7.25-7.30 PaO_2 50-70 mm Hg $PaCO_2$ 55+ mm Hg
Meconium aspiration syndrome (without PPHN)	1. Relatively rapid rate (40-60/min) 2. Low to moderate PEEP (3-5 cm H_2O) 3. Adequate T_E (0.5-0.7 sec) 4. If gas trapping occurs, increase T_E to 0.7-1.0 sec and decrease PEEP to 3-4 cm H_2O	pH 7.3-7.4 PaO_2 60-80 mm Hg $PaCO_2$ 35-45 mm Hg
Persistent pulmonary hypertension of the newborn (PPHN)	1. Higher rates from 50-70/min 2. PIP from 15-25 cm H_2O 3. Low PEEP (3-4 cm H_2O) 4. T_I 0.3 to 0.4 sec 5. High FIO_2 (80%-100% O_2)	pH 7.35-7.45 PaO_2 70-100 mm Hg $PaCO_2$ 35-45 mm Hg
Congenital diaphragmatic hernia (CDH)	1. Relatively rapid rates (40-80/min) 2. Lowest PIP sufficient for chest excursion (20-24 cm H_2O) 3. Moderate PEEP (4-5 cm H_2O) 4. Short T_I (0.3-0.5 sec)	pH greater than 7.25 PaO_2 50-70 mm Hg $PaCO_2$ 45-65 mm Hg (Sicker neonates may need less aggressive goals for oxygenation, as long as preductal SpO_2 is greater than 85%)
Apnea of prematurity	1. Relatively slow rates (10-15/min) 2. Minimal peak pressures (7-15 cm H_2O) 3. Low PEEP (3 cm H_2O) 4. FIO_2 usually less than 0.25	pH 7.25-7.30 PaO_2 50-70 mm Hg $PaCO_2$ 55+ mm Hg
Hypoxic-ischemic encephalopathy (HIE)	1. Rates 30-45/min or slower depending on spontaneous rate 2. PIP 15-25 cm H_2O 3. Low to moderate PEEP (3-4 cm H_2O) 4. FIO_2 to maintain SpO_2 90%-95%	pH 7.35-7.45 PaO_2 60-80 mm Hg, $PaCO_2$ 35-45 mm Hg

PEEP, Positive end-expiratory pressure; *PIP,* peak inspiratory pressure.

room that limits endotracheal intubation and mechanical ventilation to only those extremely low-birth-weight infants with respiratory failure does not appear to increase mortality or morbidity.[29] Moreover, the use of a T-piece resuscitator to provide consistent PIP and PEEP during delivery room resuscitation may limit overventilation, which occurs frequently during hand ventilation in this setting. Although observational and retrospective data suggest that a selective approach to the initiation of intubation and assisted ventilation may decrease the incidence of BPD, this strategy of airway management needs to be tested further in randomized controlled trials.

Prophylactic CPAP in relatively larger infants (28-31 weeks gestation) does not improve outcome.[30] Early nasal CPAP initiated in small preterm infants with respiratory distress may decrease the need for assisted ventilation,[31-35] but this strategy may increase the risk of pneumothorax.[31,32] A randomized trial of initiating CPAP in the delivery room in infants less than 28 weeks gestation showed that initiation of CPAP immediately after birth did not affect the need for intubation.[34] Furthermore, in larger preterm infants of 1250 g or more, early intubation and surfactant (at FIO_2 of 40% or greater) did not improve outcomes.[35] Early surfactant with rapid extubation to CPAP decreases air leaks (rate difference [RD], 0.04; confidence interval [CI], 0.08, 0.00; number needed to treat [NNT], 25), BPD at 28 days (RD, 0.08; CI 0.15, 0.01; NNT, 12), ventilation (RD, 0.19; CI, 0.26, 0.11; NNT, 5), and the initiation of mechanical ventilation.[36] A factorial designed trial of early CPAP versus mechanical ventilation, and with prophylactic versus rescue surfactant, showed no benefits of the combination of strategies.[37]

Early Respiratory Distress Syndrome

Optimal management of mechanical ventilation requires astute bedside clinical assessment as well as accurate interpretation of blood gas data and chest radiographs. Blood gas analysis performed soon after the initiation of mechanical ventilation, and at regular intervals thereafter, will facilitate decisions regarding ventilator management. However, pulmonary mechanics change rapidly in infants with RDS, and it may be necessary to make ventilator adjustments more frequently based on changes in chest excursion, oxygen saturation, and transcutaneous oxygen and carbon dioxide tension measurements. Meticulous attention to the pulmonary status and rational ventilator management will avoid the potential hazards of hyper- and hypoventilation of infants with RDS.

Recommended initial settings for pressure-limited, time-cycled ventilation of neonates with RDS are a respiratory rate of 60 or more breaths per minute, PIP set to achieve minimal chest excursion during inspiration

(10-20 cm H_2O), moderate PEEP (4-5 cm H_2O), and a T_I of 0.3 to 0.4 sec. The rationale for these settings is derived from clinical trials and physiologic principles.

Rapid ventilator rates and short T_Is are generally tolerated because of the characteristically low pulmonary compliance and short time constant in infants with RDS. Clinical trials comparing rapid versus slow respiratory rates and short versus long T_I have been conducted. Strategies that use rapid respiratory rate and short T_I are associated with a lower incidence of air leaks.[6-9] The optimal ventilator rate for any given neonate will depend not only on the pathophysiology of the underlying disorder but also on the target $PaCO_2$. Generally, it is preferable to increase minute ventilation by increasing rate rather than using other maneuvers such as elevating the PIP. Although minute ventilation can improve by increasing PIP or inspiratory time, these maneuvers increase tidal volume and are more likely to induce pulmonary volutrauma. Likewise, if a mechanically ventilated infant is hypocapnic, the PIP rather than ventilator rate should be reduced first to decrease minute ventilation.

In pressure-limited ventilation, changes in alveolar airway pressure and lung volume are closely linked. Changes in PIP determine the pressure gradient between the onset and end of inspiration and thus affect alveolar ventilation. Tidal volume is a function of the pressure gradient between PIP and PEEP. The required tidal volume for infants with RDS is generally less than 5 to 6 mL/kg of body weight. Animal models have demonstrated that a strategy of rapid, shallow ventilation produces less lung injury than slow, deep breaths.[38] Although these studies demonstrate that small tidal volume ventilation reduces lung injury, human data in neonates are less definitive and generally inferential.

Overventilation, as indicated by low $PaCO_2$ levels in infants receiving mechanical ventilation, has been associated with adverse pulmonary and neurologic outcomes. In one retrospective analysis, ventilated infants whose highest $PaCO_2$ levels at 48 or 96 hours were less than 40 mm Hg were 1.45 times as likely to develop BPD as those whose highest $PaCO_2$ levels were higher than 50 mm Hg (95%; CI 1.04-2.01).[15] Similarly, in another study, infants with hypocapnia before the first dose of surfactant had a higher risk for development of BPD, with an odds ratio for BPD of 5.6 (CI 2.0-15.6) for a $PaCO_2$ level of 29 or less versus 40 or greater mm Hg.[16] Using multiple logistic regression analysis, these studies independently concluded that ventilator strategies that lead to hypocapnia during the early neonatal course increase the risk of BPD.[15,16] Furthermore, hypocapnia has also been shown to predispose infants to periventricular leukomalacia[39,40] and cerebral palsy.[41]

A randomized trial showed that ventilatory strategies that maintained mild hypercapnia ($PaCO_2$, 45-55 mm Hg) were safe and reduced the need for assisted ventilation in the first 96 hours after randomization.[10] A larger, multicenter, randomized trial reported that use of "minimal ventilation" (target $PaCO_2$ greater than 52 mm Hg as opposed to normal values of less than 48 mm Hg) in conjunction with a tapered dexamethasone dose or saline for 10 days resulted in a reduction in ventilatory need at 36 weeks (16% versus 1%, $p < 0.01$) but did not decrease death and/or the need for supplemental oxygen at 36 weeks (68% versus 63%).[11] A third smaller trial of permissive hypercapnia did not show benefits of this intervention.[12] Although mild hypercapnia is thought to be safe in neonates, a $PaCO_2$ greater than 60 mm Hg may be an indication for mechanical ventilation in preterm infants because of concerns of altered cerebral blood flow and the potential increased risk of intraventricular hemorrhage.[42] In the early phase of RDS, it may be appropriate to maintain an elevated $PaCO_2$ with a pH above 7.20 to 7.25. By postnatal day 3 to 4, metabolic compensation gradually develops that permits a higher $PaCO_2$ for the same pH. However, the efficacy and safety of permissive hypercapnia requires further clinical research. Further trials of ventilatory strategies that may prevent ventilator-associated lung injury seem warranted.

The initial level of PIP should be determined by the extent of chest excursion. The PIP required cannot be predicted on the basis of the neonate's birth weight, gestational age, or postnatal age. A good starting point for the first few breaths in infants with RDS is a PIP of 10 to 20 cm H_2O. The PIP level can be adjusted in increments of 1 to 2 cm H_2O until adequate chest movement is obtained. If there is excessive chest rise with the initial PIP, the PIP should be reduced rapidly. Frequent adjustments in PIP may be required because pulmonary mechanics can change rapidly, particularly after administration of exogenous surfactant. The evaluation of frequent blood gases and continuous transcutaneous monitoring may assist in the initial ventilator management (see Chapter 17).

In the acute phase of RDS, when alveolar atelectasis caused by surfactant deficiency predominates, PEEP levels of 4 to 5 cm H_2O may be necessary. During the latter stages of RDS, PEEP levels of 3 to 4 cm H_2O may be adequate to prevent alveolar collapse. Reduction of PEEP levels below 2 to 3 cm H_2O is not recommended because the endotracheal tube eliminates the infant's physiologic maintenance of FRC by vocal cord adduction.

During the period of increasing ventilatory support, FIO_2 can be first increased to 0.6 to 0.7 before increasing mean airway pressure. During weaning, once the PIP has been brought down to relatively safer levels, FIO_2 can be decreased. Maintenance of an adequate mean airway pressure and $\dot{V}/\dot{Q}$ matching may permit a substantial reduction in FIO_2. Mean airway pressures should be reduced before a very low FIO_2 (less than 0.3) is reached, in order to reduce the likelihood of lung injury.

Several ventilatory strategies effective in reducing air leaks/pneumothoraces include the following: (1) early surfactant followed by rapid extubation (RD, 0.04; CI, 0.08, 0.00; NNT, 25),[36] (2) volume-targeted ventilation (RD, 0.11; CI, 0.20, 0.03; NNT, 9),[43] and (3) high-frequency positive pressure ventilation with short inspiratory times (RD, 0.09; CI, 0.16, 0.02; NNT, 11) (Figure 15-2).[9] In contrast, trials of optimizing ventilatory strategies have shown inconsistent effects on the rate of BPD.

Weaning Ventilator Support

Discontinuation of ventilatory support may be attempted when there is spontaneous breathing and mechanical ventilation contributes only minimally to total ventilation. In practice, weaning can be attempted when ventilator settings are relatively low. Weaning may be successful when

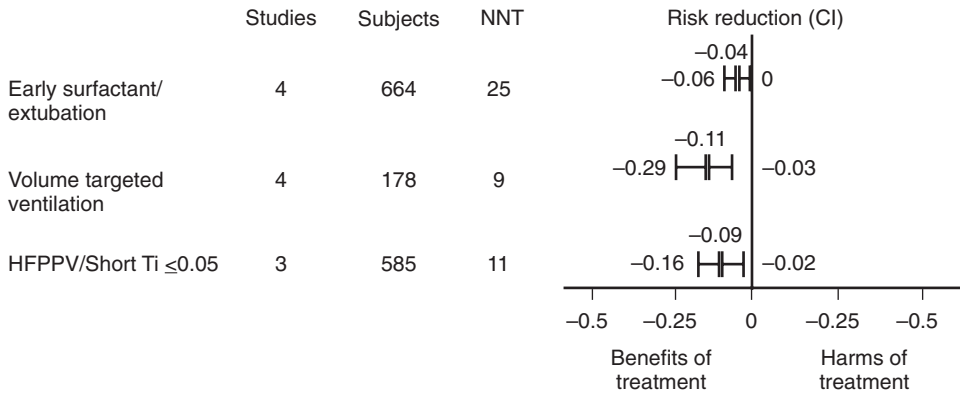

Figure 15-2 ■ Ventilatory strategies effectiveness in reducing air leaks/pneumothoraces in neonates. *CI,* Confidence interval; *NNT,* number needed to treat; *Ti,* inspiratory time.

the ventilator rate is 15/min or less, when the delivered PIP minimally moves the chest, and when the F_{IO_2} is less than 0.40. The small endotracheal tubes used in premature neonates add a high resistive load, and most infants can be extubated from a low ventilator rate, without a period of endotracheal CPAP. A meta-analysis showed that extubation from low rates is more successful than extubation after a period of endotracheal CPAP.[44] Techniques such as patient-triggered ventilation (PTV), synchronized intermittent mandatory ventilation (SIMV), pressure support (P/S), and breath termination sensitivity may facilitate weaning, because there may be less patient agitation and "fighting the ventilator" as a result of ventilator synchrony and termination of ventilator breaths during the infant's attempts to exhale.[46-48] A meta-analysis demonstrated that SIMV and PTV shortened the duration of mechanical ventilation by almost 32 hours in preterm infants (95%; CI; 10-54 hr).[45]

Neonates can be extubated to an oxygen hood, nasal canula, nasal CPAP (NCPAP), or to nasal CPAP with synchronized ventilator breaths (NCPAP + SIMV). The elective postextubation use of NCPAP reduces the need for additional ventilatory support in preterm infants (RD, 0.11; CI, 0.24, 0.10; NNT, 6).[48,49] A combination of NCPAP with SIMV may increase the likelihood of successful extubation by 30%.[51-52]

Methylxanthines (theophylline, caffeine) may also aid the weaning and extubation process, resulting in a reduction in failed extubations (RR, 0.44 [0.27-0.72]), especially in extremely low-birth-weight infants.[53] Restriction of caffeine resulted in increased BPD (36% to 47%, $P < 0.001$) and neurodevelopmental disability/death (40% to 46%, $P < 0.01$) rates and an additional week of ventilatory support.[54,55] In contrast, high-dose caffeine (20 mg/kg/day) reduced extubation failure (30% to 15%; $P < 0.05$; NNT, 7) without adverse effects.[56] (See Chapter 21 on Pharmacologic Adjuncts).

Ventilatory Strategies in Neonates with Respiratory Disorders Other Than RDS

Persistent Pulmonary Hypertension of the Newborn

Persistent pulmonary hypertension of the newborn (PPHN) is characterized by severe hypoxemia secondary to extrapulmonary shunt. The hypoxemia may be out of proportion to clinically evident lung disease. Elevated pulmonary arterial pressure resulting from increased pulmonary vascular resistance exceeds systemic arterial pressure and drives a pulmonary-to-systemic shunt through a patent ductus arteriosus or a right–to-left shunt at the atrial level in a structurally normal heart. Increased pulmonary vascular resistance may result from hypoxemia, sepsis, meconium aspiration syndrome, asphyxia, maternal drug therapy (e.g., nonsteroidal antiinflammatory agents, which inhibit vasodilator prostaglandin synthesis), or various other causes. Many cases are idiopathic.

There is little evidence from controlled clinical trials to guide conventional ventilator management, and treatment principles are primarily based on lung pathophysiology. Strategies for mechanical ventilation in PPHN should decrease pulmonary vasoconstriction and improve pulmonary blood flow. Hypoxemia and acidosis are known to elevate pulmonary arterial pressure in the neonatal pulmonary circulation.[57] Therefore, ventilator adjustments are made to prevent hypoxemia and produce alkalosis. Hypoxemia can be prevented by maintaining the arterial P_{O_2} at 60 to 80 mm Hg or greater. If oxygenation is extremely labile, a higher target of Pa_{O_2} (greater than 80-100 mm Hg) may be attempted, although the benefits and risks of such a strategy have not been evaluated. Alkalosis can be achieved by hyperventilation (to maintain arterial P_{CO_2} in the 30 to 40 mm Hg range) and infusion of sodium bicarbonate (0.25-1 mEq/kg/hr) to maintain a pH between 7.5 and 7.6. Retrospective clinical data suggest that the alkalosis induced by hyperventilation may be more beneficial than that induced by infusions of alkali alone. In a multicenter retrospective study in which hyperventilation was used in almost two thirds of the neonates, hyperventilation reduced the risk of extracorporeal membrane oxygenation (ECMO) without increasing the use of oxygen at 28 days of age.[58] In contrast, the use of alkali infusion was associated with increased use of ECMO (odds ratio: 5.03, compared with those treated with hyperventilation).[58] Although hyperventilation has been shown to reduce pulmonary pressures and improve oxygenation,[59] there are concerns regarding the possible risks of induced respiratory alkalosis. Very low Pa_{CO_2} of less than 20 to 25 mm Hg causes cerebral vasoconstriction and may lead to long-term neurologic morbidity including sensorineural hearing loss. In a small study, the need for prolonged hyperventilation

in infants with PPHN was associated with poorer neurodevelopmental outcome.[60] The volutrauma associated with hyperventilation may lead to air leaks.[61]

Ventilator rates higher than 60 to 80/min may actually decrease, rather than increase, minute ventilation.[19] Therefore, although the ventilator rate is relatively high, subsequent attempts to increase minute ventilation must aim at increasing tidal volume, usually by increasing PIP, decreasing PEEP, or optimizing I:E ratio.

Alternatively, some clinicians prefer a more "gentle" approach to ventilation and tolerate mild hypoxemia and/or hypercapnia to diminish lung injury. In this strategy, ventilator settings and fractional inspiratory oxygen (F_{IO_2}) are selected to maintain a P_{aO_2} between 50 and 70 mm Hg and P_{aCO_2} is allowed to increase as high as 60 mm Hg.[62] Hyperventilation and muscle relaxants are typically not used, although vasodilators such as nitric oxide may be used.

Inhaled nitric oxide (iNO) has been shown in several studies to improve oxygenation in neonates with PPHN.[7] If hypoxemia or acidosis persists despite conventional ventilator therapy, iNO with or without high-frequency ventilation is often attempted. Treatment with high-frequency oscillatory ventilation (HFOV) combined with iNO may be more often successful than treatment with either HFOV or iNO used alone in severe PPHN (see Chapter 14).[64]

After the initial period of 3 to 5 days, there is typically a transition period when the oxygenation stabilizes. During the transition period, there are fewer fluctuations in the P_{aO_2} as the pulmonary vasculature becomes less responsive to changes in arterial pH and P_{aCO_2}.[66] Hyperventilation can usually be discontinued gradually (over 1-2 days) and ventilatory settings adjusted to "normalize" blood gases until extubation. If the infant has received high-frequency ventilation or iNO therapy, these may also be gradually reduced and withdrawn. Rapid weaning of ventilator and vasodilator support occasionally results in recurrence of shunting.

Meconium Aspiration Syndrome

Airway obstruction, pneumonitis, surfactant inactivation, and increased pulmonary vascular resistance characterize the meconium aspiration syndrome (MAS). Meconium partially obstructs airways resulting in a ball-valve phenomenon. The ball-valve phenomenon leads to gas trapping and airway distension and increases the risk of pneumothorax. A chemical pneumonitis of variable severity results from direct toxicity of meconium and release of inflammatory mediators. Surfactant is inactivated directly by meconium and by mediators of inflammation. Surfactant inactivation predisposes the lungs to atelectasis. Atelectasis, gas trapping, and pneumonitis lead to $\dot{V}/\dot{Q}$ mismatch causing hypoxemia, hypercapnia, and acidosis. Hypoxemia and acidosis, coupled with antenatal pulmonary vascular remodeling that occurs in utero because of chronic hypoxemia, may lead to hypoxic pulmonary vasoconstriction and pulmonary hypertension.

There is little evidence from controlled clinical trials to guide conventional ventilator management, and treatment principles are primarily based on lung pathophysiology. Infants with hypoxemia (P_{aO_2} less than 50 mm Hg) without significant evidence of right-to-left shunting either at the ductal or atrial level probably have severe $\dot{V}/\dot{Q}$ mismatch and intrapulmonary shunting of blood past poorly ventilated or nonventilated areas of the lung. Ventilator management of the neonate with MAS is challenging because of the conflicting demands of areas of atelectasis and hyperinflation. Meconium-stained infants who have hypoxemia (P_{aO_2} less than 50 mm Hg), hypercapnia (P_{aCO_2} greater than 60 mm Hg), or acidosis (pH less than 7.25) in an oxygen environment with an F_{IO_2} greater than 0.80, are often considered candidates for mechanical ventilation.

In infants with MAS without associated PPHN, it is sufficient to maintain a pH of 7.3 to 7.4, with a P_{aO_2} between 60 to 80 mm Hg and a P_{aCO_2} of 40 to 50 mm Hg. A moderate rate (40-60/min), the minimum effective PIP for chest rise, a low to moderate PEEP (PEEP 3-5 cm H_2O), and an adequate expiratory time (0.5 to 0.7 sec) are required to prevent gas trapping and air leaks. If gas trapping is noticed, expiratory time should be increased (0.7-1.0 sec) and PEEP decreased (2-4 cm H_2O). If oxygenation is borderline (P_{aO_2} 50-60 mm Hg) despite moderate ventilator settings and a high F_{IO_2}, it may be appropriate to conservatively manage the infant without further increases in ventilator settings to reduce the risk of volutrauma and air leaks. Some infants with MAS, especially those with spontaneous respirations or who actively oppose the ventilator, may benefit from sedation with narcotics or muscle relaxants.

Ventilator strategies differ in infants with MAS and concomitant PPHN. Hypoxemia should be prevented by maintaining the arterial P_{O_2} at 60 to 80 mm Hg or greater. Poor oxygenation secondary to $\dot{V}/\dot{Q}$ mismatch may improve with increased inhaled oxygen concentration. It is preferable to increase F_{IO_2} before increasing ventilatory pressures. Compared to premature neonates, there is less concern about the risks of hyperoxemia because neonates with MAS are generally term or postterm.

If hypoxemia or hypercapnia does not respond adequately to conventional mechanical ventilation, high-frequency ventilation in the form of either HFOV or high-frequency jet ventilation (HFJV) may be effective.

When these modalities fail, these patients may become candidates for ECMO (see Chapter 16).

Congenital Diaphragmatic Hernia

The pathophysiology of impaired gas exchange in congenital diaphragmatic hernia (CDH) results from lung hypoplasia with decreased surface area for gas transfer complicated by pulmonary hypertension. The current surgical approach in most centers is one of cardiopulmonary stabilization and delayed surgical repair of the diaphragmatic hernia.

The ventilatory management of neonates with CDH is often challenging. Prospective randomized trials in this population to determine which ventilatory strategy is best have not been done. There is preliminary evidence from recent retrospective studies that suggest "gentle ventilation" with the avoidance of hyperventilation and alkalosis may be associated with improved survival.[67-70] A preliminary analysis from a large retrospective multicenter study indicated that gentle ventilatory strategies with permissive hypercapnia and permissive hypoxemia are being used more frequently and may result in a reduced need for ECMO and increased survival.[63]

Early ventilatory management focuses on avoidance of bag and mask ventilation or CPAP that may increase gaseous distension of the herniated loops of bowel and impair pulmonary gas exchange. The insertion of a nasogastric or orogastric tube and connection to suction is usually indicated to decompress bowel that is in the chest. The objectives of mechanical ventilation in CDH should be to attain sufficient oxygenation (PaO_2 50-60 mm Hg or even lower) and a pH higher than 7.25. Very low pH values (less than 7.20) may increase pulmonary vascular resistance. It is usually sufficient to achieve a $PaCO_2$ of 40 to 65 mm Hg, unless the presence of pulmonary hypertension requires it to be lower (30-40 mm Hg). Relatively rapid rates (40-80/min) with low PIP sufficient for chest excursion (20-24 cm H_2O), short T_I (0.3-0.5 sec), and moderate PEEP (4-5 cm H_2O) in combination with mild sedation are usually indicated to attain these objectives.[68] For critically ill patients who do not meet these goals, marginal pulmonary gas exchange can be tolerated as long as there is good perfusion and adequate cerebral oxygen delivery indicated by preductal saturations of 85% or higher. Postductal PaO_2 as low as 30 mm Hg or a $PaCO_2$ greater than 65 mm Hg can also be tolerated if the patient is otherwise stable. Patients who do not maintain preductal saturations greater than 85% or postductal PaO_2 greater than 30 mm Hg or who show evidence of inadequate oxygen delivery based on rising serum lactate levels can be given a trial of iNO and placed on HFOV. Some infants will not respond to these measures and require treatment with ECMO.[68]

Although iNO has been used in many centers to treat PPHN in these patients, iNO does not significantly improve outcomes in CDH.[65,71,72] Clinicians in some centers follow a policy of elective HFOV, followed by surfactant or iNO, and ECMO for preoperative stabilization if HFOV alone is not sufficient. However, there are no controlled trials to conclude that HFOV is superior to IMV in neonates with CDH.

Refractory Apnea of Prematurity

Infants born prematurely may have apneic episodes that are of either central (central nervous system mediated), obstructive, or mixed (central + obstructive) etiology (see Chapter 3). Apnea in neonates is frequently due to immature control of breathing; however, other causes of apnea must be excluded. Apnea may be due to infection, hypoxemia, metabolic disturbances such as hypoglycemia, anemia, and central nervous system disorders such as intraventricular hemorrhage and hydrocephalus. Infants without a specific treatable cause of apnea may be given a trial of methylxanthines (theophylline or caffeine), and/or CPAP. In premature infants, CPAP reduces apnea by relief of upper airway obstruction, possibly via splinting of the pharyngeal airway. Therefore, CPAP can decrease the incidence of both mixed and obstructive apnea episodes but is usually ineffective in central apnea.[73] High flow nasal cannulae (flows 1-2.5 L/min) also generate positive distending pressure and may be as effective as CPAP for apnea.[74] However, the delivered pressure is not measured and is variable. Infants with persistent apnea on CPAP can be tried on nasal intermittent positive pressure ventilation (CPAP + IMV or NIPPV),[50] although more studies are required to evaluate the benefits and risks of this technique in infants with refractory apnea.

Infants unresponsive to CPAP or NIPPV may require intubation and positive pressure ventilation. Because the lungs are generally healthy or in the healing phase after the initial respiratory disorder, it is important to avoid ventilator-associated lung injury. The ventilator rate is usually set at between 10 and 15 breaths per minute with minimal peak pressures (7-15 cm H_2O), enough to produce minimal chest rise. A physiologic PEEP (2-3 cm H_2O) and low FIO_2 (usually less than 0.25) are often sufficient. Planned attempts of extubation to CPAP or NIPPV should be considered when the infant shows regular, spontaneous breathing patterns on the ventilator.

Asphyxia with Hypoxic-Ischemic Encephalopathy

Neonates with hypoxic-ischemic encephalopathy (HIE) may present with mild to severe lung pathology and with impaired control of breathing. Infants may be tachypneic secondary to acidosis or apneic because of severe cerebral insult. Lung pathology can be seen secondary to meconium aspiration, pulmonary hypertension, pulmonary edema, or acute RDS (ARDS). Some infants, especially those with meconium aspiration, may have pulmonary hypertension as a result of acute hypoxia or abnormal pulmonary vascular remodeling secondary to chronic intrauterine hypoxia. Infants with severe HIE may also have cardiac or renal failure that may result in pulmonary edema.

The ventilatory management strategy for neonates with asphyxia and HIE, if no other pulmonary pathology is present, targets maintenance of arterial blood gases in the normal range (pH 7.35-7.45, PaO_2 60-90 mm Hg, and $PaCO_2$ 35-45 mm Hg). Hyperventilation and hypoventilation should be avoided, because cerebral blood flow is in part dependent on $PaCO_2$. Hypoxemia must be avoided to reduce accentuation of the hypoxic-ischemic damage, and hyperoxia must also be avoided to reduce free radical production and potentiation of cerebral injury. If minimal or no spontaneous respiratory efforts are present due to encephalopathy or due to high doses of anticonvulsants administered, a ventilator rate of 30 to 60/min with low peak pressures (8-15 cm H_2O), physiologic PEEP (2-3 cm H_2O), and the FIO_2 adjusted to maintain normal oxygen saturation is usually appropriate. If the infant is spontaneously breathing, the ventilator rate may be reduced accordingly.

The ventilator management for infants with PPHN caused by asphyxia or meconium aspiration syndrome is based on the underlying lung pathophysiology and the goal should be to maintain normocapnia with adequate oxygenation. Therefore, hyperventilation, alkalosis, or permissive hypercapnia strategies may not be suitable for infants with hypoxic-ischemic encephalopathy.

Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia (BPD) was the term originally used to describe lung injury in preterm infants as a result of oxygen and assisted ventilation. BPD is now most often used for infants who have oxygen or ventilator dependence for at least 28 days. Newer definitions of BPD

have been proposed by a National Institute of Health consensus conference and are fully discussed in Chapter 23.[75] BPD is considered moderate or severe if oxygen or ventilator dependence persists at a postmenstrual age of 36 weeks.[75] BPD is a heterogeneous lung disease characterized by airway, alveolar, and vascular abnormalities.[76]

Over the last two decades, the pathology has changed as smaller and more premature infants survive. Prior to the exogenous surfactant era, airway injury, inflammation, and parenchymal fibrosis were prominent findings in BPD. More recently, lungs of infants dying from BPD show more uniform inflation. The small airways are relatively free of epithelial metaplasia, smooth muscle hypertrophy, and fibrosis. Early pathologic descriptions of BPD included epithelial metaplasia and fibrosis, but the "new BPD" is characterized by more disturbance of alveolar septation and development, and less epithelial metaplasia or fibrosis.[76]

The main objective of the ventilatory management in BPD is to maintain adequate gas exchange while minimizing ventilator-associated lung injury. In view of the prolonged time constant in portions of the lungs, rapid ventilatory rates may not be optimal and may lead to gas trapping or inadequate tidal volume delivery. Older infants with BPD often tolerate higher levels of PEEP (5-7 cm H_2O) with improvements in oxygenation without CO_2 retention,[77] although higher levels of PEEP have not been systematically investigated in this population.

Infants with the noncystic form of BPD, a predominantly homogeneous hazy appearance of the lungs on the chest radiograph with minimal or no cysts or coarse reticulation, may tolerate faster rates and higher PEEPs. Infants with the cystic form of BPD, who have a tendency for gas trapping, are less likely to tolerate rapid rates and high PEEP. Pulmonary function in infants with BPD shows short-term variability despite apparent clinical stability,[78] and therefore, ventilatory parameters may require frequent modifications.

The emphasis should be on gradual weaning despite fluctuation in the clinical condition. Some neonates with marked variability in compliance and resistance over time may benefit from volume-controlled ventilation or patient-initiated, pressure-regulated, volume-controlled (PRVC) ventilation in an attempt to deliver an adequate tidal volume with the least pressure. Although these modes of ventilation have theoretical benefits and many experienced clinicians use these modes routinely, there is insufficient evidence from randomized controlled trials or other studies to identify the superiority of one technique over another. Management of these neonates is empiric, based on pathophysiologic considerations as well as the experience of the clinician.

Newer ventilators with sensitive patient-triggered modes may benefit older infants with BPD who have a tendency to get agitated and "fight the ventilator." The term "fighting the ventilator" is usually applied to infants who actively exhale against a ventilator-delivered breath. In addition to patient-triggered ventilation, sedation may be required to calm the infant in this situation.

Many neonates with BPD do not have indwelling arterial catheters, and ventilator adjustments are often made on the basis of pulse oximetry and venous or capillary pH and P_{CO_2}. If the infant is on low ventilator settings, attempts should be made to extubate the infant after optimizing fluid, nutrition, and pulmonary status. If the infant continues to require high ventilator settings, the P_{aCO_2} may be allowed to rise to high levels, as long as the arterial pH continues to stay above 7.25 (or venous/capillary pH greater than 7.20). A small retrospective study suggested that oxygen saturation should be maintained higher than 90% to prevent or treat pulmonary hypertension and cor pulmonale; however, this target has yet to be verified in controlled clinical trials. Weaning ventilator support should continue as long as the pH and oxygenation are adequate.

Inhaled nitric oxide (iNO) or sildenafil may have a therapeutic effect in infants with ventilator-dependent BPD. In a small nonrandomized trial iNO improved oxygenation but not carbon dioxide elimination in some infants with severe BPD.[79] The role of iNO in BPD at present is unclear, and further research is needed. Tracheobronchomalacia may complicate BPD[80] and is associated with the occurrence of "BPD spells." BPD spells are sudden episodes of respiratory deterioration usually associated with expiratory airflow limitation caused by tracheobronchial narrowing after agitation and vigorous diaphragmatic and abdominal muscle activity.[81] Infants with "BPD spells" may require sedation and occasionally pharmacologic muscle paralysis if they do not respond to a transient increase in ventilator settings.

High-frequency ventilation (HFV) is unlikely to have a major role in the management of established moderate to severe BPD, because high airway resistance in the lungs decreases the efficacy of gas exchange during HFV. There are no randomized controlled trials of HFV in the management of BPD.

In some patients who have required prolonged intubation and ventilation, typically for more than 8 to 10 weeks and who are not weaning from the ventilator, tracheostomy to reduce dead space, improve patient comfort, and assist in pulmonary toilet has proven helpful in weaning these patients from the ventilator or allowing them to be discharged to a facility with a lower level of acuity or on a home ventilator program.

Summary

Small, premature infants survive today in large part because of advances in mechanical ventilation. These surviving infants are at high risk for ventilator-induced lung injury. The degree of lung injury is partially dependent on the ventilatory strategies employed. Ventilatory strategies that prevent high tidal volume, minimize gas trapping, prevent alveolar overdistension, and minimize rapid changes in P_{CO_2} may lead to improved outcomes.

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16 Extracorporeal Membrane Oxygenation

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Advances in the field of assisted ventilation include the following: (1) advanced computer-assisted ventilators with a continually increasing number of settings and devices to modify the types of ventilation, (2) new pharmacologic agents to modulate the pulmonary vascular bed, the gaseous tension within alveoli, and the complications of ventilation, (3) novel ventilatory strategies to decrease damage and complications, and (4) bedside availability of pulmonary function measurements and graphics to help the clinician tailor the ventilatory assistance to the physiologic needs of the infant. Nevertheless, the condition of some neonates fails to improve with ventilation, and they die of respiratory failure unless alternative treatment is available. Neonates afflicted with either persistent pulmonary hypertension of the newborn (PPHN) or congenital diaphragmatic hernia (CDH) are two excellent examples of children who may fail with conventional ventilation and require alternative therapy for survival.

In addition to the problem of nonsurvival, many children who receive aggressive ventilatory support continue to experience unacceptably high rates of ventilator-induced pulmonary complications: barotrauma including pulmonary air leak, bronchopulmonary dysplasia, and chronic lung disease. These subsequent complications of ventilation impose increased rates of mortality even after the newborn period. For all these reasons, judicious use of cardiopulmonary bypass techniques for temporary respiratory support of selected term and near-term newborns is needed and useful (Figs. 16-1, 16-2).

This technique is most frequently referred to as *extracorporeal membrane oxygenation (ECMO)*, a name which unfortunately puts an undue emphasis on the role of oxygen support. Equally important may be the role of carbon dioxide extraction, cessation of toxic ventilatory settings, and cardiovascular support. Consequently, these processes of support may be referred to instead as *extracorporeal life support (ECLS)*. In reality, both terms are frequently used and are generally interchangeable.

History of Cardiopulmonary Bypass

Artificial maintenance of circulation was pioneered by John and Mary Gibbon beginning in 1934[1]; it was first reported in 1937 but not used in a widespread fashion by cardiac surgeons until the 1950s. It was soon discovered that if used for more than 1 to 2 hours, the device itself was lethal because of protein denaturation,[2] which was thought to be caused by the gas exchange device. This finding led to the use of the biologic lung as the oxygenator for extracorporeal circulation, as described by Lillehei and colleagues.[3] Because the major problem with artificial circulation was the oxygenator, many new devices were developed, including the filming oxygenator[4] and the bubble oxygenator,[5] which became the standard for cardiac surgery.

During attempts to use these oxygenators for prolonged bypass, it was noted that the oxygenator, which directly exposes blood to oxygen (O_2), damages cells and proteins. This damage is apparent within a few hours after beginning bypass. The large reservoir used for the oxygenation also complicates management of volume and necessitates complete suppression of coagulation in the low-flow component.

Development of Membrane Oxygenators

The problems associated with early cardiopulmonary bypass equipment were solved with the development of a streamlined unit that had no reservoir and incorporated a membrane oxygenator instead of a bubble oxygenator, eliminating the direct blood-gas interface (Fig. 16-3). The first membranes were made of polyethylene and Teflon but required large surface areas for adequate oxygenation.[6] In 1957, Kammermeyer[7] first reported the excellent gas transfer properties of a polymer of dimethylsiloxane, which became commonly known as *silicone* (Fig. 16-4). This led to the development of many oxygenators and to the first trials in infants.[8]

Once these membrane lungs and the circuits that bring blood to and take blood from them become coated with a protein monolayer, the blood is no longer in direct contact with a thrombogenic foreign surface. This protein monolayer allows gas exchange to proceed for a prolonged period of time without causing excessive damage to the blood cells. The large reservoir is also eliminated, and this allows the use of less anticoagulant. For most patients, bleeding events are reduced and manageable.

Development of a Pump

In the development of neonatal ECMO, most devices were readily adapted from devices already in use by the cardiac surgery teams. Consequently, multiactivated Sigma motor pumps were used initially. Soon thereafter, roller pumps

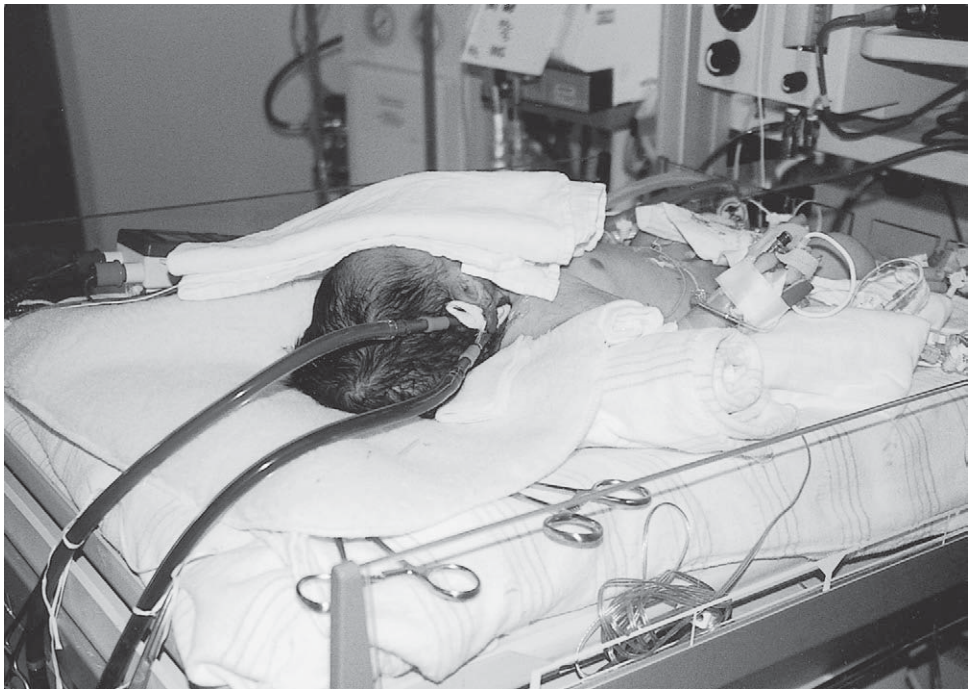

Figure 16-1 ■ Photograph of a neonate on venovenous extracorporeal membrane oxygenation.

gained popularity because of their reliability and ease of use. With these devices, blood-conducting tubing is compressed, and the fluid is forced forward. To prevent increased hemolysis of red blood cells, partially occluding systems are used. More recently, the centrifugal pump has gained popularity. This type of pump has the advantages of low hemolysis, usability over a wide range of flows, and little risk for air pumping.

The great disadvantage of all of the pumps currently in use is the lack of pulsatile blood flow to the patient. This variation from the normal cardiac flow has physiologic effects on the end organs. Consequently, use of venovenous bypass whenever possible with preservation of pulsatile flow may confer advantage to the sick neonate (see further discussion of venovenous cannulation later in this chapter, p. 284).

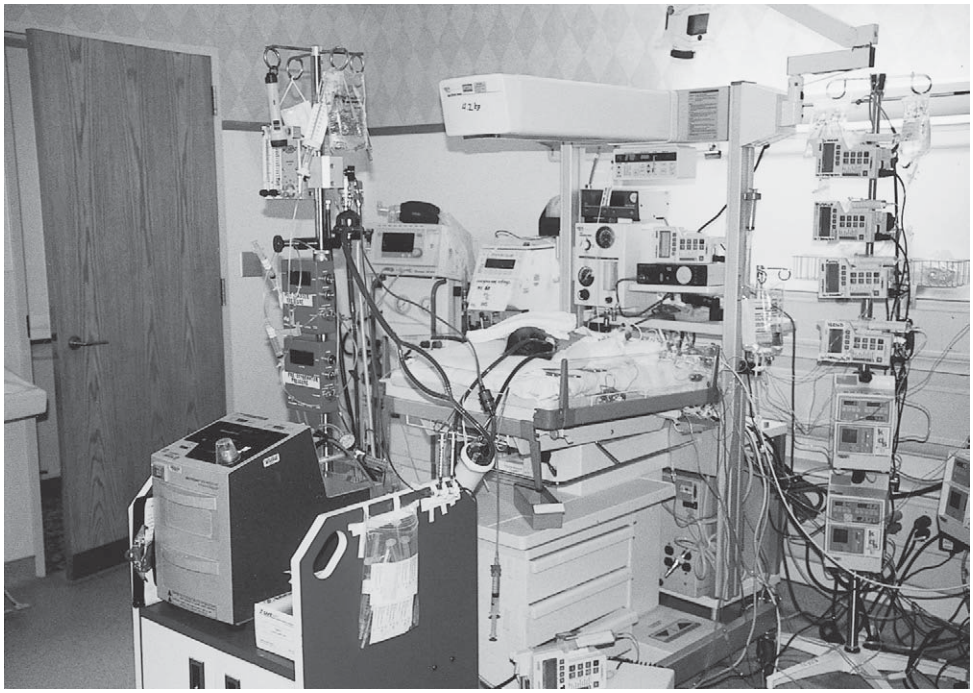

Figure 16-2 ■ Photograph of the bed space for infant on extracorporeal membrane oxygenation (ECMO) showing a centrifugal ECMO pump in the foreground.

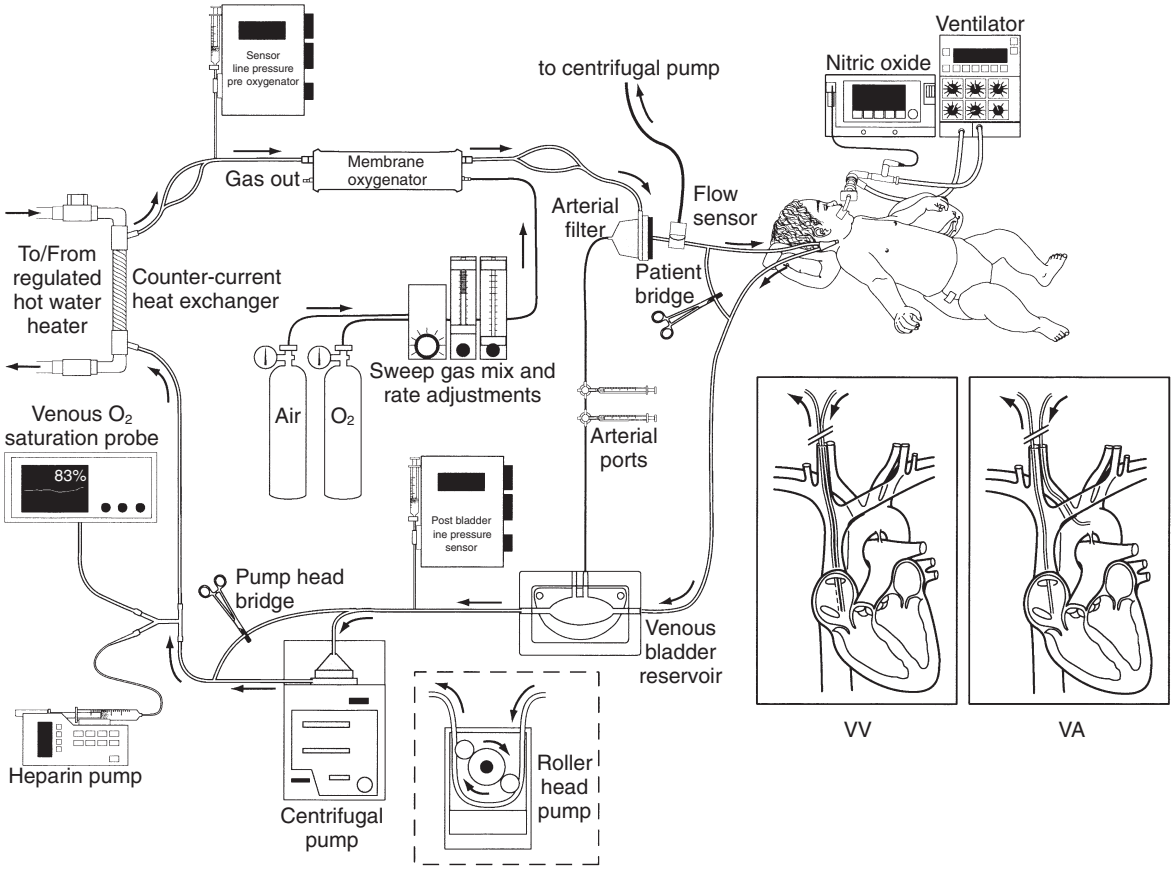

Figure 16-3 ■ Extracorporeal membrane oxygenation circuit diagram. *VA*, Venoarterial; *VV*, venovenous.

Vascular Access

The last major problem to be overcome in the quest to perform successful bypass in the neonate was vascular access. Early investigators used umbilical vessels, which did not provide adequate flow for substantial respiratory and cardiac support. Later, investigators cannulated the internal jugular vein and the common carotid artery. These sites allow sufficient flow to permit near-total cardiopulmonary bypass if needed. The successful solution of these multiple problems enabled Bartlett and his colleagues[9] to complete the first successful application of extracorporeal membrane oxygenation for respiratory failure in a neonate in 1975.

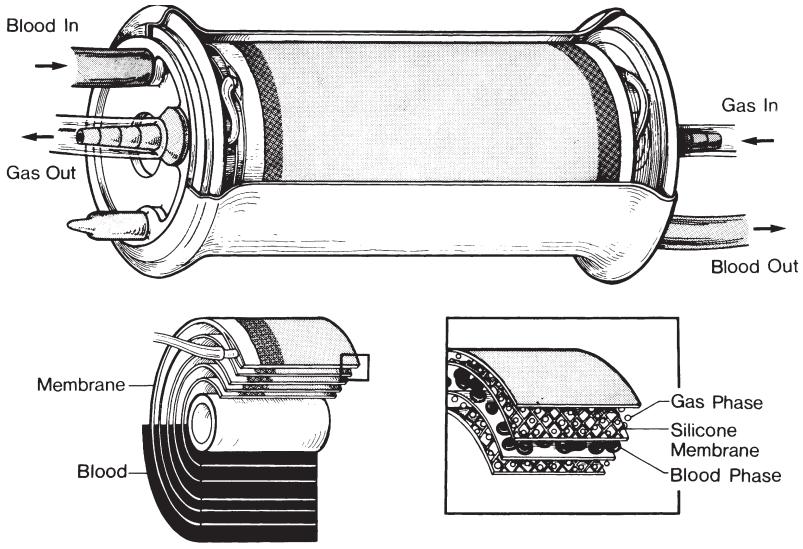

Figure 16-4 ■ The SciMed Kolobow spiral silicone membrane lung.

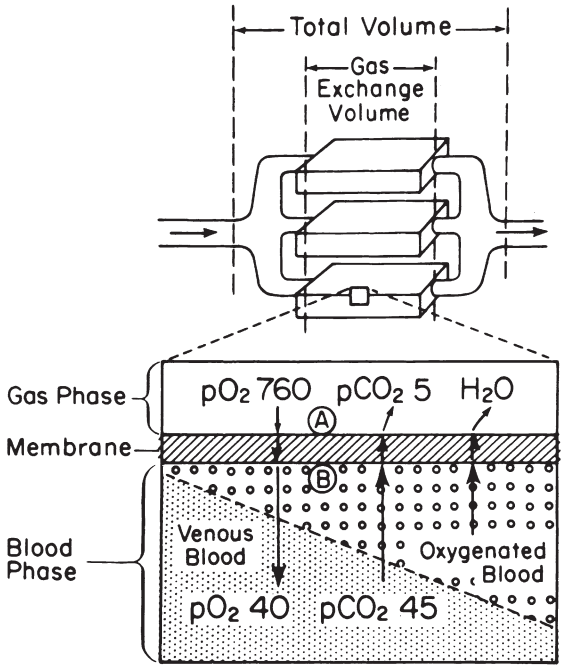

Figure 16-5 ■ Principles of gas transfer in a membrane oxygenator. This expanded view shows interactions across the gas exchange membrane. Venous blood enters from the left and becomes arterialized as O_2 diffuses through the membrane and blood film and as CO_2 diffuses from the blood film into the gas phase. (From Bartlett RH, Gassaniga AB: Curr Prob Surg 15:9, 1978.)

Physiology of Extracorporeal Circulation

Membrane Lung

The membrane lungs currently in use have two compartments that are divided by a gas-permeable membrane of silicone polymer. The ventilating gas (gas phase) is on one side, and the blood (blood phase) is on the other, so that the gas and blood phases never come into contact with one another. The oxygen (O_2) and carbon dioxide (CO_2) diffuse across the membrane at the molecular level (Fig. 16-5).

The gradient for O_2 diffusion across the membrane is the difference between the O_2 content in the ventilating gas and that in the venous blood of the patient. The inherent potential for O_2 transfer across a silicone membrane is 1210 mL O_2/m^2 per minute (min) per mil thickness at a diffusion gradient of 706 mm Hg (where the thickness of the silicone is expressed as mil [0.001 inch = 25 µm]). However, the AVECOR 0800 silicone membrane lung (a standard size for a neonate undergoing ECMO) has a surface area of 0.8 m^2 and thickness of 1.5 mil; therefore the maximum O_2 transfer across this membrane is 645 mL O_2/min. Oxygen diffusion through the blood phase is 110 mL O_2/m^2 per minute per 100 µm of film thickness at a gradient of 720 mm Hg, where film thickness is defined as the thickness of the blood film between two layers of the silicone membrane. Transmembrane pressure is defined as the sum of the pressures in the blood phase and the gas phase. When the sum is greater than 750 mm Hg, the membrane alters its geometric configuration; this results in decreased O_2 transfer. The delta (Δ) pressure is the difference between the pressure of the blood entering and that of the blood leaving the membrane. When this gradient exceeds 350 mm Hg, the blood film thickness widens, and this results in decreased O_2 transfer. Under normal operating conditions, the transmembrane pressure should not exceed 400 mm Hg, and the Δ pressure should be 100 to 200 mm Hg.

When these conditions are met, the result is the thinnest blood film possible, which, in the AVECOR 0800 membrane lung, is 200 µm. Therefore, the maximum diffusion of O_2 into the blood phase for a 0.8-m^2 membrane is approximately 40 mL O_2/min (compare with the potential of 645 mL O_2/min for the silicone membrane). Because diffusion of O_2 through the blood film is the limiting factor, the potential of the membrane can never be reached. Actual O_2 delivery is also limited by the O_2 carrying capacity of the blood. Each gram of hemoglobin has the capacity to bind 1.34 mL of O_2.[10,11]

Oxygen and Carbon Dioxide Transfer

Red blood cells closest to the membrane become saturated with oxygen first, and the local partial pressure of O_2 (P_{O_2}) increases. Dissolved O_2 then diffuses deeper into the blood film, saturating more red blood cells. For complete saturation of the blood film to occur, it must remain in contact with the membrane long enough for O_2 to diffuse to the center of the film. For any given membrane lung, the amount of venous blood that can be completely saturated is a function of the O_2 content of the venous blood returning to the membrane and the amount of time spent in the membrane. As flow increases, the blood spends less time in the membrane. Oxygen transfer increases in proportion to the flow rate until a limitation to O_2 transfer is imposed by the thickness of the blood film. When venous blood entering the membrane is 75% saturated, the flow rate at which blood leaving the membrane is 95% saturated is termed the *rated flow* of that device, a number that allows for standardization of various membrane lungs (Fig. 16-6).[12] If it is assumed that the membrane is large enough, the amount of O_2 that can be delivered is dependent on

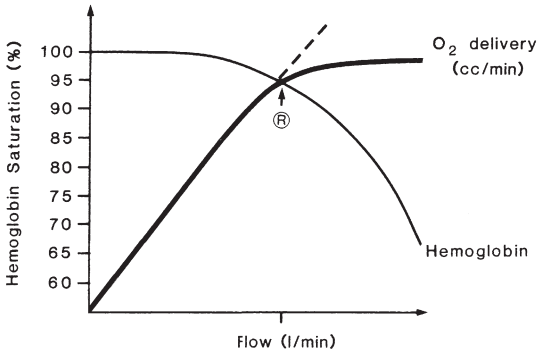

Figure 16-6 ■ Rated flow. As flow through the membrane increases, actual O_2 transfer increases proportionally until the residence time of the venous return prevents complete hemoglobin saturation. At this point, the absolute O_2 transfer becomes fixed, but as the flow continues to increase, a smaller percentage of the venous return to the membrane becomes saturated. ® represents the rated flow, which is the flow at which the blood leaving the membrane is 95% saturated. (Adapted from Galletti PM, Richardson PD, Snider MT: Trans Am Soc Artif Intern Organs 18:359, 1972.)

the blood flow available, not on the capacity of the membrane to transfer O_2.

Carbon dioxide is much more diffusible through plasma than O_2, and CO_2 transfer is limited by its diffusion rate across the membrane. For the 0.8-m^2 AVECOR silicone membrane lung, the potential for CO_2 transfer is about 160 mL/min. This is four times greater than the amount of O_2 that can be transferred to the blood film. Carbon dioxide transfer is so efficient that CO_2 must often be added to the gas phase; this decreases the gradient, so respiratory alkalosis does not develop. Because CO_2 transfer is independent of blood flow but dependent on surface area of the membrane, an increasing partial CO_2 pressure (PCO_2) can be a sensitive indicator of loss of surface area and oxygenator function, which generally indicates clot formation or water in the gas phase.

Blood flow to the membrane is limited by the total circulating blood volume and the diameter of the venous catheter. The system must allow at least 120 mL/kg/min of flow to achieve near total support of cardiorespiratory function. The ECMO circuit is designed to permit this blood flow volume with the membrane lung having a greater rated flow.

Patient Selection

There are two critical issues in the application of ECMO: (1) which patients can be helped? (alternatively, who is likely to die without this therapy?) and (2) when should this therapy be instituted? Because this is an invasive procedure, great effort to determine appropriate entry criteria for the procedure should be undertaken before its institution. The National Cooperative ECMO Study in adults showed that most forms of acute end-stage respiratory failure are not reversible even with prolonged respiratory support. The results showed that ECMO did not improve survival rates in these patients.[13] Autopsy studies confirmed that severe respiratory failure in adults is associated with resolution by pulmonary fibrosis. This fibrosis prevents return of normal lung function even if the primary lung problem has been treated adequately. However, improved selection criteria for adults and earlier ECMO treatment have produced better adult survival rates (up to 60%) in individuals who would be predicted to have 90% mortality.[14]

In contrast to adults, most of the problems that lead to respiratory failure in the newborn period are potentially reversible, and 90% of lung growth occurs after the neonatal period. This makes neonates ideal candidates for ECMO therapy. In term infants, the major underlying cause of profound hypoxia is PPHN.[15] This final common pathway may be idiopathic or associated with a variety of common neonatal conditions, including meconium aspiration syndrome, congenital diaphragmatic hernia (CDH), sepsis, and perinatal asphyxia. PPHN is characterized by pulmonary hypertension, which causes right-to-left shunting either through a patent ductus arteriosus or a patent foramen ovale, or via intrapulmonary shunting. Pulmonary blood flow is decreased, and right ventricular overload occurs. Decreased pulmonary blood flow contributes to hypoxia and acidosis, which causes further pulmonary vasoconstriction and a vicious cycle occurs.[16] Pulmonary hypertension can lead to an increase in pulmonary arterial musculature (already increased at birth), which counteracts attempts to reverse the cycle.[17] Therapy, therefore, is directed at the resolution of pulmonary hypertension by correction of the acidosis and support of pulmonary function. Ventilatory and pharmacologic treatment of PPHN are discussed in detail in Chapters 14 and 15.

Disease States

The major criterion for ECMO selection is that the disease process must be reversible, usually within 2 to 4 weeks. Extracorporeal life support beyond this time is difficult but has been successfully done for up to 2 months. Disease processes that lend themselves to ECMO therapy include meconium aspiration syndrome, many pneumonias, neonatal sepsis, primary PPHN, CDH, perinatal asphyxia, respiratory distress syndrome, barotrauma with air-leak syndrome, and perioperative support of newborns with congenital cardiac lesions (Fig. 16-7).

In general, congenital cardiac defects can be identified and corrected without the need for ECMO. One cardiac condition that causes PPHN and may mimic some of the other conditions just listed is total anomalous pulmonary venous return. Unless there is an associated intracardiac defect, the heart itself may appear normal on a two-dimensional echocardiogram. The common pulmonary venous channel and absence of pulmonary veins entering the left atrium can only sometimes be demonstrated with noninvasive techniques. If the anomalous pulmonary

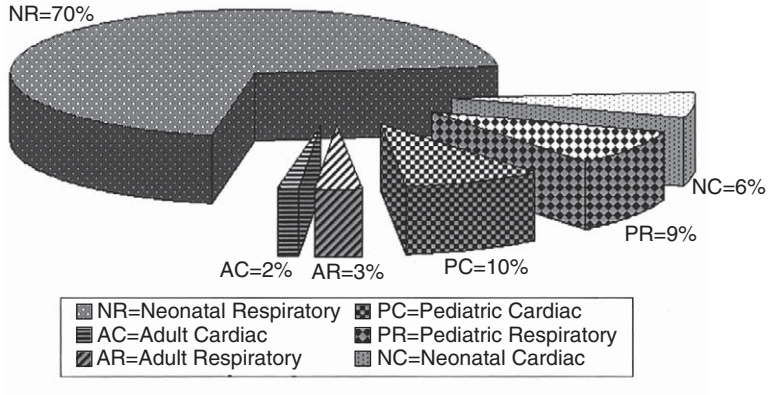

Figure 16-7 ■ Pie chart showing percentage of extracorporeal membrane oxygenation (ECMO) patients by category. Neonatal respiratory causes are the most common ECMO diagnoses. (Data are from the ECMO Registry of the Extracorporeal Life Support Organization (ELSO), Ann Arbor, Michigan, 1980-2001. Data from 2001 are incomplete.)

venous drainage is obstructed, most commonly in the infradiaphragmatic variety, then pulmonary hypertension results.[18]

ECMO may be useful for perioperative stabilization of very seriously ill infants with this condition and allows for completion of the workup and preparation for surgery in a more hemodynamically stable baby. ECMO can also be used as a ventricular assist device in the management of infants with perioperative ventricular failure, often allowing babies who would otherwise be unable to come off operative bypass to survive. The use of ECMO therapy for patients with cardiac conditions, however, is associated with a lower survival rate than is this therapy for the other conditions mentioned.

Selection Criteria

Selection criteria for ECMO treatment would ideally predict which infants will not do well while receiving mechanical ventilation before life-threatening complications or irreversible lung damage ensues. Theoretically, a child should *escape* to ECMO support when the danger of mechanical ventilation (conventional or high-frequency with or without inhaled nitric oxide) outweighs the risks of extracorporeal support. Unfortunately, it has never been possible to absolutely determine when that moment occurs, so most centers turn to numerical scoring systems that have been tested in individual institutions or adopted from larger, older ECMO centers. Box 13-1 details the criteria used at many centers and particularly those at which the authors have been associated. None of these scoring systems is perfect, but all suggest that when a baby is not tolerating mechanical ventilation or is deteriorating despite maximal ventilatory and pharmacologic management, at least a discussion of ECMO use should be occurring.[19]

Alveolar-Arterial Oxygen Gradient

One of the original, and therefore the oldest, predictors of mortality in the neonate with respiratory failure is the alveolar-arterial O_2 gradient:

$$\text{A-a}DO_2 = PAO_2 - PaO_2 \quad (1)$$

where PAO_2 is the alveolar O_2 tension and PaO_2 is the arterial O_2 tension.

The PaO_2 is measured directly from a postductal arterial blood sample, and the PAO_2 can be calculated from the alveolar air equation:

$$PAO_2 = PIO_2 - PACO_2/R + PaCO_2 \times FIO_2(1-R)/R \quad (2)$$

where PIO_2 is the partial pressure of inspired O_2 and is calculated by the following equation:

$$PIO_2 = FIO_2 \times (PATM - PH_2O) \quad (3)$$

where PATM is the atmospheric pressure, PH_2O is the partial pressure of water vapor, $PACO_2$ is the alveolar CO_2 tension, and R is the respiratory exchange ratio.

If it is assumed that the FIO_2 is 1.0 during maximum ventilation therapy, that the $PACO_2$ is equal to the $PaCO_2$, and that R is 1.0, substitution of equations 2 and 3 into equation 1 yields a simplified equation for calculation of the gradient[20]:

$$PAO_2 - PaO_2 = (PATM - PHO) - (PaO_2 = PaCO_2) \quad (4)$$

Krummel et al.[21] and Ormazabal et al.[22] showed that a gradient greater than 620 mm Hg for 12 consecutive hours predicted a 100% mortality rate, even in the presence of maximum conventional therapy, including alkalinization and tolazoline (Priscoline® no longer available). However, by the time one third of patients met this criterion, they were so moribund that ECMO salvage was no longer possible. A gradient of greater than 600 mm Hg for 12 consecutive hours predicted a mortality rate of 94%. Beck et al.,[23] in a retrospective study of 30 infants with PPHN, found that a gradient of 610 mm Hg for 8 consecutive hours predicted a mortality rate of 79% (see Box 16-1). Others have studied babies within their own institutions and found this criterion has a different value, but there is little doubt that high figures over prolonged times indicates high probability of a poor outcome.

Oxygenation Index

The ventilatory management improvements in the 1980s made the alveolar-arterial O_2 gradient somewhat less sensitive as a predictor of outcome. Dworetz et al.[24] showed that the previous gradient criterion predicted only 10% mortality for their cohort of babies. Thus other investigators attempted to develop new indices, none perfect, but with somewhat greater precision. Today, probably the most used index in most ECMO centers is the oxygenation index (OI). This criterion assesses a neonate's oxygenation status but also accounts for the amount of ventilator support needed to achieve it by measuring the mean airway pressure (MAP).

The OI is calculated by dividing the product of the FIO_2 (times 100) and the MAP by the postductal PaO_2:

$$OI = FIO_2 \times MAP \times 100/PaO_2 \quad (5)$$

If it is assumed that the FIO_2 is 1.0, as it is in most patients who are candidates for ECMO, the equation can be simplified to read as follows:

$$OI = \frac{MAP \times 100}{PaO_2} \quad (6)$$

Ortega and colleagues[25] found that an OI greater than 40 for 2 hours in patients who were candidates for ECMO predicted an 82% mortality rate even though the alveolar-arterial O_2 gradient in the same population was not an accurate measure. This had been correlated by Ortiz and colleagues[26] who found an 80% to 90% mortality rate for patients with an OI of 40 or more for greater than 2 hours. It should be stressed that the reliance on these or any historical criteria has pitfalls, and each ECMO center should constantly reassess the criteria they are employing for entry into ECMO therapy.

Acute Deterioration

A term or near-term neonate who was previously doing well may have a sudden and drastic deterioration. Such an infant may not survive the necessary 3 to 12 hours needed to calculate the alveolar-arterial O_2 gradient or OI. Therefore, many ECMO centers have adopted criteria to alleviate this problem. The most common criteria considered are a pH less than 7.15 and a PaO_2 less than 40 mm Hg. If an infant has one or both of these measures for 2 consecutive hours, he or she is considered a candidate for ECMO.[27] In

addition, if the baby is in severe distress or cardiac arrest, clinical judgment supervenes and a decision must be made as to whether ECMO may be used to attempt life salvage.

Barotrauma

In addition to the criteria that are used to evaluate an infant's oxygenation, criteria have been designed to take into account the effect that assisted ventilation has on a baby's lungs, in particular, if evidence of barotrauma is identified. Barotrauma is pulmonary injury caused by the pressure created by the ventilator. Indicators of barotrauma are as follows:

1. Pulmonary interstitial emphysema or pseudocyst
2. Pneumothorax or pneumomediastinum
3. Pneumoperitoneum
4. Pneumopericardium
5. Subcutaneous emphysema
6. Persistent air leak for 24 hours
7. MAP of 15 cm H_2O or greater

If a neonate meets four or more of these criteria, significant barotrauma is present. The barotrauma not only increases the mortality rate but also significantly increases the morbidity. If pulmonary damage and chronic lung disease are to be prevented, a neonate demonstrating these problems should be seriously considered for ECMO therapy.

Contraindications

The contraindications to ECMO are those clinical situations that preclude either a quality outcome or a successful ECMO run (see Box 16-1). Weight less than 2000 g is associated with an increased risk of intraventricular hemorrhage. Infants with this characteristic are generally premature and have an immature germinal matrix that is susceptible to vascular rupture.[28] In their initial pilot study, Bartlett and Andrews[29] treated 15 infants weighting less than 2000 g and had only 3 (20%) survivors. Patients with an estimated gestational age of less than 35 weeks have been found to have almost a 100% incidence of intracranial hemorrhage and die within 1 year when treated with ECMO.[30] The estimated gestational age seems to be an even more important factor than weight. The anticoagulation and thrombocytopenia associated with ECMO appear to increase the incidence of intracranial bleeding, which is already high in this patient population and is caused by hypoxia and acidosis.

Generally, neonates with chromosomal abnormalities or syndromes known to be associated with profound retardation or a fatal outcome in infancy should be excluded from ECMO therapy. In addition, children with already existing, severe intracranial hemorrhage should be excluded, although many centers will accept children with a grade I hemorrhage. These neonates, if very closely monitored (low activated clotting times and high platelet counts), may undergo ECMO without extension of the blood.

Evaluation Before Extracorporeal Membrane Oxygenation

When an infant is considered for ECMO, special attention must be directed toward the cardiovascular and neurologic systems. A thorough physical examination is mandatory to exclude congenital defects. Although any abnormality in laboratory analyses rarely precludes ECMO, baseline values, such as an initial platelet count and coagulation studies, are important for management.

A cardiologic evaluation is performed to rule our congenital heart disease. Two-dimensional echocardiography is performed to demonstrate signs of pulmonary hypertension: elevated right-sided heart pressure, septal bulging, tricuspid valve regurgitation, and right-to-left shunting at the ductal or foramen ovale sites. The degree of ventricular dysfunction and the presence of any structural abnormalities are noted. Poor ventricular function secondary to hypoxia coexisting with pulmonary hypertension is frequently seen and is not a contraindication to ECMO. In babies with this problem, ECMO increases the myocardial oxygen supply and decreases the ventricular workload by decreasing preload, which usually improves the

Box 16-1 ECMO SELECTION CRITERIA

Indications

- A-aDO_2 greater than 610 × 8 hours or greater than 605 × 4 hours, if PIP is greater than 38 cm H_2O
- Oxygen index greater than 40
- Acute deterioration with PaO_2 less than 40 × 2 hours and/or pH less than 7.15 × 2 hours
- Unresponsive to treatment: PaO_2 less than 55 and pH less than 7.4 × 3 hours
- Barotrauma (any four concurrently)
  - Pulmonary interstitial emphysema
  - Pneumothorax or pneumomediastinum
  - Pneumoperitoneum
  - Pneumopericardium
  - Subcutaneous emphysema
  - Persistent air leak for more than 24 hours
  - MAP greater than 15 cm H_2O and subcutaneous emphysema
- Postoperative cardiac dysfunction
- Bridge to cardiac transplantation

Relative Contraindications

- Prolonged severe hypoxia
- Prolonged mechanical ventilation for longer than 7 days
- Structural cardiac disease
- History or evidence of ischemic neurologic damage
- Lack of parental consent

Absolute Contraindications

- Lack of parental consent
- Inadequate conventional therapy
- Weight less than 2000 g
- Gestational age less than 35 weeks
- Contraindications to anticoagulation
  - Severe pulmonary hemorrhage
  - IVH grade II or greater
  - Gastrointestinal hemorrhage
  - Head trauma
- Prolonged mechanical ventilation longer than 7 to 14 days
- History of severe asphyxia or severe global cerebral ischemia
- Lethal genetic condition or unrelated fatal diagnosis (trisomy 13, trisomy 18, untreatable malignancy)
- Untreatable nonpulmonary disease, significant untreatable congenital cardiac malformation or disease

ECMO, Extracorporeal membrane oxygenation; *IVH,* intraventricular hemorrhage; *MAP,* mean airway pressure; *PIP,* peak inspiratory pressure.

hypokinesia. If congenital heart disease is strongly suspected and the results of echocardiography are not conclusive, then cardiac catheterization should be performed before ECMO is initiated if the patient can tolerate this procedure. If a congenital cardiac lesion is found, then discussion should be undertaken with the cardiac surgery team to determine the timing of the operation and the value of ECMO in the perioperative period.

The degree of ischemic neurologic damage before ECMO can be very difficult to determine. When Apgar scores are evaluated, three important points must be considered. First, Apgar scores often do not correlate with intrauterine asphyxia.[31] Second, neonatal asphyxia is not the only cause of depressed Apgar scores.[32] Third, because an infant can have good Apgar scores and then experience a prolonged period of asphyxia, Apgar scores cannot predict neurologic outcome and are of limited value in the determination of candidates for ECMO.[33]

Seizure activity and focal neurologic deficits can be difficult to assess because most infants who are candidates for ECMO are paralyzed, sedated, or both for the purpose of better ventilator management. Cranial ultrasound is done to rule our intracranial hemorrhage, but may not detect ischemic lesions. If an intracranial hemorrhage is found, reconsideration of the procedure should occur because there may be rapid extension of the hemorrhage from systemic anticoagulation. Von Allmen and colleagues[34] showed that grade I intracranial hemorrhage is not associated with a significant risk for major intracranial complications after ECMO but that severe edema or periventricular leukomalacia are associated with a 63% incidence of major intracranial complications. Grade II or greater intracranial hemorrhage is still associated with major morbidity and is still a relative contraindication to ECMO.

In the paralyzed term infant, the most reliable readily obtainable bedside indicator of hypoxic-ischemic encephalopathy is the electroencephalogram (EEG). The presence of low-voltage, burst-suppression or isoelectric patterns on the EEG indicate a poor neurologic outcome[35] and are therefore relative contraindications to ECMO. Seizure activity on the EEG is not an absolute contraindication to ECMO if none of the already mentioned underlying ominous patters are present. Consultation with a pediatric neurologist is helpful in questionable cases.

Technique for Beginning ECMO

Before Cannulation

When an infant appears to be a candidate for ECMO, the perfusion team and operating crew are notified and put on standby while the workup is completed. Blood samples are sent to the blood bank for preparation of the blood components necessary for the priming solution.

When a child meets criteria for ECMO, parental consent is obtained. Special attention is devoted to ensuring that the parents are well informed of the possible complications and various outcomes, including neurologic deficits, chronic lung disease, and death. Next, the preparation of the patient for bypass and the final priming of the ECMO circuit are carried out simultaneously. The circuits are preassembled and sterilized. The components consist of polyvinyl chloride tubing and incorporate a silicone membrane lung (AVECOR 0.8), a small venous bladder (50 mL), multiple ports for sampling and infusions, a heat exchanger, and computer-aided perfusion system (several current models are available). The tubing runs through a 5-inch roller pump or a centrifugal pump (personal choice of the perfusion team, ECMO team, ECMO director), which is servo-regulated by the venous return in the bladder reservoir. If the bladder collapses because of inadequate venous return, the pump is automatically retarded or shut off; this prevents the system from creating a negative pressure and sucking in air if a roller pump is being used.

Today very sophisticated systems are commercially available to monitor pressure throughout the system, such as the transmembrane pressure, the Δ pressure, inlet and outlet pressure, bladder volumes, and so on. These systems can adjust the flow very minutely to match the volumes available for perfusion.

The ECMO circuit is primed with packed cells, fresh-frozen plasma, and platelets. The pH and electrolytes in the priming solutions are corrected as time allows so that an adverse reaction in the neonate can be prevented because priming volumes may be two to three times the neonatal blood volume.

Venoarterial Versus Venovenous Cannulation

ECMO can be done via double cannulae venoarterial (VA) (Fig. 16-8) or a single cannula (double lumen) venovenous (VV) (Fig. 16-9) approach. A combination of techniques may also be used. Historically, most infants underwent VA bypass, but single-catheter VV bypass has assumed

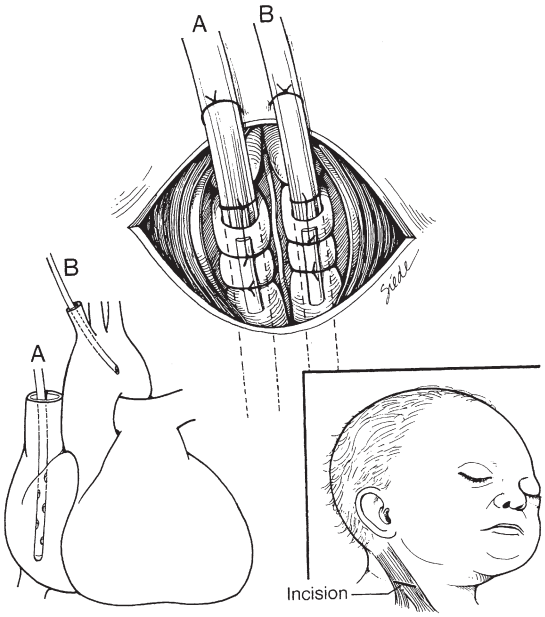

Figure 16-8 ■ Vessel cannulation for venoarterial extracorporeal membrane oxygenation. Both the internal jugular vein (*A*) and the carotid artery (*B*) are ligated. The cannulae are then secured in the vessels with two ligatures over a small piece of vessel loop. When these ligatures are removed, they are cut over the vessel loop without risking damage to the vessels or the cannulae. Both cannulae are also secured to the skin of the neck.

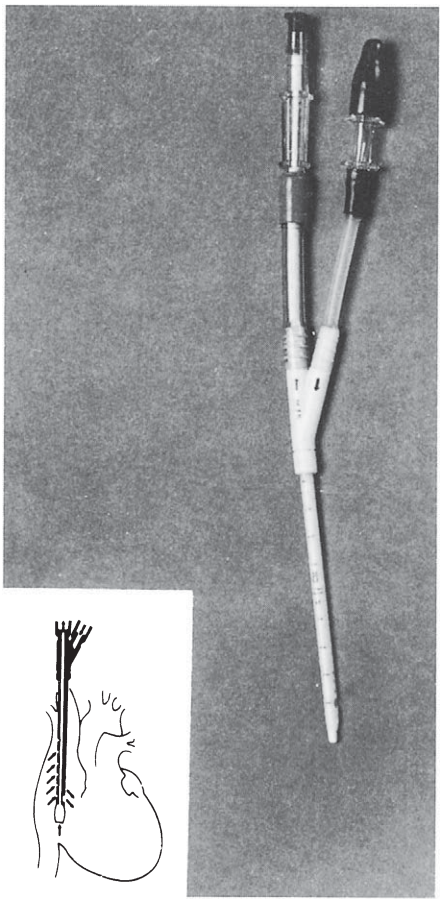

Figure 16-9 ■ Double-lumen venovenous catheter for single-site access. The indwelling obturator seen in the venous drainage lumen. The two lumens, separated by an eccentrically located septum, allow both venous blood drainage and reinfusion of warmed oxygenated blood. The catheter is inserted through a venotomy in the internal jugular vein such that the tip of the catheter, and thus the reinfusion port, is located in the right atrium (*inset*). (From Anderson HL, Snedecor SM, Otsu T, et al: J Pediatr Surg 28:530, 1993.)

the major role if cardiac function is relatively normal and the need is primarily for gas exchange and oxygenation support.

In VA bypass, venous outflow is established from the right atrium via the internal jugular vein with a 10- to 16-French cannula. Blood is returned to the aortic arch through an 8- to 12-French cannula within the right common carotid artery. This method allows support of cardiac function and oxygenation; therefore, in the very sick neonate with an asphyxiated myocardium or in a baby requiring maximum pressor support, this is generally the procedure of choice.

VV ECMO functions to oxygenate the blood but relies on the infant's heart for cardiac output. VV ECMO also does not decompress the pulmonary circulation to the same extent as does VA ECMO. Infants undergoing VV ECMO can be more difficult to manage and may have to be converted to VA ECMO if cardiac failure ensues. Thus this modality is often best used in those infants who come early to ECMO, are in the more stable category, and require help primarily with gas exchange.

Venous outflow is still via the internal jugular vein with a 12- to 16-French cannula, and venous return is via the second lumen of the double-lumen cannula. Alternatively, one can, in extraordinary cases, return the blood via a femoral cannula. There is now sufficient experience with both techniques to prove them both efficacious. Clearly, one (VV) is less invasive than the other (VA), so that approach should be the determinant choice, unless there is a clear advantage or need to have VA bypass.

Operative Procedure

The operative procedure is performed in the intensive care nursery with operating room personnel in attendance. Surgeons generally have magnifying loupes, headlights, and electrocautery on hand as necessary. The patient is positioned under a radiant warmer during the procedure to prevent hypothermia. If not done previously, the infant is paralyzed to prevent spontaneous respiration and air embolism during venous catheter insertion. In addition, local anesthesia or morphine is given.

Incision is made over the right sternocleidomastoid muscle and the carotid sheath is exposed. The vessels are isolated from surrounding tissues, taking care to preserve the vagus nerve that also runs within the carotid sheath. The neonate is given an intravenous bolus of heparin at a dose of 100 to 200 units/kg.

For VA bypass, the common carotid artery is ligated distally and controlled proximally with a clamp and suture ties. Through a transverse arteriotomy, the arterial cannula is passed a premeasured distance into the common carotid artery almost or just to the aortic arch. The cannula is tied securely in position. The venous cannula is then passed in a similar fashion into the right atrium through the internal jugular vein. During venous cannulation, care is taken to prevent air embolization from occurring.

For VV bypass, the procedure is much the same. The carotid artery is visualized but left in place; only the jugular vein is opened. Care is used to place the double-lumen venous cannula so that the blood return orifices are directed toward the tricuspid valve. Cannulae are secured to vessels, skin and scalp, and to the patient bed, because dislodgement often will prove fatal to the child (Table 16-1).

A chest radiogram is needed to confirm correct placement. If further information is needed, an echocardiogram is very useful, especially to assure that a cannula or cannula flow is not across or directed at the aortic valve (Fig. 16-10).

Daily Management

Once bypass is established, ventilator settings are reduced to allow *lung rest*. Typically, the F_{IO_2} is reduced to 0.21 to 0.40; the respiratory rate is set to 10 to 20 breaths per minute with a peak inspiratory pressure (PIP) to 15 to 20 cm H_2O and a positive end-expiratory pressure (PEEP) of 3 to 4 cm H_2O. Ventilator settings generally remain low throughout an ECMO run because gas manipulation now occurs via the ECMO circuit.

Typically, during the first 1 to 2 days on ECMO therapy, the infant's pulmonary status worsens, and almost no gas exchange occurs within the lungs. Keszler et al.,[36] in a multicenter randomized study, evaluated the effect of

TABLE 16-1 Comparison of VV and VA ECMO

VV ECMO	VA ECMO
Advantages	**Advantages**
• Requires venous access only	• Good oxygenation and CO_2 removal
• Pulsatile flow to organs preserved via native cardiac function in series with ECMO circuit	• ECMO circuit both in parallel and in series with native cardiopulmonary circuit. The fraction of blood flowing in parallel is dependent upon the ECMO pump velocity.
• Good CO_2 removal	• Can provide partial cardiac bypass and cardiac rest
• Easy to wean off ECMO support	• Rapid wean of ventilator, inotropes, and pressors
Disadvantages	**Disadvantages**
• Dependence on native cardiac function for cardiac output	• Nonpulsatile pump flow
• Flow through circuit may be limited by smaller cannula compared to single-lumen VA venous cannula	• Cannulation of right carotid artery support
• Decreased oxygen delivery to periphery compared to VA ECMO	• Somewhat more difficult to wean off ECMO
• Decreased flow if mediastinum is displaced	

ECMO, Extracorporeal membrane oxygenation; *VA,* venoarterial; *VV,* venovenous.

increased PEEP on lung function during ECMO. They found that patients treated with higher levels of PEEP had a significantly shorter course of ECMO therapy and demonstrated measurably better lung compliance in the first 72 hours of bypass. In addition, the high-PEEP group had overall fewer complications than the low-PEEP group.

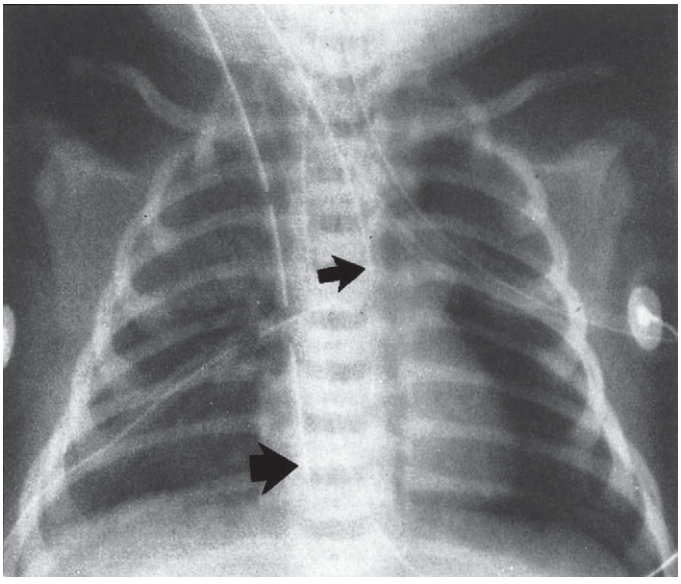

Figure 16-10 ■ Chest radiograph in venoarterial extracorporeal membrane oxygenation patient showing the venous cannula (*large arrow*) in the right atrium, with the tip at the right atrium–inferior vena cava junction, and the arterial cannula (*small arrow*) in the aortic arch, with the tip directed down the descending aorta.

Consequently, some centers manipulate this parameter to try to improve lung function more quickly.

Activated clotting times are measured hourly at the bedside and are maintained at approximately two times normal values (160-200 sec) by variations in the rate of a continuous heparin infusion. The usual heparin dose is 25 to 50 units/kg per hour. Good correlation has been found between the activated clotting time and blood heparin levels in patients undergoing ECMO.[37] The hematocrit is maintained at between 35% to 45% with transfusions of saline-washed packed red blood cells. Platelet counts are maintained at greater than 75,000/mm^3 with infusion of platelet concentrates as needed. This level may be increased to more than 100,000 to 125,000/mm^3 in patients with bleeding problems or in those for whom surgical intervention is planned. Fibrinogen levels are maintained with infusion of cryoprecipitate as needed, and other clotting factors are given with fresh-frozen plasma if active bleeding is excessive.

Complete nutritional support is established with standard hyperalimentation techniques that provide trace elements, multivitamins, and lipids in addition to protein and carbohydrate. When the volume administration is determined, insensible water losses across the membrane must be taken into consideration. These losses can be up to 5 to 7 mL H_2O/m^2/4.0-mL thickness per hour at 37° C. Excessive free water loss can occur if this is not remembered and added to the calculation as necessary. Electrolyte values are determined daily, and adjustments are made according to laboratory results.

During bypass, prophylactic antibiotics are given by many ECMO centers. Some provide antibiotics throughout an ECMO run; others provide coverage only for the first few days. Cultures of blood, sputum, urine, and tube insertion sites are frequently required, and antibiotics are determined by culture results. All other medications are given as needed. Sedation is almost routinely and universally given.

Echocardiography is extremely useful during ECMO therapy. This modality is an excellent tool for determining correct placement of cannulae. Serial evaluation of pulmonary vascular resistance, the direction and location of shunts, ventricular function, and atrial size contribute greatly to clinical management. For example, resolution of pulmonary artery hypertension, with reversal of shunt flow, indicates success and the ability to wean from ECMO. Cardiac dysfunction resolution is an excellent indicator of success in reperfusing the myocardium.[38]

Similarly, serial cranial ultrasound examinations are used to screen for intracranial hemorrhage during ECMO. These exams are done fairly routinely for the first 5 to 7 days. Some centers will then discontinue them on the basis of studies that suggest that most intracranial bleeds will occur within that timeframe if they are going to occur. Other centers continue twice weekly screening throughout the ECMO run. Of course, a study should be performed whenever clinical evidence suggests a sudden change that might indicate a fresh bleed (seizure, bulging fontanelle, sudden unexplained fall in hematocrit). A severe bleed is indication for the cessation of ECMO. Small bleeds or initiation of therapy with a grade I bleed mean close control of anticoagulation and maintenance of a

higher platelet count throughout the ECMO period (Fig. 16-11).

Respiratory therapy continues during ECMO with attention to the anticoagulated status. Chest x-rays are generally a daily or every other day event to monitor progress. Even with initiation of ECMO, barotrauma events may occur and will need therapeutic intervention if they do occur.

Rarely surgical intervention is required while a baby is on ECMO. If truly needed, this kind of intervention can go forward with special emphasis on maintenance of platelets and very close attention to the anticoagulation status of the child.

Weaning

Total flow through the bypass circuit controls the patient's mixed Pa_{O_2} by varying the relative contributions from the pump and infant's heart and lungs. Arterial O_2 content, as measured in the distal aorta (from umbilical artery catheters), represents a mixture of pump blood and the blood that traverses the pulmonary circuit. Because the pump blood is greater than 99% saturated, any increase in distal aorta Pa_{O_2} represents an increase in the contribution of the patient's cardiovascular system (provided the pump flow remains constant). Early in the course of ECMO, when the infant's lungs provide little or no function, the circuit flow is maintained at 100 to 120 mL/kg/min, which is adequate to achieve near-total gas exchange via the oxygenator. As the infant's lungs improve, the additional oxygenation taking place via the lungs increases the systemic Pa_{O_2}, which allows the flow through the extracorporeal circuit to be reduced. This process continues stepwise, gradually decreasing the extracorporeal support, until the child can maintain adequate blood gas levels with a total bypass flow of 50 to 80 mL/min.

At this point, the baby is excluded from the circuit by clamping the cannulae but not removing them. If the vital signs are stable and the arterial blood gas values remain acceptable for some time at low ventilator settings, the cannulae are removed, and the vessels ligated or repaired. The wound is then closed, with or without a drain left in place. During the exclusion from the pump, if the infant's condition deteriorates, then bypass is reestablished, the infant is stabilized, and the weaning process is begun again.

The infant's volume status is monitored by evaluation of several parameters, including blood pressure, heart rate, capillary refill, skin turgor and color, urine output, and venous blood gas levels. Venous pH and O_2 content are sensitive indicators of adequate perfusion (aerobic cellular respiration), and changes in these parameters may be seen before any changes in arterial blood gas values. Blood volume can be increased or decreased simply with the infusion or withdrawal of blood from the ECMO circuit. In general, an increase in total body water (specifically, an increase in extracellular fluid) occurs; this increase is manifested by an increase in weight.[39] When natural diuresis occurs, pulmonary status generally improves, and weaning can begin.

Carotid Artery Repair

For many years, the carotid artery has been ligated at time of decannulation. This practice is still probably the norm

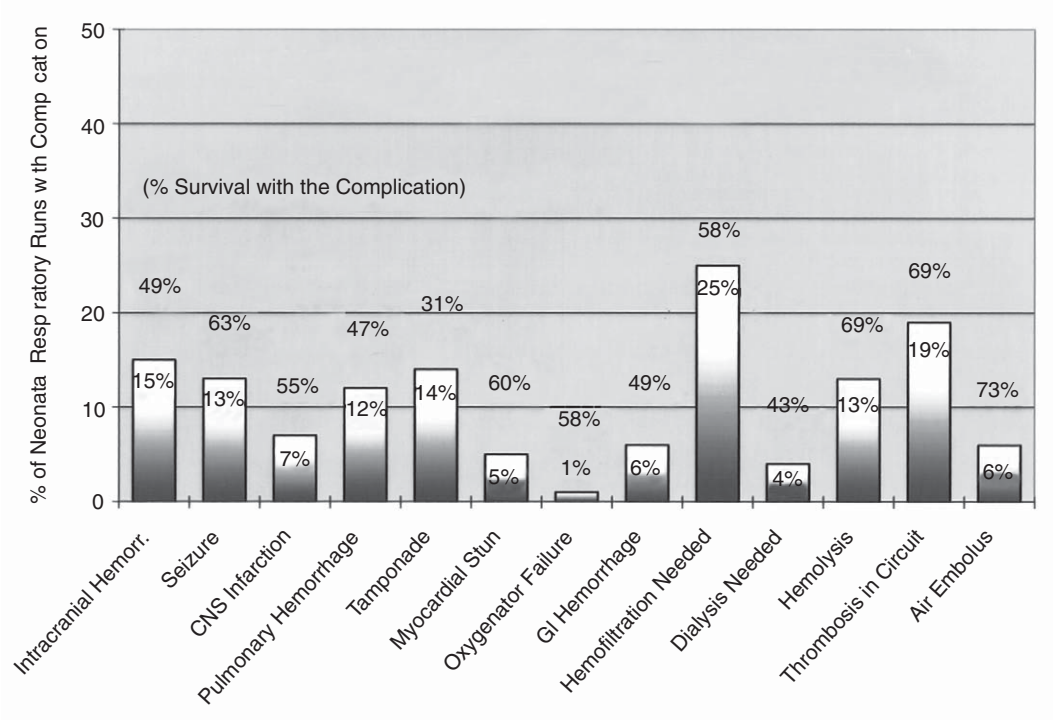

Figure 16-11 ■ Incidences of the most commonly seen complications in neonatal respiratory extracorporeal membrane oxygenation (ECMO). (Data are from the ECMO Registry of the Extracorporeal Life Support Organization [ELSO], Ann Arbor, Michigan, 1980-2001. Data from 2001 are incomplete.)

at most centers. Although studies have shown retrograde flow from the external carotid artery on the right side to the internal carotid artery after ligation,[40] there is still an inherent fear that ligation of one of the major blood vessels to the brain may create long-term problems in these neonates. Therefore, attempts have been undertaken to reconstruct the carotid artery after ECMO decannulation. For carotid artery repair, the cannula is removed, and the proximal vessel is controlled with a vascular clamp. The distal ligature on the artery is then removed; the distal aspect of the artery is also controlled with a vascular clamp. Backbleeding is allowed, both to prevent emboli from reaching the brain and to assess adequacy of distal blood flow. The artery is then repaired with a variety of techniques. Adolph and colleagues[41] use a longitudinal arteriotomy at the time of cannulation and then close the site transversely to prevent stricture formation. Moulton and colleagues[42] found that on histologic section, the vessel wall had undergone greater than 50% transmural necrosis, and they advocate resection of the involved segment (between the distal and proximal ligatures) with primary anastomosis. Both techniques have met with good results on preliminary evaluation. Other methods have suggested simple closure of a transverse arteriotomy with Gortex® patching of the artery (Table 16-2).

TABLE 16-2 Rationale for Carotid Artery Repair vs. Ligation

Carotid Ligation	Carotid Artery Repair
Benefits • Faster decannulation procedure • No worry about future stenosis, aneurysm, or leak • No vascular repair in contaminated wound • No risk of air or thrombus embolism during repair • No evidence that repair has clear benefit • No need for follow-up vascular studies • As child grows, remaining vasculature will compensate and deliver needed flow	**Benefits** • Restore normal flow to vessel • No need to rely on collateral perfusion from circle of Willis or vertebrobasilar system
Risks • Permanently remove right carotid artery from circulation • Risk of relative ischemia of right cerebral hemisphere	**Risks** • Blowout at repair site from ischemic vessel at arteriotomy or rupture of repair from tension after segmental resection • Future stenosis or aneurysm, with alteration of flow or showers of emboli • Need for serial follow-up vascular studies to evaluate flow and rule out stenosis

Outcome

To date 22,429 neonates with respiratory failure have been treated with ECMO; 85% were successfully decannulated and 76% survived to discharge.[43] The cumulative survival statistics are highest for meconium aspiration syndrome (MAS) at 94% and lowest for CDH at 51% (Fig. 16-12). Changes in intensive care and the introduction of new therapies such as surfactant, selective antibiotic prophylaxis for mothers and babies, high-frequency ventilation, and inhaled nitric oxide have reduced the numbers of infants who require ECMO. Currently approximately 800 infants per year are placed on ECMO for respiratory failure. Newer therapies and the greater use of a gentle ventilation approach have reduced the number of CDH infants requiring ECMO.[44]

Medical and neurodevelopmental outcomes of the ECMO patient is encouraging considering the severity of illness in the newborn period. Analysis of outcome studies performed in PPHN survivors treated with conventional medical therapy, inhaled nitric oxide, and ECMO yield grossly equivalent morbidities and outcomes.[45] This suggests that neurodevelopmental outcome is more related to the underlying illness than to the therapeutic interventions used.

Chronic lung disease (defined as oxygen use at 28 days) is seen in 15% of ECMO survivors, but long-term oxygen use is uncommon except in infants with CDH. Hospitalization for respiratory problems in the first year of life is needed in approximately 25% of survivors.[46] Normal somatic growth is seen in ECMO-treated children except those with CDH.

Progressive high-frequency sensorineural hearing loss is seen in 3% to 21% of ECMO-treated infants.[47] An important aspect of this morbidity is the delayed onset, making diagnosis problematic. The position statement by the Joint Committee on Infant Hearing in 2000 added PPHN and ECMO as risk indicators for hearing loss and stated that babies with these risk factors should receive audiologic evaluation every 6 months until 3 years of age.[48]

Numerous investigators have studied the neurodevelopmental outcomes of ECMO patients and consistently report Bayley scores in the normal range in the first 2 years of life.[49-52] Fewer studies of ECMO survivors at older ages have been performed. By 5 years of age, mean IQ scores remain in the normal range, but are lower than normal controls (96 vs. 115, $p < 0.001$).[52] Glass et al.[52] reported that approximately 15% of ECMO survivors at age 5 years had a major handicap, most commonly mental retardation, whereas less than 5% had severe or profound impairment. Nevertheless, 50% of ECMO survivors have an increased risk of learning and behavioral problems when compared to normal controls. As a result of these deficits, ECMO survivors are vulnerable to academic and psychosocial difficulties. All ECMO patients and the near-miss ECMO population should be followed closely into school age so that interventions can be started early if needed. But, in general, the ECMO population is doing quite well and if patients are selected appropriately, the risk of short-term and long-term morbidities and mortality should not deter the initiation of this procedure (Figs. 16-13, 16-14, and 16-15).

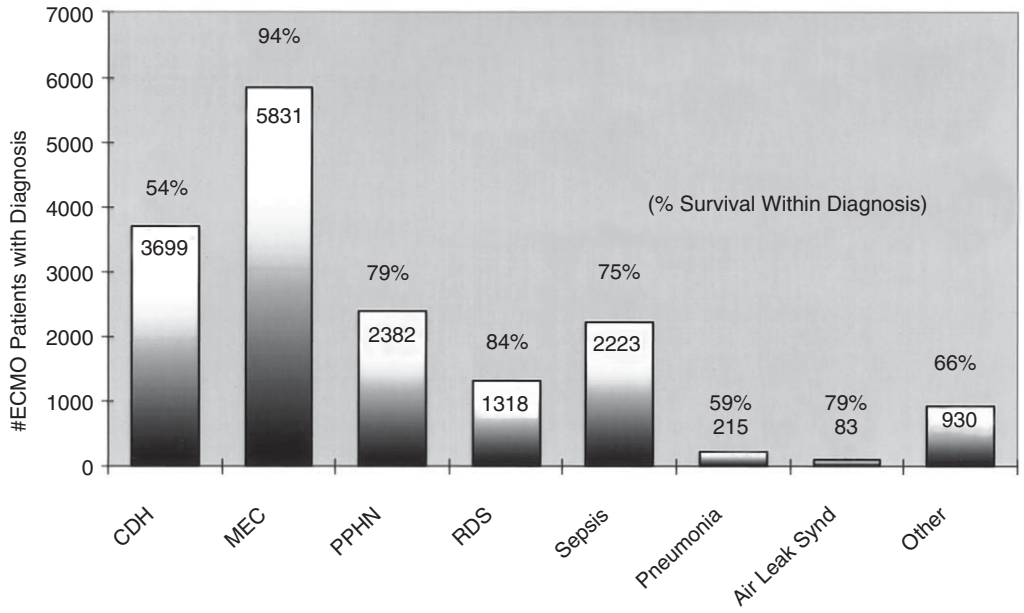

Figure 16-12 ■ Distribution of extracorporeal membrane oxygenation (ECMO) between neonatal respiratory diagnoses and survival rates to hospital discharge with each diagnosis. (Data are from the ECMO Registry of the Extracorporeal Life Support Organization [ELSO], Ann Arbor, Michigan, 1980-2001. Data from 2001 are incomplete.)

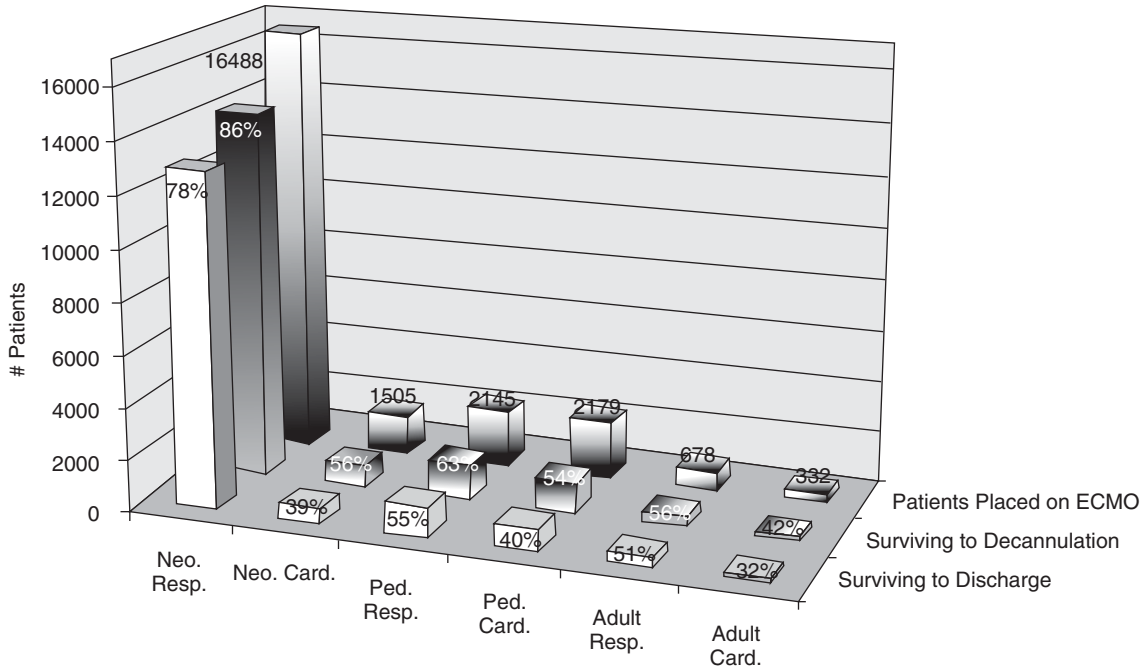

Figure 16-13 ■ Distribution of extracorporeal membrane oxygenation (ECMO) between patient categories and survival rates to decannulation and discharge within each category. (Data are from the ECMO Registry of the Extracorporeal Life Support Organization [ELSO], Ann Arbor, Michigan, 1980-2001. Data from 2001 are incomplete.)

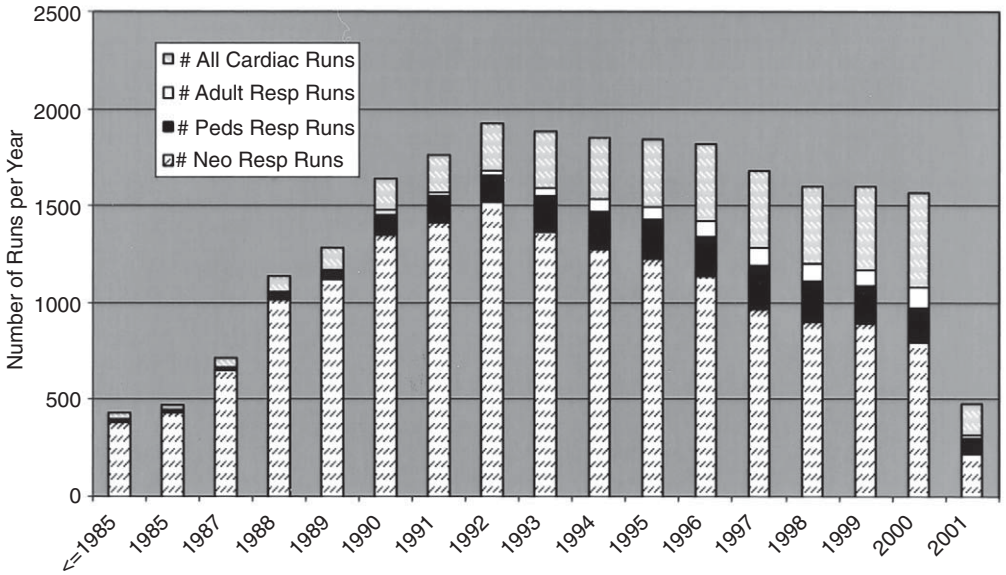

Figure 16-14 ■ Number of extracorporeal membrane oxygenation (ECMO) runs each year by patient category. There is a steady decline over the past 9 years in neonatal respiratory ECMO cases. (Data are from the ECMO Registry of the Extracorporeal Life Support Organization [ELSO], Ann Arbor, Michigan, 1980-2001. Data from 2001 are incomplete.)

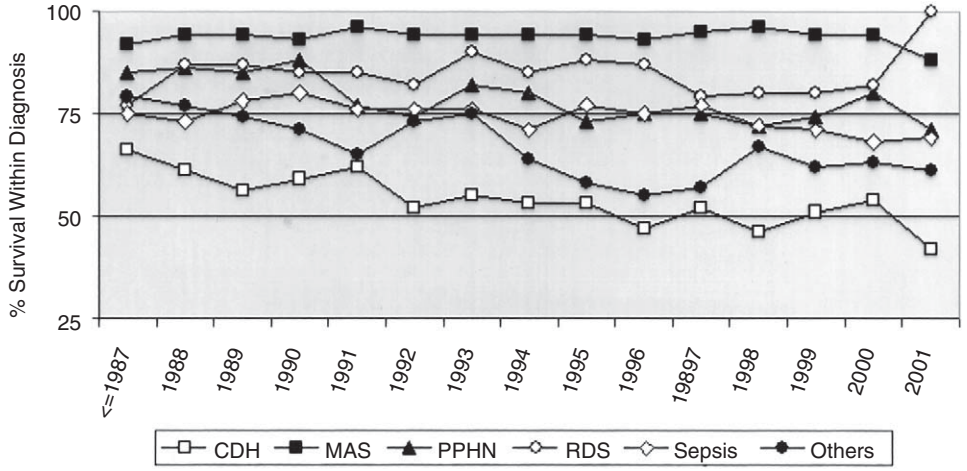

Figure 16-15 ■ Trends in survival to hospital discharge over time for extracorporeal membrane oxygenation (ECMO) patients with neonatal respiratory diagnoses. There is decrease in survival over the last year in survival for ECMO infants with meconium aspiration and persistent pulmonary hypertension in the neonate (PPHN). There is also a steady decline in survival for ECMO infants with congenital diaphragmatic hernia (CDH). Selection of patients with more severe disease or patients with longer pre-ECMO mechanical ventilation may explain these trends. The success of high-frequency oscillatory ventilation, permissive hypercapnia, nitric oxide, and other intensive strategies also selects the more severely ill patients for ECMO therapy. (Data are from the ECMO Registry of the Extracorporeal Life Support Organization [ELSO], Ann Arbor, Michigan, 1980-2001. Data from 2001 are incomplete.) *MAS,* Meconium aspiration syndrome; *RDS,* respiratory distress syndrome.

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17 Blood Gases: Technical Aspects and Interpretation

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Arterial blood gas measurements are the gold standard by which the adequacy of oxygenation and ventilation are assessed. Arterial blood gas values can be directly measured from indwelling arterial catheters or estimated from intermittent peripheral artery punctures, arterialized capillary bed samples, and central venous blood samples. Continuous noninvasive monitoring devices, particularly pulse oximeters and transcutaneous carbon dioxide monitors, play an essential role in the respiratory management of critically ill newborns by giving ongoing estimates of blood gas values. The relative advantages and disadvantages of these techniques are discussed below.

Techniques for Obtaining Blood Samples

The most accurate arterial blood gas values are obtained from indwelling arterial catheters. Although it is possible to manage a sick newborn without arterial access, the presence of an arterial catheter often simplifies care significantly. It not only allows the accurate measurement of arterial blood gases without disturbing the patient but also allows direct measurement of arterial blood pressure and provides a route for obtaining other blood samples.

Umbilical Artery Catheters

Umbilical artery catheters are the preferred route for arterial access in most intensive care nurseries, particularly for infants in the first few days of life. They usually can be quickly and easily placed with small risk of complications. The umbilical arteries are readily accessible during the first several days of life and often can be cannulated in patients as old as 2 weeks.

An umbilical catheter should be flexible, nonkinking, radiopaque, transparent, and nonthrombogenic and should have an end hole but no side hole.[1] There are two common catheter sizes, 3.5 French and 5.0 French. Some feel that the larger catheter should be used whenever possible to minimize problems with thrombus formation within the catheter, making it less prone to "clotting off." Others feel that the smaller catheter is better because it minimizes the changes in aortic blood flow that occur when a catheter is in place. Because almost no published data is available about the relative merits of the two catheter sizes, the decision about which catheter size to use is usually based on personal preference. Our usual approach is to use a 3.5-French catheter in infants weighing less than 1500 g, and a 5.0-French catheter in infants who weigh more than 1500 g.

The procedure for cannulation of the umbilical vessels can be seen in an on-line video published by the *New England Journal of Medicine*; it is described in a 2008 article in the Journal.[2]

Prior to insertion, the catheter is attached to a three-way stopcock and syringe containing a heparinized saline solution and then flushed thoroughly. When the catheter has been inserted and is functioning adequately, the stopcock should be attached to a continuous infusion of heparinized fluid and to a pressure transducer. Care should be taken in stabilizing stopcock connections to minimize the possibility of accidental disconnection.

The catheter is inserted while the infant is under a radiant warmer or in a heated isolette where the infant's temperature can be maintained and the vital signs monitored. The infant's legs should be loosely restrained, and it may be helpful to also loosely restrain the arms. The insertion of the catheter should be done under sterile conditions, after the umbilical cord is cleaned with povidone iodine or chlorhexidine. A sterile umbilical tie is then placed around the lower portion of the cord and tied loosely with a single knot. The tie is placed so it can be either tightened if bleeding occurs when the cord is cut, or loosened if it prevents passage of the catheter. Next, the cord is cut approximately 0.5 cm above the skin. Cutting the cord with a scalpel in a single cut, rather than with a sawing motion, results in a flat umbilical surface from which the umbilical arteries usually protrude. The two thick-walled arteries and the single, larger thin-walled vein can easily be identified.

The most important step in the insertion of an umbilical arterial catheter is dilation of the arterial lumen. Failure to dilate carefully is the most common cause of catheter insertion failure. The goal of dilation is to open the lumen enough to allow smooth catheter passage without tearing the intima of the vessel. If the catheter tip tears the intima and creates a "false lumen" within the vessel, it will not reenter the lumen and successful catheter passage is nearly impossible. The dilation of the vessel should begin by placing one arm tip of a small forceps into the lumen. When using forceps with teeth, great care should be used to avoid shearing the intima. If done gently, the vessel will dilate, allowing both arms of the forceps to be placed into the lumen (Fig. 17-1). Once both arms have been placed, they can be slowly spread, gradually dilating the vessel to

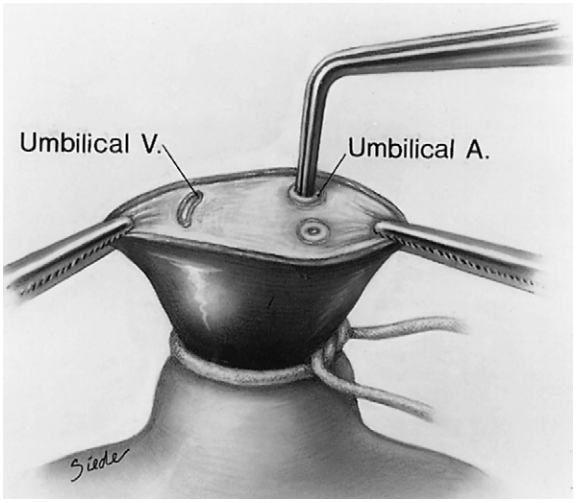

Figure 17-1 ■ Umbilical stump with two umbilical arteries and one vein. A small forceps is used to gently dilate one artery.

the caliber of the catheter. As the vessel lumen dilates, the forceps should be advanced with the goal of dilating at least 5 to 8 mm of the vessel. Once the vessel has been adequately dilated, the catheter can be inserted. It is easier to pass the catheter if the vessel is stabilized with one or two small curved forceps. Usually, the catheter passes smoothly. When the catheter meets significant resistance, it usually means that the catheter has dissected through the intima, and has created a false lumen within the wall of the vessel. When this occurs, the catheter should be removed. Forcing the catheter at this point is more likely to result in damage to the vessel or perforation of the peritoneum than to success.

On occasion, a catheter will travel down into the iliac artery, rather than up into the aorta. If this occurs, a second catheter can usually be inserted into the same umbilical artery, without removing the first catheter. With the first catheter lodged in the iliac artery, the second is often directed into the aorta.[3]

Once the catheter enters the aorta, it should be advanced to either "high position" or "low position." The goal of both positions is to place the tip of the catheter so that it is not adjacent to the junction of the aorta and the renal, mesenteric, or celiac vessels. If a low position is chosen, the catheter tip should be between the level of the third and fourth lumbar vertebrae, safely below the renal and mesenteric arteries. If a high position is chosen, the catheter tip should be between the sixth and tenth thoracic vertebrae, above the origin of the celiac plexus. Although both positions are commonly used, several prospective randomized studies and a subsequent meta-analysis comparing low versus high catheter placement have found a greater rate of peripheral vascular complications in infants with catheters in the low position, however, most of these complications were minor.[4]

Several published graphs are useful for estimating the distance a catheter must be inserted to correctly place it in the lower position.[5,6] The simplest method is based on the infant's weight.[7] For a 1-kg infant, the catheter should be inserted approximately 7 cm, for a 2-kg infant, it should be inserted approximately 8 cm, and for a 3-kg infant, it should be inserted approximately 9 cm. For a catheter to be placed in the high position, the formula "3 times the weight plus 9" gives a rough estimate of the required catheter insertion length in centimeters. For either method, the catheter position should be checked radiographically (Fig. 17-2).

Once correct position is confirmed, the catheter should be sutured and taped in place. We use a 3-0 or 4-0 silk suture tied in a "purse-string" around the circumference of the umbilical cord, then tied to the catheter. The catheter is then secured with a tape bridge.

Subumbilical Cutdown

If attempts to cannulate both umbilical arteries are unsuccessful, and the patient cannot be adequately managed without an umbilical catheter, the arteries can be cannulated via subumbilical cutdown.[8] This is a surgical procedure and should not be attempted by anyone other than a surgeon who has previous experience with the technique. In our neonatal intensive care unit (NICU), this procedure has been almost entirely replaced by noninvasive monitoring and peripheral arterial catheterization.

With a subumbilical cutdown, the arteries are exposed through an incision approximately 1 cm below the umbilical stump. The subcutaneous tissues are dissected to the anterior rectus sheath, then the sheath is incised, and the rectus muscles are retracted laterally from the midline. The arteries are identified and separated from the urachus. Two sutures are placed around one artery, and a small arteriotomy is made between the sutures. The catheter is then inserted, and the distal suture is secured around the catheter and artery. The artery is tied off with the proximal suture, and the fascia and skin are closed. The position of the catheter should be confirmed radiographically.

Complications of Umbilical Artery Catheterization

Although umbilical artery catheterization is safe and well tolerated in most patients, it is important to remember that it is not without risks. Occasionally, catheter placement is associated with severe thrombotic complications, including frank gangrene and necrosis of the buttocks or leg. An echocardiographic study found intracardiac thrombi in 5% of infants with umbilical catheters.[9] A more recent small study suggests that umbilical artery catheters in the first 5 days are not associated with a high risk of thrombosis.[10]

Infants with umbilical artery catheters in place will occasionally develop dusky or purple discoloration of their toes, presumably from microemboli or vasospasm. In some cases, warming of the contralateral leg may cause reflex vasodilation and increased perfusion in the compromised extremity. Although this is a common practice, a study in normal infants without vasospasm showed that local warming has no effect on peripheral blood flow to the contralateral heel.[11] Regardless of whether there is any value in warming the contralateral foot, the compromised leg should not be warmed because of the risk that this might increase the metabolic rate of the warmed tissues, leading to increased hypoxic tissue injury. Although the majority of patients with dusky toes have adequate

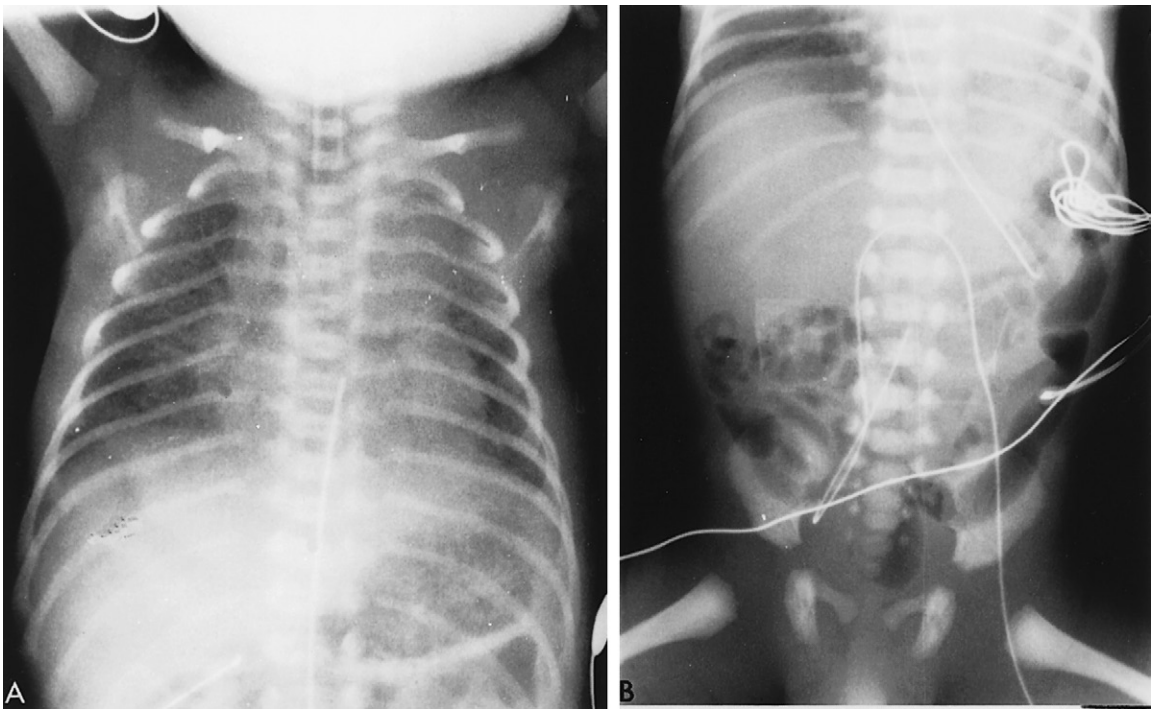

Figure 17-2 ■ **A,** X-ray film showing umbilical artery catheter in "high" position. **B,** X-ray film showing umbilical artery catheter in "low" position.

perfusion and suffer no ill effects, one must always be aware of the risk that this represents potential significant vascular compromise. Failure to recognize worsening perfusion may result in necrosis and loss of a portion of the foot. If the toes remain dusky, with poor capillary filling, the catheter should be removed. Similarly, if the dusky discoloration involves more of the foot or leg, the catheter should be removed.

In rare instances, an infant with an umbilical catheter will develop blanching of the foot or part of the leg. Because blanching represents severely compromised arterial blood flow, the catheter should be immediately removed.

If perfusion to the limb does not immediately improve with withdrawal of the catheter, the infant should be evaluated for possible severe thrombotic complications. Evaluation in this case usually includes some combination of ultrasound or Doppler assessment, or even angiography. Both systemic vasodilators and topical vasodilators have been described as having some efficacy in this situation.[12,13] When a significant clot is identified, there may be a role for treatment with tissue plasminogen activator, either infused directly into the effected vessel or systemically.[9,14] The potential advantages of thrombolytic therapy must be weighed against the theoretical risks of such therapy, particularly in the infant with a preexisting intracranial hemorrhage that could potentially extend. Unfortunately, there is little literature available regarding the optimal approach to infants with severe vascular obstruction.

The incidence of infection associated with umbilical artery catheters appears to be lower than the incidence of infections associated with central venous catheters. However, as with all central catheters, meticulous care must be taken to maintain sterility during catheter insertion, and during subsequent withdrawal of blood from the catheter. A Cochrane review suggests that there is inadequate data to recommend either for or against routine antibiotic use in infants with umbilical catheters in place.[15]

Some centers avoid feeding infants with an umbilical artery catheter in place because of a theoretical concern that the catheter may interfere with mesenteric blood flow. A recent study evaluating practice in United States intensive care nurseries (US NICUs) revealed that 79% of respondents prescribe small-volume enteral feeds in infants with umbilical catheters, and that over 50% prescribe larger enteral feedings.[16] There are studies evaluating blood flow with umbilical arterial catheters in place, including a recent study specifically measuring superior mesenteric artery flow, showing no impact on either mesenteric flow or blood flow velocity when feeding with an umbilical catheter in place.[17,18]

One of the most concerning side effects of umbilical artery catheters is the effect of blood sampling on cerebral blood flow. At least two studies have suggested that the routine blood sampling alters cerebral hemodynamics and oxygenation.[19,20] This effect seems to be less with lower-position catheters than with high-position catheters. Markedly slowing the rate of withdrawal to 40 seconds seems to prevent the change in cerebral blood flow.[21] Although it is unknown whether these changes in cerebral hemodynamics have any long-term effects, it seems advisable to be cautious about rapidly withdrawing from or infusing into any umbilical catheter.

There is little published data on which to base decisions about how long an umbilical artery catheter can remain safely in place. In some institutions, they are usually

removed within several days. Other institutions maintain them for as long as 3 weeks. As with all therapies, the potential risks of umbilical artery catheterization must be balanced against the potential advantages for each infant.

Other Indwelling Catheter Sites

In approximately 10% of infants, umbilical artery catheterization is unsuccessful. In these cases, percutaneous cannulation of a peripheral artery may be the best alternative. Percutaneous arterial cannulation is also the best option for infants who no longer have an umbilical artery cannula but still require arterial access. Other techniques, such as umbilical artery or peripheral artery cutdown, are more difficult to perform and involve more risk to the patient. Although percutaneous cannulation of a peripheral artery is technically challenging, especially in infants weighing less than 1 kg, cannulation of the radial, ulnar, dorsalis pedis, or posterior tibial artery is often possible. One should avoid cannulating the temporal artery because cerebral emboli and stroke have been reported in patients with temporal artery catheters.[22,23]

If the radial artery is to be cannulated, an Allen's test should be performed to ensure ulnar artery patency. Conversely, if the ulnar artery is to be cannulated, radial artery patency should be assessed. Begin the Allen's test by gently squeezing the hand to empty it of blood. Apply pressure to both the radial and ulnar arteries, then remove pressure from the hand and the artery that will not be cannulated. If the entire hand flushes and fills with blood, it is safe to proceed with cannulation.

The artery can be localized by either palpation or transillumination. If the radial or ulnar artery is to be cannulated, the hand should be restrained in mild hyperextension. We usually administer an analgesic dose of morphine or fentanyl to the infant before beginning the cannulation. Local anesthesia with lidocaine is less effective, and leaves a wheal over the area where one needs to feel the pulse.

The insertion site should be cleaned prior to proceeding with an iodine or chlorhexidine solution. The radial artery is usually most easily cannulated at the point of maximal pulsation over the distal portion of the radius, proximal to the superficial palmar branch of the artery. In this position, the artery lies between two tendons, superficial and lateral to the median nerve (Fig. 17-3).

The catheter can be used either dry or flushed with a heparinized saline solution. The catheter and needle are advanced at an angle of approximately 30 degrees until the vessel is entered and a pulsatile blood return is encountered. The needle is held stationary and the catheter is threaded into the artery. The needle is then withdrawn.

An alternative technique is to puncture the artery through both the anterior and posterior walls, then withdraw the needle. The catheter is then withdrawn until its tip reenters the vessel lumen and a brisk blood return is obtained, at which point it is threaded into the vessel. We have found that in some cases where there is blood return, but the catheter cannot be advanced, insertion of a small guide wire through the catheter into the vessel lumen will help guide the catheter into the vessel.

Once in place, the catheter should be taped securely and connected to an infusion of heparinized saline with a T connector and a three-way stopcock. The tape securing the catheter must allow for unobstructed view of all five digits because hypoperfusion, potentially leading to ischemic necrosis, is the major complication of peripheral arterial catheters.

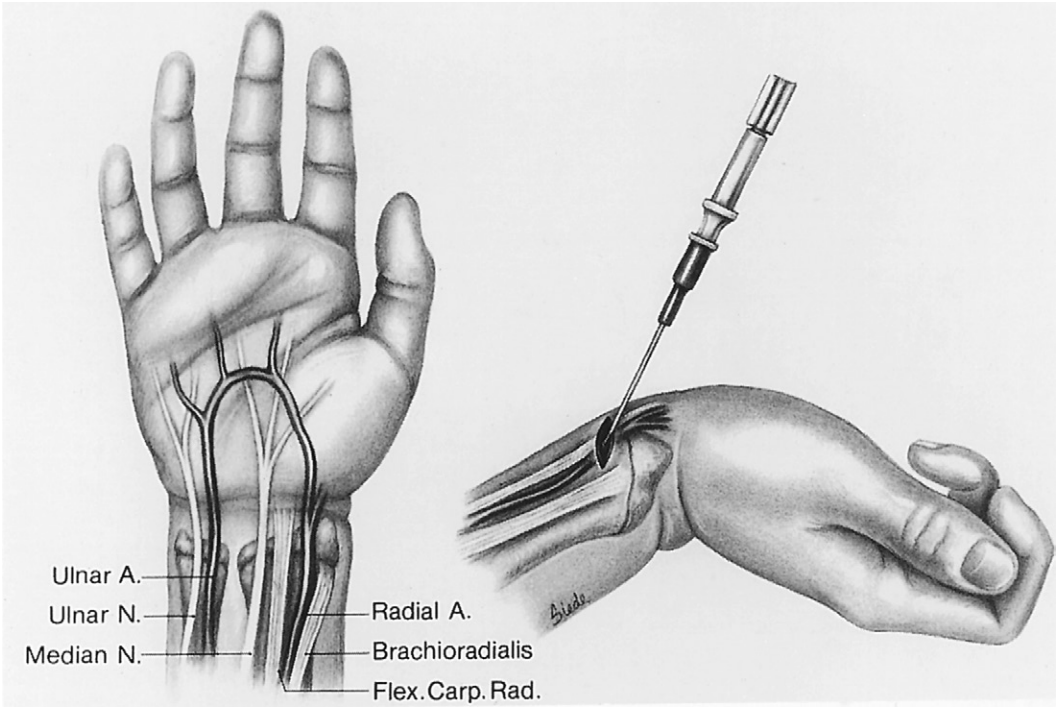

Figure 17-3 ■ Anatomy of the hand demonstrating radial and ulnar arteries and surrounding structures.

Infusion of Fluids Through Arterial Catheters

Patency of both central and peripheral arterial catheters should be maintained with a heparinized solution. In most centers, the heparin concentrations range from 0.25 unit/mL to 1.0 unit/mL. It does not appear that differences in the heparin concentration affect the incidence of intracranial hemorrhage.[24] However, care must be taken to infuse the correct concentration of heparin, because overdoses have been reported from the use of an adult concentration. Although there is no published data on safe rates at which to run fluids through arterial catheters, we usually try to run peripheral catheters at 1 mL/hr and umbilical catheters at a rate of at least 1 mL/hr. We never run either peripheral or umbilical arterial catheters at a rate of less than 1 mL/hr.

Although saline, glucose, and hyperalimentation solutions can all be infused into an umbilical artery catheter, one study suggests that infusing an amino acid containing solution of normal osmolarity causes less hemolysis than does a quarter normal saline solution.[25] In contrast to umbilical arteries where we have infused a wide range of solutions, we are concerned about the irritant effects of anything other than a physiologic saline solution infused into a peripheral artery. In small infants for whom 1 ml/hr of a physiologic saline solution provides an excessive sodium load, we sometimes infuse 0.45% saline. In cases where extra base is required, we infuse sodium acetate rather than sodium chloride. Medications or blood products are never administered through a peripheral arterial catheter.

Arterial Puncture

Blood gas samples can be obtained from intermittent puncture of the radial, ulnar, temporal, posterior tibial, or dorsalis pedis arteries. In general, the femoral and brachial arteries should not be used for arterial puncture because significant thrombus formation could lead to loss of the extremity, and median nerve damage has been reported with brachial puncture.[26] As noted above, an Allen's test should be performed before puncture of the radial or ulnar artery.

After the exact location of the desired artery has been determined by transillumination or by palpation, the skin should be prepared with a povidone iodine or chlorhexidine solution. A 25-gauge needle is inserted in the bevel-up position at a 45-degree angle through the skin, against the direction of the arterial flow. Blood should flow into the tubing spontaneously or with gentle suction. After the needle is removed, continuous pressure should be applied to the artery for 5 minutes. If hematoma formation is prevented, multiple specimens can be obtained from the same artery.

The main drawback to arterial puncture is that the procedure can rarely be done without disturbing the patient. One study showed that venipuncture, generally regarded as less traumatic than arterial puncture, caused a 6 mm Hg decrease in $PaCO_2$, and a 17 mm Hg decrease in PaO_2.[27] Although subcutaneous administration of lidocaine (without epinephrine) over the artery before arterial puncture will provide partial analgesia, most infants still become agitated during the puncture. For this reason, we rarely use arterial puncture to obtain blood gasses.

Arterialized Capillary Blood

Arterialized capillary blood can provide a crude estimate of arterial blood values. In theory, blood flowing through a dilated peripheral capillary bed has little time for O_2 and CO_2 exchange to occur, making capillary blood gas values approximate those in the arterial blood.

Capillary samples can be obtained from a warmed heel or from the sides of the distal phalanges. To arterialize the capillary blood, the extremity should be warmed for several minutes. Warming should be performed with exothermic chemical packs specifically designed for arterializing capillary blood, rather than with warm compresses, which provide poor control over temperature. The site should be carefully cleaned, and a small lancet should be used to puncture the skin. When obtaining blood from the heel, the puncture should be made on the medial or lateral aspect of the plantar surface. The posterior curvature should not be used (Fig. 17-4).

There are multiple technical challenges to obtaining optimal capillary blood samples. Inadequate warming of the site will result in inadequate arterialization of the blood. Excessive squeezing will cause contamination of the "arterialized" blood with venous blood or interstitial fluid. Exposure of blood to air during collection will skew the PO_2 and PCO_2 values. Longer-term problems associated with capillary samples include calcaneal osteochondritis and calcified heel nodules.[28] These calcified nodules may persist for several months to years, but do not seem to cause permanent problems for the infant.

Capillary puncture can be done only rarely without disturbing the infant. This, plus the fact that arterialized capillary blood is not the same as true arterial blood, means that a capillary blood gas represents only an approximation of the infant's baseline arterial blood gas status. One study and review of the literature regarding capillary blood

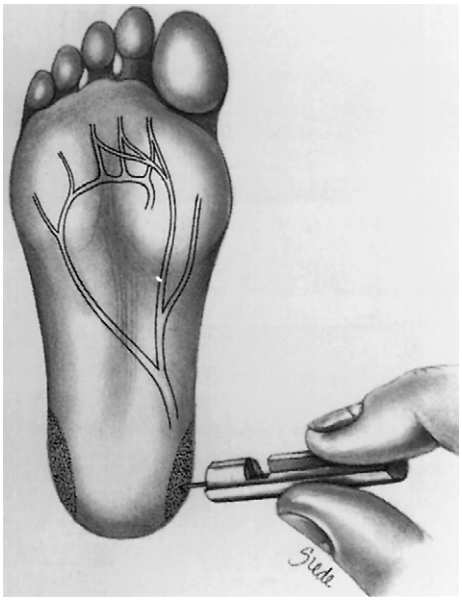

Figure 17-4 ■ Technique for obtaining arterialized capillary heel sample. Stippled sections denote correct areas for sampling.

gases concluded that capillary blood gases are "at best, only gross predictors of arterial values and, at worst, misleading assessments that may result in inappropriate management decisions."[29] We find that they are moderately useful for tracking gross changes in pH and P_{CO_2}. In an era of routine pulse oximetry, we find no value in tracking capillary P_{O_2}.

Continuous Invasive Monitoring

Over the last two decades, a number of devices have been developed for the direct intravascular or inline measurement of hemoglobin saturation, P_{O_2}, and P_{CO_2}.[30,31] However, despite their apparent advantages, these devices still have not made it into common use in most US NICUs, both because of their cost and complexity, and because of the ease of use of noninvasive technology. One study has demonstrated a reduction in the need for blood transfusions in premature infants using an inline blood gas analyzer.[31]

Errors in Blood Gas Measurements

Even small air bubbles in a blood gas sample can cause significant errors. Room air has a P_{CO_2} of essentially zero and a P_{O_2} of approximately 150 mm Hg. If air bubbles contaminate a blood gas sample, they lower the P_{CO_2} and can either raise or lower the P_{O_2}, depending on whether the P_{O_2} is below or above 150 mm Hg.[32] One study showed that the amount of air that comes in contact with arterial blood drawn through a butterfly infusion set is enough to alter the P_{O_2} measurement.[33]

Dilution of a blood sample with intravenous fluids lowers the P_{CO_2} and increases the base deficit without affecting the pH. This effect is probably due to the diffusion of CO_2 from blood into the intravenous fluid, which contains no CO_2.[32,34,35] Because of the buffering capacity of the blood, the pH changes little, despite the decrease in P_{CO_2}, giving the appearance of a combined metabolic acidosis and respiratory alkalosis. Dilution of a blood gas sample with a lipid emulsion does not appear to have any effect on the blood gas measurements.[36] Dry heparin does not appear to affect blood gas results.[35]

After blood is withdrawn from an artery, it continues to consume oxygen and produce carbon dioxide. Blood gas results may be inaccurate if the specimen is not processed promptly. Placing the sample in ice minimizes these changes. Immediate measurement, as with "point of care" techniques, also minimizes these changes.

Most blood gas analyzers measure P_{O_2}, then calculate the saturation, assuming that the blood sample is from an adult. However, if the sample contains a significant amount of fetal hemoglobin, the calculated saturation will be inappropriately low. If it is important to exactly measure the patient's saturation, this should be done with a co-oximeter rather than with a standard blood gas analyzer.

Noninvasive Estimation of Blood Gases

The development of techniques for simply and safely obtaining continuous noninvasive estimates of blood gases was one of the most important advances in neonatal care of the last 30 years. Pulse oximeters are so ubiquitous in intensive care nurseries that many think oxygen saturation is as important a vital sign as heart rate or blood pressure. Although less widely used than pulse oximeters, with recent technologic advances, both transcutaneous monitoring and end-tidal CO_2 monitoring have an important role in the management of neonates. Near infrared spectroscopy (NIRS) is a technology that is gradually moving from experimental to routine clinical use in selected infants.

Pulse Oximetry

Pulse oximeters work on the principle that saturated hemoglobin is a different color than desaturated hemoglobin, and thus absorbs light at a different frequency.[37-40] A sensor, consisting of a light source and a photosensor, is placed so that the light source and photosensor are on opposite sides of an artery. As light passes through the artery and the surrounding tissues, the saturated and desaturated hemoglobin absorb different frequencies. By measuring the difference between light absorbed during systole and diastole, the amount absorbed due to arterial flow can be calculated. Then, by comparing the absorption at the two appropriate frequencies, the percentage of saturated hemoglobin can be calculated. Refinements of this system include complex algorithms for calculating exact saturation, and for separating arterial pulsations from motion artifact. The calculation of saturation is dependant on sensing light, so that ambient light striking the sensor can lead to a false reading.

In general, pulse oximeters provide excellent data about oxygenation in the physiologic range. However, the values they provide must not be accepted without care. Poor perfusion, ambient light, and motion all interfere with an adequate signal. Also, different manufacturers use different algorithms for calculating saturation, and so may give slightly different results. It is important to know that manufacturers are constantly updating the software in their devices, making many published articles on the limitations of specific devices out of date.

Pulse oximeters are dependent on an adequate arterial pulse. In situations such as shock, or if severe edema obscures the pulsatile arterial flow, the oximeter may not function reliably. Similarly, in patients on total support from venoarterial extracorporeal membrane oxygenation (ECMO) who have minimal arterial pulsations, we have found that pulse oximeters rarely function if the pulse pressure is less than 10 mm Hg.

The shape of the oxygen-hemoglobin dissociation curve (Fig. 17-5) makes it impossible for pulse oximeters to differentiate between degrees of hyperoxia. For example, a Pa_{O_2} of 80 and a Pa_{O_2} of 180 mm Hg both represent essentially 100% saturation in a preterm neonate. At least one study suggests that this is a significant limitation of pulse oximetry compared with transcutaneous oxygen monitoring, particularly in an era when avoiding hyperoxia to decrease the risk of retinopathy of prematurity is a significant concern.[41] Pulse oximeters are also less accurate in the low end of the saturation range (e.g., less than 70% saturation) than in the normal physiologic range. Fortunately, this does not usually pose a clinically significant problem because the exact degree of severe desaturation is usually less important than the desaturation itself.

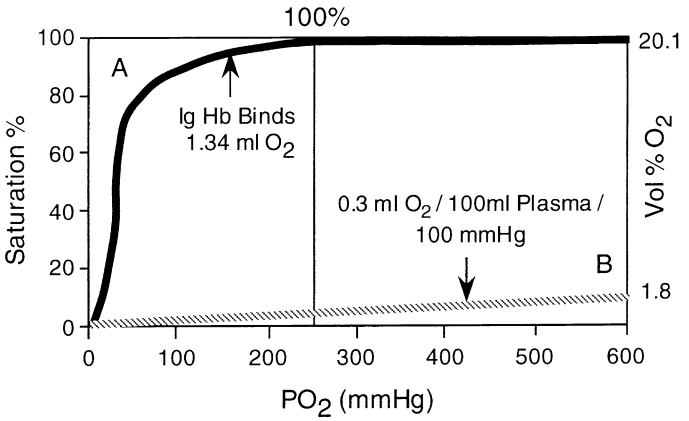

Figure 17-5 ■ Comparison between the dissociation curve of hemoglobin (*curve A*) and the amount of oxygen dissolved in plasma (*curve B*). Note that the hemoglobin is almost 100% saturated at Po_2 80 mm Hg. When fully saturated, 15 g Hb will bind 20.1 mL O_2. (From Duc G: Pediatrics 48:469, 1971.)

One major advantage of pulse oximetry is that oxygen saturation is a more physiologically relevant measure than is PaO_2. Also, because fetal and adult hemoglobin have significantly different oxygen dissociation curves, it is often impossible to determine an "ideal" PaO_2. In an extremely preterm infant with a large percent of fetal hemoglobin, a PaO_2 of 40 mm Hg may be adequately saturated, whereas in a postterm infant with relatively little fetal hemoglobin, the same PaO_2 may represent significant desaturation.

Transcutaneous Monitoring

Transcutaneous oxygen and carbon dioxide electrodes allow continuous indirect estimation of PaO_2 and $PaCO_2$. Although pulse oximetry has largely replaced transcutaneous monitoring as a tool for estimating oxygenation, many centers find an important role for transcutaneous CO_2 monitoring. Current transcutaneous CO_2 monitoring devices are run at lower temperatures than previous generations of monitors and are therefore much less likely to cause thermal injury to immature skin. There are several good reviews of the theory of transcutaneous monitoring.[37,39,42,43]

Transcutaneous PO_2 ($tcPO_2$) essentially measures the PO_2 of skin. Although the PO_2 of skin is usually lower than the PaO_2, local cutaneous vasodilation causes the skin PO_2 to approach PaO_2. This cutaneous vasodilation is accomplished by heating the area directly under the $tcPO_2$ electrode. Although heating the skin causes several effects other than vasodilation, these effects on the oxygen dissociation curve, tissue oxygen consumption, and electrode oxygen consumption cancel out for most patients. Studies have shown that $tcPO_2$ approximates PaO_2 even in patients with poor perfusion; however, in older infants with chronic lung disease, $tcPO_2$ underestimates PaO_2.[44]

The relationship between $PaCO_2$ and transcutaneous PCO_2 ($tcPCO_2$) is more complex than that between PaO_2 and $tcPO_2$. Transcutaneous PCO_2 is always greater than $PaCO_2$ because of the combination of several effects. Among these effects is the fact that heating causes increased production of CO_2 by blood and skin cells, there is a significant arterial-cellular CO_2 gradient, and the skin has a cooling effect on the electrode. These effects are fairly uniform at a given temperature and combine to create a linear relationship between $tcPCO_2$ and $PaCO_2$.[45]

Despite its limitations, transcutaneous CO_2 measurement is helpful for trending $PaCO_2$ values, particularly in the absence of reliable clinical indicators of adequacy of ventilation. We have found it to be particularly helpful in the management of infants on high-frequency ventilation where it is impossible to assess tidal volume, and in cases where the patient's work of breathing may be difficult to assess.

Capnography

Capnography, also known as *end-tidal CO_2 monitoring*, is the measurement of exhaled CO_2. This is a technique that has found widespread use in adult and pediatric intensive care units, as well as in the operating room, and may be helpful in larger infants. It is an attractive technology because it is relatively inexpensive, portable, noninvasive, and easy to use. However, it has not been as widely accepted into intensive care nurseries, primarily because it gives only a rough estimate of $PaCO_2$ in patients with significant lung disease.

Because alveolar PCO_2 approximates $PaCO_2$, a sample of pure alveolar gas will provide an estimate of $PaCO_2$. Capnography measures the concentration of CO_2 in exhaled gas and displays this concentration as a function of time. If there is a good end-tidal plateau in exhaled PCO_2, this usually represents the alveolar PCO_2. In adult and pediatric patients with relatively large tidal volumes and relatively low respiratory rates, this alveolar plateau is readily measured. In sick neonates, the limitation of capnography is the difficulty in obtaining a sample of alveolar gas that is not mixed with gas from the airways. Ill newborns are usually too tachypneic and have tidal volumes that are too small to obtain an adequate end-tidal sample of alveolar gas. In addition, animal studies suggest that alveolar disease interferes with the relationship of end-tidal CO_2 compared to $PaCO_2$, independent of respiratory rate and tidal volume.[46] Studies in newborns demonstrate that capnography is an accurate method of estimating $PaCO_2$ in healthy infants, but only provides a rough estimate of $PaCO_2$ in infants with significant lung disease.[47-49] One study of capnography during transport of infants found that the end-tidal PCO_2 significantly underestimated $PaCO_2$, but that the degree of underestimation was independent of either $PaCO_2$ or severity of lung disease.[50]

In addition to using capnography to estimate $PaCO_2$, some investigators have tried to tease more information about lung function from the capnogram.[51] Although this is an intriguing concept, it has not gained widespread use in NICUs. We suspect that with the gradual increase in the use of capnography in nurseries, we will soon see more novel ways of using the capnogram data.

One of the most useful applications of exhaled CO_2 monitoring is in determining whether an endotracheal tube is actually in the trachea.[52] Small, disposable colorimetric devices can be attached to the hub of an endotracheal tube immediately after intubation to ensure that exhaled CO_2 is being detected. We have used this approach in our nursery for a number of years, and have found

it an extremely useful tool for determining successful intubation. Moreover, the Neonatal Resuscitation Program (NRP) suggests that during resuscitation, if the baby's heart rate does not respond to intubation and ventilation, a colorimetric CO_2 detector should be used to verify the placement of the endotracheal tube.

Many of the newer generations of bedside monitors and infant ventilators now have built-in end-tidal CO_2 monitoring as an option, making continuous monitoring of exhaled CO_2 a realistic option for ventilated infants. We suspect that routine continuous monitoring of exhaled CO_2 to document that the endotracheal tube is in good position will become the norm for ventilated neonates, just as it is now the standard for ventilated patients in the operating room.

Near Infrared Spectroscopy

The light-absorbing characteristics of oxygenated and deoxygenated hemoglobin can be used for techniques other than pulse oximetry. Near infrared spectroscopy (NIRS) is a technique that relies on this differential absorption of light and also on the relatively transparent nature of tissue to infrared light to give an estimation of tissue oxygenation. Although this technique has been intermittently studied in infants since the 1980s and seems to be gaining acceptance in recent years, its true value in caring for patients remains largely unknown.[53,54]

Choice of Monitoring Methods

Over the last decade several factors have led to a gradual decline in the reliance on arterial blood gas samples. The heightened awareness of blood transfusion risks has led to a general decrease in the number of blood tests, including blood gases. "Permissive hypercapnea" has led to a wider range of accepted $PaCO_2$ values, and therefore less frequent blood gas measurements. The increased use of patient-triggered ventilator modes such as assist control and pressure support, where the patients control their respiratory rate and minute ventilation, has led many neonatologists to further decrease the frequency of blood gas sampling (see Chapter 12).

Despite these trends, there remains the need for reliable arterial blood gas sampling in unstable infants. Our approach is to place an umbilical catheter into any newborn with respiratory distress that is significant enough to require arterial blood sampling. We routinely place an umbilical artery catheter in infants who require intubation or nasal continuous positive airway pressure (NCPAP) with significant oxygen requirements and in most infants who weigh less than 1.0 kg. We usually remove umbilical artery catheters after 5 to 7 days, although we will sometimes leave them in for as long as 2 to 3 weeks in extremely unstable infants who weigh less than 1 kg. For other infants who are critically ill and need arterial monitoring, we place peripheral arterial catheters.

We monitor all but the most stable infants with continuous pulse oximetry. Infants requiring significant respiratory support are usually followed with transcutaneous CO_2 monitoring in addition to pulse oximetry. Capnography as a method of estimating $PaCO_2$ has gradually become more widely used in our NICU, particularly for large infants with minimal lung disease such as postoperative infants. End-tidal CO_2 detection for monitoring the presence of the endotracheal tube in the trachea is becoming the standard in our NICU. NIRS monitoring, although intriguing and potentially useful, has not yet become routine in our NICU.

Continuous monitoring of ventilated infants is supplemented with intermittent measurements of blood gases. In our nursery, stable ventilated infants without arterial access usually have capillary blood gases performed every 24 to 48 hours, whereas less stable infants have them performed as frequently as 2 to 3 times per day. In critically ill infants without arterial access, we sometimes use samples drawn from an umbilical venous catheter to provide a crude estimate of PCO_2. Although venous PCO_2 is at least several mm Hg higher than arterial (and may be significantly higher), we believe it is sometimes preferable to use this crude measure than to perform repeated arterialized capillary blood gas samples or intermittent arterial punctures.

Physiology of Blood Gases

As blood flows past ventilated alveoli, oxygen is added to the blood and carbon dioxide is removed. In simplest terms, the amount of oxygen in blood leaving the left heart reflects the matching of perfusion to ventilation. Any condition causing blood to emerge from the left heart without passing ventilated alveoli will decrease arterial oxygen content. This occurs if blood passes from the right heart to the left heart without going through the pulmonary circulation (extrapulmonary shunt) or if blood passes atelectatic or underventilated alveoli (intrapulmonary shunt). Similarly, the amount of carbon dioxide removed from the blood reflects the adequacy of alveolar ventilation. As alveolar ventilation decreases, less CO_2 is removed from the blood flowing through the lungs, and the PCO_2 in blood leaving the left heart increases. Arterial blood gases provide information about the matching of ventilation to perfusion and about the adequacy of alveolar ventilation. However, they do not provide direct information about the adequacy of oxygen delivery to the systemic vascular bed and to peripheral tissues.

The cells of the body use oxygen for the aerobic metabolism of glucose. Glucose, when aerobically metabolized to CO_2 and water, produces adenosine triphosphate (ATP). If sufficient oxygen does not reach the cells, tissue hypoxia occurs. In this case, glucose is metabolized anaerobically to pyruvate, also producing ATP. Pyruvate is then metabolized to lactic acid. As lactic acid accumulates in the blood, it is reflected by an increased base deficit (or decreased base excess) of arterial blood. Lactic acid is buffered in the blood by three major components: hemoglobin, serum proteins, and bicarbonate. The normal or ideal buffering capacity of blood is 48 mEq per liter. Base excess is defined as the difference between the actual buffer capacity and the ideal buffer capacity.

To more accurately estimate whether an adequate amount of oxygen has been delivered to tissues, one must look at blood returning from the systemic circulation to the heart.[55] Although mixed venous blood should ideally

be sampled from the pulmonary artery, this is impractical in most neonates. Instead, blood sampled from the right atrium is assumed to closely approximate mixed venous blood. Monitoring mixed venous oxygenation is an extremely useful tool for assessing adequacy of tissue oxygen delivery and is widely used in adult ICUs and in neonatal extracorporeal membrane oxygenation (ECMO). Newer devices designed to optically measure mixed venous saturation in mucous membranes are currently available and gaining favor in many units.

Oxygen Transport

The amount of oxygen that can be delivered to the tissues depends upon two major factors: cardiac output and the oxygen content of the blood. In most neonates, the cardiac output is approximately 120 to 150 mL/kg/min. The oxygen content of arterial blood (C_aO_2) depends upon several factors. Because blood carries oxygen both bound to hemoglobin and as free dissolved oxygen, the C_aO_2 of blood can be thought of as follows:

$$C_aO_2 = (\text{Hb } O_2) + (\text{Dissolved } O_2)$$

Where:

C_aO_2 = Oxygen content

Hb O_2 = Oxygen bound to hemoglobin

Dissolved O_2 = Oxygen in solution

The amount of oxygen carried in the blood by hemoglobin depends upon both the hemoglobin concentration and the percent saturation of the hemoglobin. The relationship between P_{O_2} and amount of oxygen combined with hemoglobin, or hemoglobin saturation, is sigmoidal over the physiologic range. Hemoglobin is almost fully saturated at a P_{O_2} of 80 to 100 mm Hg (Fig. 17-5, *Curve A*). The amount of oxygen combined with hemoglobin at a given P_{O_2} depends upon the position of the hemoglobin dissociation curve. The position of the dissociation curve depends mainly on two factors: (1) the concentration of red blood cell diphosphoglycerate (DPG) and (2) the ratio of adult hemoglobin (A) to fetal hemoglobin (F). With increasing age, the concentration of DPG and the proportion of hemoglobin A increase, shifting the curve to the right (Fig. 17-6). Temperature, P_{CO_2}, and the hydrogen ion concentration play smaller roles in determining the position of the curve. As the temperature, P_{CO_2}, or hydrogen ion concentration increases, the curve is shifted to the right. As the curve shifts to the right, hemoglobin releases oxygen more easily to the tissues.

Only a small amount of oxygen is dissolved in the plasma. This amount is directly proportional to the P_{O_2}. At 38° C, 0.3 mL of oxygen is dissolved in 100 mL of plasma per 100 mm Hg of oxygen. This relationship is linear over the entire range of P_{O_2} (see Fig. 17-5, *Curve B*). Because the amount of oxygen that is dissolved in the blood is much less than the amount that is bound to hemoglobin, we can simplify the above equation to an approximation:

$$C_aO_2 = (\text{Hb } O_2)$$

The amount of oxygen that is bound to hemoglobin, and therefore the approximate oxygen content of the blood, depends upon three factors: the concentration of hemoglobin in blood, the percent of hemoglobin saturation, and the oxygen capacity of hemoglobin. Mathematically this is expressed as follows:

$$C_aO_2 = (\text{Hb } O_2)$$
$$= (\text{g \% Hb}) \times (O_2 \text{ capacity}) \times (\text{\% Saturation})$$

O_2 capacity is a constant that represents the maximum amount of O_2 that can be carried by a gram of hemoglobin that is fully saturated. This value is 1.34 mL O_2 per gram of 100% saturated hemoglobin.

Assuming a normal hemoglobin level of 15 g/100 mL blood, and that arterial blood is 100% saturated, and ignoring the small amount of O_2 that is dissolved in blood, the oxygen content of normal arterial blood is approximately as follows:

$$C_aO_2 = 15 \times 1.34 \times 1.0$$
$$= 20 \text{ mL } O_2 \text{ per 100 mL arterial blood}$$

Assuming that the normal newborn cardiac output is approximately 120 mL/kg/min, the amount of O_2 that can be delivered to the systemic circulation is calculated as follows:

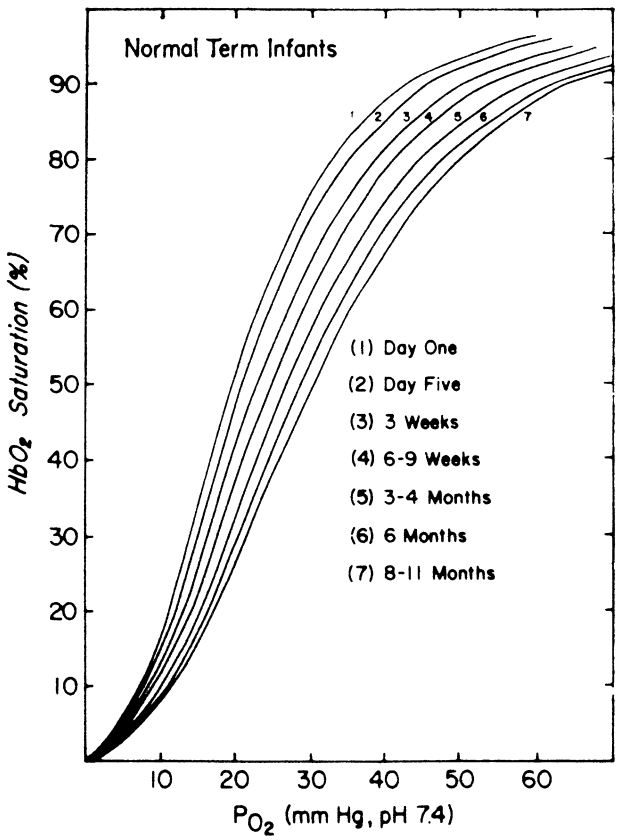

Figure 17-6 ■ Oxygen dissociation curves from term infants at different postnatal ages. (Delivoria-Popadopoulos M, Roncevic NP, Oski FA: Ped Res 5:235, 1971.)

$$\begin{aligned} O_2 \text{ delivered} &= (CO) \times (C_aO_2) \\ &= (120 \text{ mL blood/kg/min}) \times \\ &\quad (0.2 \text{ mL } O_2/\text{mL blood}) \\ &= 24 \text{ mL } O_2/\text{kg/min} \end{aligned}$$

Under normal circumstances, oxygen consumption for a neonate is approximately 6 mL/kg/min. Thus, under normal circumstances, the body extracts O_2 at a rate of 6 mL/kg/min from the approximately 24 mL/kg/min that is delivered to the systemic circulation. Therefore, approximately 25% of the oxygen has been removed from the blood by the time it returns to the heart. The mixed venous blood will therefore be approximately 75% saturated. In general, a measured mixed venous saturation of 70% to 75% represents adequate tissue oxygen delivery. In those patients where mixed venous saturation can be directly monitored (usually patients on ECMO), we try to maintain mixed venous saturation in the normal physiologic range of 70% to 75%.

Hypoxemia and Hypoxia

Hypoxia exists when there is inadequate delivery of oxygen to tissue, whereas hypoxemia exists when there is low arterial blood oxygen content. Although hypoxemia and hypoxia frequently occur together, they are not synonymous.

Hypoxemia occurs in any situation where blood reaches the aorta without perfusing adequately ventilated alveoli. Blood can bypass adequately ventilated alveoli by extrapulmonary shunts, by intrapulmonary shunts, or by some combination of the two. With cyanotic congenital heart disease, a structurally abnormal heart leads to some blood entering the aorta without passing through the lungs (extrapulmonary shunt). Similarly, patients with pulmonary artery hypertension can also have extrapulmonary shunting through the foramen ovale and/or ductus arteriosus. A right-to-left shunt across the ductus arteriosus can often be detected by comparing the PaO_2 or oxygen saturation of preductal and postductal blood (Fig. 17-7). If the saturation of the preductal blood is significantly higher (5% difference) than the saturation of the postductal blood, a clinically significant right-to-left shunt exists. However, equal pre- and postductal saturations do not exclude the possibility of pulmonary hypertension with a shunt through the foramen ovale (see Chapter 26). The hypoxemia associated with lung diseases that are characterized by atelectasis (e.g., respiratory distress syndrome, pneumonia) is caused primarily by intrapulmonary shunting. In any condition where alveoli are inadequately ventilated, the blood flowing to those alveoli is not fully saturated. Thus, the greater the degree of atelectasis, the greater the intrapulmonary shunt, and the greater the degree of hypoxemia.

Tissue hypoxia can occur despite adequate PaO_2. This will occur in any situation where there is inadequate tissue perfusion (e.g., severe myocardial dysfunction) or where there is insufficient oxygen-carrying capacity (e.g., severe anemia). It will also occur in those rare cases where abnormal hemoglobin (e.g., methemoglobin) fails to release oxygen to the tissues. Hypoxia may also occur in situations of high altitude based on the alveolar gas equation. The reader is referred to Chapter 31 for a discussion of this problem.

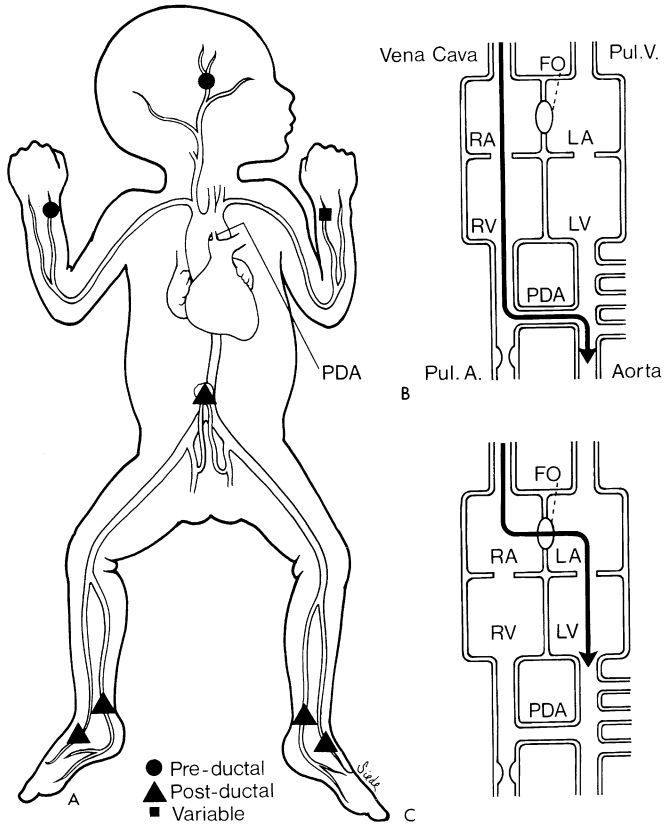

Figure 17-7 ■ Shunting of blood in pulmonary hypertension. **A**, Sampling sites. **B**, Right-to-left shunt across the ductus arteriosus. **C**, Right-to-left shunt across the foramen ovale. *FO,* Foramen ovale; *LA,* left atrium; *LV,* left ventricle; *PDA,* patent ductus arteriosus; *RA,* right atrium; *RV,* right ventricle.

Carbon Dioxide Transport

Carbon dioxide transport is significantly less complicated than oxygen transport. Carbon dioxide is produced in tissues during the aerobic metabolism of glucose, and is transported in the blood to the lungs where it is exhaled. Eighty-five percent of the carbon dioxide in blood is transported as bicarbonate ion, 10% is carried by hemoglobin as carbamate, and 5% is transported as either dissolved gas or as carbonic acid. Due to the equilibrium between dissolved carbon dioxide and the bicarbonate ion, the relationship between PCO_2 and PCO_2 content of blood is essentially linear over the physiologic range (Fig. 17-8).

Because carbon dioxide diffuses rapidly from blood into alveolar gas, the PCO_2 in blood leaving the lungs is essentially the same as the PCO_2 in alveolar gas. Thus increasing minute alveolar ventilation decreases the PCO_2 in alveolar gas and decreases the $PaCO_2$. This is the reason $PaCO_2$ is dependant on alveolar ventilation.

Metabolic Acidosis

Anaerobic metabolism of glucose leads to the accumulation of lactic acid, resulting in metabolic acidosis. Lactic

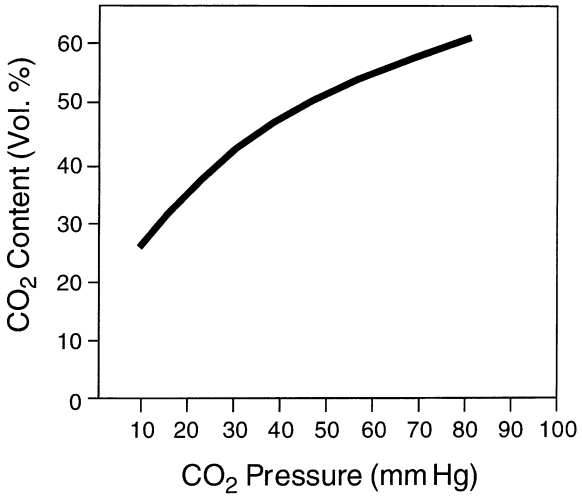

Figure 17-8 ■ Carbon dioxide curves of blood. (From Comroe JH: The Lung. Chicago, Year Book Medical Publishers, 1962, pp. 44-49.)

acid reacts with bicarbonate, causing the serum bicarbonate to fall, resulting in a base deficit. This is usually caused by inadequate tissue oxygen delivery as a result of some combination of hypoxemia, anemia, and inadequate cardiac output. Other less common causes of metabolic acidosis in the newborn include sepsis, inborn errors of metabolism, and renal bicarbonate wasting.

In most healthy newborns, the base deficit is between 0 and 5. Although it makes sense to provide base to infants who have a metabolic acidosis from bicarbonate loss, there is essentially no evidence that acute bicarbonate therapy is beneficial in patients with metabolic acidosis from tissue hypoxia. To the contrary, there is a long history of research that shows that bicarbonate administration may actually be deleterious to the patient with hypoxia and metabolic acidosis.[56-58] A recent review suggested that the value of bicarbonate administration to neonates is extremely limited and that it probably should not be used routinely.[59] In patients with metabolic acidosis, restoring tissue oxygen delivery is far more important than administering exogenous base.

If metabolic acidosis is to be treated with exogenous base, the most commonly used drug is sodium bicarbonate. The number of milliequivalents of bicarbonate needed to half correct a base deficit can be approximated from the following equation:

$$\text{Milliequivalents of bicarbonate} = (\text{Base deficit}) \times (\text{Body weight in kg}) \times 0.3$$

Because of its hypertonicity, sodium bicarbonate (1 mEq/mL) should be diluted 1:1 with sterile water and administered slowly, preferably over 30 to 60 minutes. Bicarbonate should be administered with care in the infant with a combined respiratory and metabolic acidosis, because as the bicarbonate is metabolized, the $PaCO_2$ will further increase, unless there is also an increase in minute ventilation.

Metabolic Alkalosis

By far the most common cause of relative metabolic alkalosis in neonates is a compensation for respiratory acidosis. If a compensated respiratory acidosis is corrected by rapidly lowering the PCO_2, this will result in an absolute metabolic acidosis. Other causes of metabolic alkalosis in the newborn include hypokalemia and hypochloremia from chronic vomiting, drainage of gastric secretions, chronic diuretic therapy, and the administration of excess acetate in parenteral nutrition. Mild metabolic alkalosis can also occur following an exchange transfusion, when the citrate in the anticoagulant is metabolized. It is rarely necessary to aggressively correct metabolic alkalosis with administration of acidic compounds such as ammonium chloride or arginine hydrochloride or with bicarbonate-wasting diuretic such as acetazolamide. In most cases, treating a relative metabolic alkalosis with these agents merely results in an uncompensated respiratory acidosis.

Clinical Interpretation of Blood Gases

Understanding the physiology of gas exchange makes the interpretation of blood gases a relatively straightforward process. Hypoxemia is the result of ventilation/perfusion mismatch or shunting, usually resulting from atelectasis and/or extrapulmonary shunting. It is treated by reversing atelectasis and/or decreasing pulmonary vascular resistance. Our goal in all infants should be to maintain arterial saturation, as well as hemoglobin level and cardiac output, at levels that avoid tissue hypoxia while minimizing the risks of hyperoxia. Hypercapnia is the result of inadequate alveolar minute ventilation and is treated by increasing minute ventilation, usually by increasing tidal volume and/or respiratory rate. However, we continue to struggle with what "normal" and "acceptable" ranges are, particularly in the premature infant.

Most healthy infants, including preterm infants, have arterial saturation values in the 90s.[60,61] Several studies have suggested that by slightly lowering oxygen saturation targets in the very-low-birth-weight (VLBW) infant, the rate of severe retinopathy of prematurity is reduced.[62-64] A large study on the impact of low vs. high saturation (SpO_2 89%-94% vs 96%-99%) targets on the progression of retinopathy of prematurity, showed the high saturation group to have an increased incidence of adverse pulmonary outcomes, including more pneumonia and/or exacerbations of chronic lung disease, as well as an increased need for prolonged oxygen therapy.[65] This approach is at marked variance from the more traditional assumption that infants, particularly with chronic lung disease, should have SpO_2 levels at least in the mid-90s.[66] It is important to remember that many patients with cyanotic cardiac disease tolerate long periods of time with SpO_2 in the 70% to 80% range or lower without developing signs of tissue hypoxia. This would suggest that, in the presence of adequate cardiac output and hemoglobin level, much lower arterial saturations than are usually considered ideal can be safe.

We agree with those who have stated that we really do not know the optimal level of oxygenation, particularly for very preterm infants, and that this is an area that needs

carefully designed clinical trials.[67] However, despite this uncertainty, it is our sense that most US NICUs now use a "target" SpO_2 for preterm infants of approximately 85% to 95%, often aiming for the lower part of this range. We also have a sense that most US NICUs are gradually becoming more tolerant of transient lower saturations and will not immediately increase FIO_2 in infants with saturations that are below their "target" range.

There is also uncertainty about the acceptable range of $PaCO_2$ values for neonates. Over the last decade, there has been a steady trend toward "permissive hypercapnia," where progressively higher $PaCO_2$ values are accepted. This strategy is based on the assumption that maintaining $PaCO_2$ in the normal range often requires an unacceptable degree of ventilation and associated ventilator-induced injury. Although this strategy seems reasonable and has been widely accepted, it has not been thoroughly studied. One small study of infants less than 1200 g showed that patients who were managed with $PaCO_2$ 45 to 55 mm Hg required fewer days of ventilation that did those who were managed with $PaCO_2$ 34 to 45, but did not show any difference in longer-term outcomes.[68] A large multicenter trial designed in part to test the impact of permissive hypercapnia on the incidence of chronic lung disease was terminated prematurely, secondary to complications of randomized dexamethasone administration.[69] Subsequent analysis of the infants who completed this trial suggested that there was no definite benefit to a strategy of permissive hypercapnia, except possibly in infants between 500 and 750 g birth weight.[70]

Whether there is a relationship between hypercapnia and risk for severe intracranial hemorrhage remains unclear. There are at least several studies that suggest there is an association between the risk of severe intraventricular hemorrhage and highest $PaCO_2$ values in VLBW infants,[71,72] although most of these levels would not be considered in the acceptable range of a "permissive" strategy. There is also a recent retrospective study suggesting no association between moderate hypercapnia and intracranial hemorrhage or adverse neurologic outcome.[73] As several reviews have pointed out, we are left with attractive arguments in favor of permissive hypercapnia, theoretical concerns about its side effects, and relatively little strong data to support its benefit.[74,75] The assessment of acceptable $PaCO_2$ is further complicated by the fact that rapid changes in $PaCO_2$ are at least as important as the absolute value, and that a chronic compensated hypercapnia is very different than an acute uncompensated hypercapnia.

In contrast to the uncertainties surrounding hypercapnia, there is a large body of information to suggest that hypocarbia is potentially dangerous.[74] It is well known that acute hyperventilation and hypocarbia leads to a significant decrease in cerebral blood flow.[76,77] Studies have linked significant hypocarbia ($PaCO_2$ greater than 25 mm Hg) to an increased risk of cystic periventricular leukomalacia.[78] There also appears to be an association between degree of hyperventilation and hearing loss.[79,80] Low $PaCO_2$ levels have for decades been associated with increased risk for development of BPD.[81-83] Although deliberate hyperventilation to a target $PaCO_2$ in the 20s or 30s was once the standard of care for pulmonary hypertension, we believe this practice can no longer be justified, particularly when there is ready access to inhaled nitric oxide and to ECMO. Both anecdotal experience and retrospective studies support the belief that it is possible to obtain good outcomes in infants with pulmonary hypertension while avoiding hyperventilation.[84,85] Avoiding wide swings in $PaCO_2$ is probably at least as important as maintaining $PaCO_2$ within a specified range because abrupt changes in $PaCO_2$ can have significant effects on systemic blood pressure and cerebral blood flow.

It is our impression that most US NICUs now aim to keep $PaCO_2$ in the mid-40s to mid-50s for most patients, but readily accept $PaCO_2$ levels in the 60s in sicker patients. For chronic patients with a compensatory respiratory alkalosis, even higher $PaCO_2$ levels are frequently seen.

Over the last few years, we have seen an increasing trend of clinicians making ventilator decisions based on pH more than on $PaCO_2$, a strategy that makes a great deal of sense if there is no metabolic acidosis. Given the wide range in severity of lung disease in the typical NICU, and given how well most infants develop a compensatory metabolic alkalosis in response to chronic hypercapnia, targeting a range of acceptable pH may be simpler than specifying $PaCO_2$ target ranges. Unfortunately, there is essentially no good clinical data on what are "acceptable" pH ranges for neonates. It is our impression that the range of acceptable pH values has gradually become lower over the last 5 to 10 years. In our NICU, we generally aim to keep pH at 7.25 to 7.35, but will sometimes tolerate pH values as low as 7.20 or (rarely) 7.15.

Final Caveat

Although arterial blood gas values are frequently invaluable in managing patients with respiratory distress, they should not be interpreted in the absence of other clinical data. A blood gas result that is significantly different than previous results may indicate a major change in the patient's status, or may represent an error in blood gas measurement. Similarly, if the blood gas results do not correlate with the patient's physical examination, further evaluation is needed. Neither a blood gas laboratory nor the most sophisticated noninvasive monitors can replace careful clinical observation.

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18 Pulmonary Function and Graphics

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Bedside measurements of neonatal pulmonary function, previously only feasible in a research setting, have been made possible by the technologic enhancements of neonatal ventilators. Spirometry lung volumes and their concurrent measurement to static pressure changes were the traditional bedside applications of pulmonary function testing (Fig. 18-1). Now with advanced microprocessor and sensor technologies, manufacturers and designers of ventilatory equipment have provided clinicians with continuous and real-time analysis of ventilatory function and online depictions of pulmonary graphics. Pulmonary function data can be collected and downloaded for analysis and subsequent interpretation (Tables 18-1 and 18-2). Newer technology allows for continuous visualization of real-time data; however, the clinician still has to cope with "spot" measured values of respiratory vectors and with calculated measures of dynamic pulmonary mechanics. When combined with known physiologic principles, the clinician can gain access to a rich source of previously untapped information to better assess the respiratory status of a sick newborn.[1]

Pulmonary graphics refers to the direct and online visualization of the three fundamental parameters of the respiratory system, namely, driving pressure, air flow, and tidal volume. These parameters are continuously displayed on a monitor either as scalar waveforms along a time axis or as X-Y plots of one variable versus another. The graphic displays may be accompanied by running average calculated values of pulmonary function parameters, such as compliance and resistance, as well as the more basic respiratory measurements, such as tidal volume and minute ventilation. Visualization of pulmonary gas exchange, a graphic assessment of blood gases and their relationship to respiratory support settings, also may be considered an extension of pulmonary graphics. The clinician's ability to use these technologies to advantage will transform this available information to relevant knowledge that assesses neonatal pulmonary status. This new data source can then be used along with blood gas data, chest radiographs, and other clinical and laboratory data for a decision-making process to assist in the ventilatory management of neonates with respiratory failure.

In this chapter, we provide an overview of how we use pulmonary graphics in our clinical management. The reader is referred to classic descriptions of physiologic principles in the Suggested Readings at the end of the chapter that have led to our understanding of neonatal pulmonary function and graphics.

Background

Signals of Respiration

Respiratory cycles are described by three fundamental signals: driving pressure (P), flow ($\dot{V}$), and volume (V). The first two signals are directly measurable; volume usually is derived from integration of the flow signal, which is simply the rate of change of volume. Thus the usual mode of evaluating physiologic changes in respiration is by studying the standard scalar interrelationships of pressure, flow, volume, and time (Fig. 18-2). Breathing requires the generation of a driving pressure. For inspiration to occur, alveolar pressure must be less than the pressure at the mouth. For expiration to occur, alveolar pressure must be greater than the mouth pressure. During spontaneous breathing, this pressure gradient is generated by the respiratory muscles. In mechanical ventilation the ventilator produces the driving pressure. In either case, the driving pressure initiates a flow that overcomes the elastic, resistive, and inertial properties of the entire respiratory system resulting in a volume change in the lungs (see Chapter 2 for further discussion of physiologic principles). This relationship has been best described by Röhrer[2] using an equation of motion in which the driving pressure is equal to the sum of elastic (P_E), resistive (P_R), and inertial (P_I) pressure components, or:

$$P = P_E + P_R + P_I \quad (1)$$

In this relationship, the elastic pressure is assumed to be proportional to volume change by a constant (E) representing the elastance (or elastic resistance) of the system. The resistive pressure component is assumed proportional to air flow $\dot{V}$ by a constant (R) representing inelastic airway and tissue resistances. The inertial component of pressure is assumed to be proportional to gas and tissue acceleration ($\ddot{V}$) by an inertial constant (I) and is usually negligible during conventional ventilation. Thus:

$$P = EV + R\dot{V} + I\ddot{V} \quad (2)$$

This linear model of respiratory system mechanics has become one of the fundamental principles used in respiratory physiology for the study of pulmonary function. Based on an ideal single-compartment model, this equation assumes linear relationships between pressure and volume and pressure and flow, such that the coefficients E, R, and I remain constant throughout the ventilatory cycle. The assumption of linearity breaks down at (1) extremes of

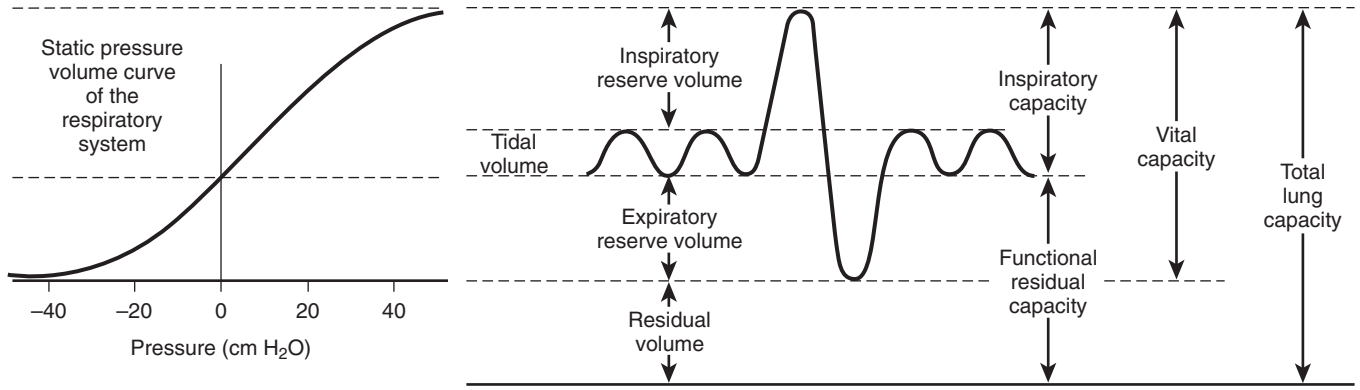

Figure 18-1 ■ Traditional spirometry (*right panel*) and the associated static deflation pressure-volume relationship measured for a vital capacity maneuver (*left panel*).

TABLE 18-1 **Basic Respiratory Parameters Observed in Spontaneously Breathing Neonates in Several Weight Ranges**

Weight Range (g) Percentiles	Peak Inspiratory Flow (L/min)			Peak Expiratory Flow (L/min)			Tidal Volume (mL/kg)			Minute Ventilation (mL/min)		
	10th	50th	90th	10th	50th	90th	10th	50th	90th	10th	50th	90th
500-1000	0.8	1.3	2.1	0.5	0.9	1.6	3.2	5.4	8.3	230	400	600
1001-2500	1.3	2.3	3.5	1.0	1.8	3.0	3.4	5.7	8.1	250	400	600
2501-5000	1.8	3.2	5.2	1.6	2.9	4.8	2.4	4.7	7.2	170	300	500
5001-15000	4.1	5.9	9.9	3.4	4.9	8.6	5.2	6.9	8.9	180	240	400

ventilation or (2) in infants with abnormal elastic and resistive pulmonary characteristics, as frequently is the case during mechanical ventilation. Although more complex multicompartment and nonlinear models of the respiratory system have been investigated,[3-5] the simple linear model with its inherent limitations has remained the most widely used for general pulmonary function measurements because of its simplicity.

The interrelationships between the components of the Röhrer equation can be easily visualized using two-dimensional graphic plots of its variables, that is, pressure versus volume (P-V), flow versus volume ($\dot{V}$-V), and pressure versus flow (P-$\dot{V}$). Such simple X-Y plots provide valuable insight into pulmonary status and the pattern of breathing and are the basis of pulmonary graphics. Physiologic interpretations of pulmonary function can be further enhanced by mathematical evaluations of compliance (inverse of elastance) and resistance based on the Röhrer equation. Because of the inherent nature of respiratory signals to be variable, it is important to evaluate the signals during resting conditions and over a sufficient period of time to avoid artifacts and to allow averaging of random variations, thus providing a more representative time-averaged sample.

Need to Assess Accuracy and Precision

The accuracy and reproducibility of the neonatal pulmonary graphics testing system is integral to obtaining high-quality online pulmonary function test results. The American Thoracic Society and European Respiratory Society Joint Committee have published guidelines for standardization[6]; however, there have been few formal

TABLE 18-2 **Predicted Probability of BPD Based on Pulmonary Mechanics and Gestational Age Based on a Predictive Model for the Study Infants with RDS Categorized by Birth Weight***

Birth Weight (g)	Gestational Age (weeks)	Pulmonary Compliance (Cl) mL/cm H_2O/kg	Pulmonary Resistance (Rt) cm H_2O/l/s	Likelihood Ratio (LR) for BPD	Percent Predicted Probability
500-750	26 ± 0.4	0.3 ± 0.03	102 ± 16	537 ± 171	93% ± 3%
751-1000	28 ± 0.3	0.5 ± 0.05	176 ± 24	76 ± 35	73% ± 5%
1001-1250	29 ± 0.3	1.0 ± 0.2	96 ± 1.1	5.5 ± 1.8	42% ± 7%
1251-1500	31 ± 0.3	1.5 ± 0.2	69 ± 8	0.8 ± 0.3	15% ± 5%
1501-2000	32 ± 0.3	1.8 ± 0.3	69 ± 11	0.3 ± 0.1	8% ± 3%

Data from Bhutani VK, Bowen FW, Sivieri E: Biol Neonate 87:323-331, 2005.
*Predicted probability and likelihood ratio (LR) of BPD evaluated on the previously reported predictive model based on gestational age (GA) and pulmonary mechanics: LR = exp (33.6 – 1.13 GA – 0.93 Cl/kg – 0.001 Rt).
BPD, Bronchopulmonary dysplasia; *RDS,* respiratory distress syndrome.

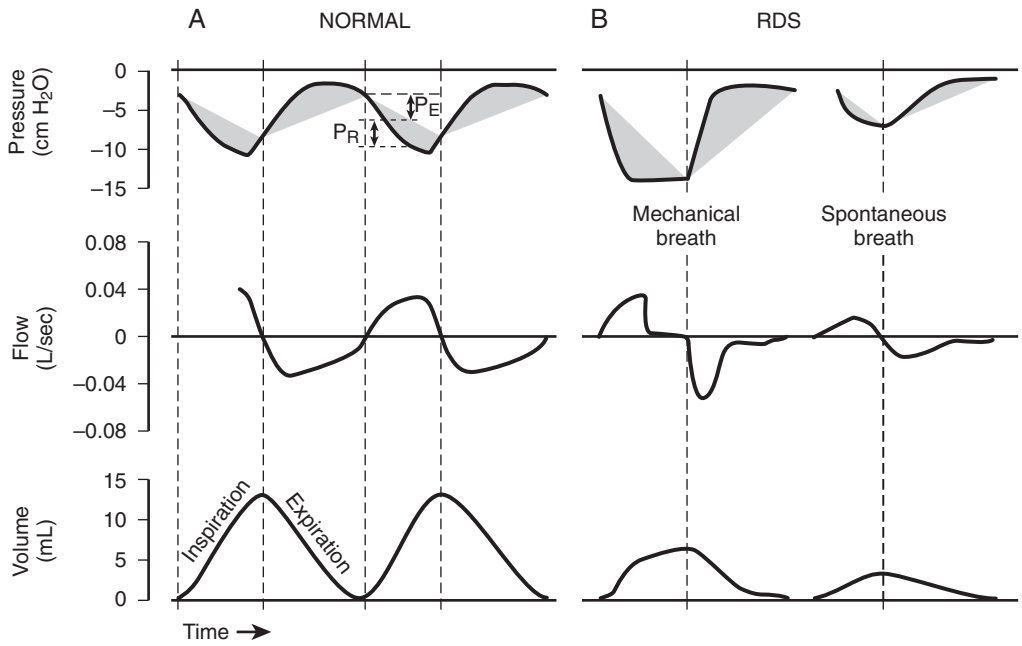

Figure 18-2 ■ **A,** Scalar monitoring of pressure, flow, and volume signals during spontaneous breathing. The pressure signal has been divided (as demarcated by a *straight line* connecting points of zero flow) to differentiate the elastic pressure from the resistive pressure (*shaded portion*). **B,** Scalar monitoring of pressure, flow, and volume signals during mechanical ventilation. Driving pressure can be approximated as peak inflating pressure minus positive end-expiratory pressure.

studies of the accuracy and reproducibility of contemporary pulmonary testing instruments in very-low-birth-weight infants.[7] Perhaps, a computer-driven mechanical syringe device to delineate standard volume-time waveforms and simulate ranges of physiologically relevant lung function values would be amenable to simulation testing and performance evaluation of current online systems.

Signals of Bedside Pulmonary Graphics: Pressure, Volume, and Flow

Pressure Signal

Driving pressure (or compression pressure) is the net pressure change required to overcome elastic, airflow resistive, and inertial properties of the respiratory system during inspiration. During spontaneous breathing, it is the gradient between the mouth and intrapleural pressures and is defined as the transpulmonary pressure (see Fig. 18-2). During positive-pressure ventilation, the driving pressure usually is measured as the gradient between the peak inflating pressure (PIP) and the positive end-expiratory pressure (PEEP). The driving pressure at the end-inspiratory portion of the ventilation cycle provides a close estimate of elastic pressure as described by the Röhrer equation. It is in this context that the ratio of tidal volume to driving pressure provides an indirect approximation of total respiratory compliance. In the absence of overinflation or underinflation and when ventilation is being administered in the most linear portion of the respiratory pressure-volume relationship, this value of respiratory compliance (in mL/cm H_2O) provides an estimation of the volume change (in milliliters) per 1 cm H_2O change in driving pressure (Fig. 18-3). These estimated data can provide a

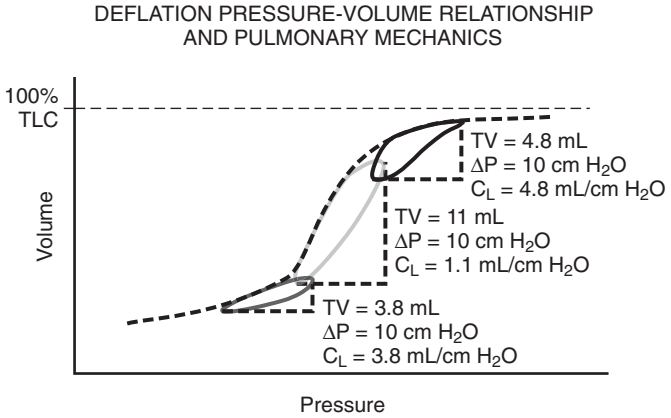

Figure 18-3 ■ Deflation limb of the respiratory pressure-volume (P-V) curve (*dashed sigmoid line*, defined from total lung capacity to residual volume) is shown on an X-Y plot. In this simulated example, tidal volume ventilation is occurring at the functional residual capacity (FRC, or the lung volume at end-expiration) that is governed by the positive end-expiratory pressure (PEEP). Thus, for a baby (birth weight = 1190 g and GA = 28 weeks) who is being administered a peak inflating pressure (PIP) of 15 cm H_2O and PEEP of 5 cm H_2O and has a recorded tidal volume of 11 mL, then the estimated compliance is 11 divided by 10 (difference of 15 and 5), which is 1.1 mL/cm H_2O. Thus two inferences may be calculated: (a) tidal volume = 9.2 mL/kg and (b) for a change in driving pressure (either PIP or PEEP), the tidal volume should change by 1.1 mL per 1 cm H_2O. For example, a decrease of PIP from 15 to 14 cm H_2O or PEEP from 5 to 4 cm H_2O should linearly decrease the tidal volume from 11 to 9.9 mL. If the infant was being ventilated with the PIP close to the "flattened" segment of the overdistended P-V relationship, the decrease in tidal volume would be nonlinear and weaning of PEEP would result in an improvement of the tidal volume. On the other hand, if the baby is being ventilated at flattened portion of the atelectatic lung, the change in tidal volume will be nonlinear and the tidal volume will fail to improve upon weaning the PEEP.

crucial understanding of the anticipated change in tidal volume for a given incremental change in ventilator driving pressure. Based on this observation, the clinician can differentiate between the effects of overdistending or underdistending the lung. As demonstrated in Figure 18-3, when ventilation is shifting away from the linear portion of the P-V loop, actual tidal volume becomes smaller than anticipated. Likewise, when ventilation is moving into the linear portion of the P-V loop, actual tidal volume becomes larger than anticipated.

The driving pressure should be distinguished from the mean airway pressure, which is a function of inspiratory time, flow, PIP, end-distending pressure, and respiratory rate. Driving pressure provides an insight into respiratory elastic status, whereas mean airway pressure has a direct relationship to oxygenation.

Instrumentation for Pressure Measurement

The pressure sensor used for monitoring airway pressure (PIP and PEEP) in ventilated neonates is an integral ventilator component. The measurement is obtained from a side port where the ventilator circuit connects to the endotracheal tube adapter. This type of pressure sensing is adequate for basic waveform monitoring and for real-time display of pressure-volume loops. Measurement of pulmonary function requires a more dedicated pressure sensor placed close to the measurement point of interest. This can be a differential type that can be used to measure a pressure difference between two points, such as between mouth and pleural pressure (via esophageal balloon or catheter) to yield transpulmonary pressure or between mouth and atmospheric pressure to yield transthoracic pressure for use in calculating combined lung and chest wall mechanics. Two independent transducers, instead of a single differential transducer, are also commonly used for this purpose. A typical measurement range for such pressure transducers is ±50 cm H_2O (±4.9 kPa).

Instrumentation also includes pressure transducer measurements of airway pressure (Paw) and esophageal pressure (Pes). Paw is measured at the proximal airway. Mechanical breaths generate a positive Paw. Conversely, spontaneous breaths generate both negative Paw and negative intrapleural pressure. Direct measurement of intrapleural pressure requires placement of catheters within the pleural space. An indirect means of approximating intrapleural pressure is the measurement of changes in Pes. When a catheter or esophageal balloon is positioned within the lower third of the esophagus, continuous Pes readings can be obtained. The sum of Paw and Pes is the transpulmonary pressure (Ptp), which is essential in the calculation of the pulmonary functions of compliance and resistance. However, studies have shown that the correlation between intrapleural pressure and Pes in very small infants is poor. Therefore, calculations based on estimates of intrapleural pressure determined with the use of Pes measurements should be considered suspect in extremely small infants.

Volume and Flow Signals

Pulmonary Graphic Representation of Tidal Volume

Tidal volume is the volume of each breath as measured during inspiration or expiration or averaged for the entire respiratory cycle. The value should be normalized to body weight or length. During spontaneous breathing, normal values in healthy neonates range from 5 to 10 mL/kg.[8-12] Based on a database of ventilatory parameters measured in our clinical laboratory, the 10th, 50th, and 90th percentile values for these parameters are listed in Table 18-1. Very small preterm infants may have spontaneous breathing tidal volumes as little as 3.2 mL/kg.[13] When measured while the infant is on respiratory support, the resultant tidal volume is highly dependent on ventilator settings; values greater than 8.5 mL/kg have been considered to suggest volume overdistension.[14] Tidal volume observations during mechanical ventilation of an infant should be considered an important monitoring parameter for infant ventilatory support, along with blood gas values and other clinical data. In addition, tidal volume measurement is essential for the determination of compliance.

Pulmonary Graphic Assessment of Minute Ventilation

The summation of individual tidal volumes over a 1-minute period gives us the minute ventilation. This can also be expressed as the product of tidal volume and respiratory rate. Respiratory rates of most preterm and term infants are 20 to 60 breaths/min. A normal full-term newborn infant at rest, breathing at a rate of 40 breaths/min and a tidal volume of 6 to 8 mL/kg, would have a minute ventilation of 320 (mL/kg)/min. Usual normal values range from 240 to 480 (mL/kg)/min.[5] Minute ventilation minus ventilated dead space equals alveolar ventilation.[15] Alveolar ventilation has a direct inverse relationship to alveolar P_{CO_2} or arterial carbon dioxide tension.[16] Thus, at extremes of infant tachypnea (~100 breaths/min or more), tidal volume is reduced, whereas anatomic dead space is unchanged and effective minute ventilation is decreased, as in untreated respiratory distress syndrome (RDS).

Pulmonary Graphic Representation of Inspiratory and Expiratory Airflow

Airflow increases at the initiation of the respiratory cycles, reaches a maximum usually at mid-cycle, and returns to zero flow at the end of each phase (see Fig. 18-2). The location of the peak value depends on the site of maximal airway resistance, such that airflow is measured at its peak rather than at mid-respiratory cycles. Typical peak flow ranges for premature infants are listed in Table 18-1. It is important to differentiate ventilator circuit airflow from the inspiratory and expiratory airflow that traverses the endotracheal tube.

Pulmonary Graphic Representation of Tidal Flow–Volume Relationships

The tidal flow–volume relationship describes the pattern of airflow during tidal breathing. It is characterized by the tidal volume and peak inspiratory and expiratory airflow. Of these, the expiratory airflow pattern for a spontaneous passive breath provides insight into the natural expiratory airflow limitation in a neonate and one that may be exaggerated by airway disease (Fig. 18-4). The location of the flow peaks in relation to the origin of inspiration and expiration and the ensuing pattern provide an insight to subtle changes in flow limitation. Usually, peak inspiratory airflow occurs during mid-inspiration, whereas peak

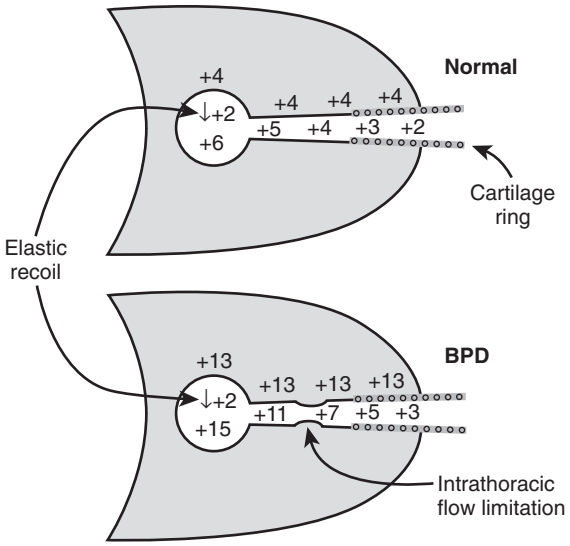

Figure 18-4 ■ Dynamics of passive expiratory flow during spontaneous breathing in a normal term infant (*upper panel*) compared to an infant with bronchopulmonary dysplasia (BPD). Intrathoracic pressures are shown in the shaded areas. Gradient of intra-tracheobronchial pressures are estimated based on likely elastic recoil pressure of the lung and its final equilibration with atmospheric pressure at end-expiration. The elevated intrathoracic pressure at end-inspiration and at the onset of expiration is a reflection of the increased work of breathing and the higher peak inflating pressure generated in an infant with moderate degree of BPD. The lower panel illustrates the mechanism of expiratory flow intrathoracic expiratory flow obstruction by external compression of the compliant airways.

expiratory airflow values precede mid-expiration (Fig. 18-5). Airflow limitation is described as abrupt downward deviation of the flow signal toward baseline and away from its normal direction. A complete flow limitation is defined as 80% or greater reduction of the airflow signal. Actual visual evidence of flow limitation during a specific phase of the respiratory cycle is an important indication of obstructive airway disease. Preterm neonates with compliant airways manifest high expiratory resistance because of expiratory phase airway collapsibility. This accounts for the peak expiratory airflow occurring early in the expiratory cycle and the "ski-slope" effect apparent in the expiratory limb of the tidal flow–volume relationship. A characteristic flow-volume profile for various types of intrathoracic and extrathoracic flow limitation is illustrated in Figure 18-6.

Evidence of expiratory flow limitation is best evidenced from flow-volume loops obtained during a maximum effort maneuver as measured in adults via the forced expiratory volume (FEV_1) test. In the neonate this may be simulated by measuring the partial expiratory flow-volume (PEFV) response using the rapid thoracic compression technique.[8,17-20]

Pulmonary Graphic Representation of Pressure-Volume Relationships

The pressure-volume (P-V) relationship describes the pattern of tidal volume as a function of driving pressure. The slope of the P-V loop represents the elasticity of the lung. Based upon the location of the P-V loop on the total respiratory P-V relationship, the shape of the P-V loop may be altered and may indicate either pressure or volume overdistension (see Fig. 18-3).

The inspiratory and expiratory portions of the P-V loop describe a hysteresis that represents the resistive work of breathing (Fig. 18-7). During spontaneous breathing, when the absolute intrapleural pressure is not known, the origin of this loop cannot be accurately determined (as shown by the off-set on the horizontal axis in Fig. 18-7). Thus it is not feasible to calculate the total work of breathing for spontaneous breaths. In babies with air trapping or obstructive airway disease, the expiratory component of the hysteresis is excessively increased (Fig. 18-7, *B*). The online display of P-V loops is an ideal indicator of endotracheal tube leakage or as gauged by the inspiratory-expiratory volume discrepancy. Generally, any inspiratory-expiratory volume discrepancy should be less than 10%. Large discrepancies may be indicative of a faulty flow signal.

Instrumentation for Flow and Tidal Volume Measurements

Flow Measurement

Several flow-sensing technologies have evolved for measurement of airflow for the purpose of monitoring pulmonary graphics and for pulmonary function determination in small neonates.[22-24] These include the following:

1. *Pneumotachometers.* These are resistive-type devices in which gas flowing through a fixed resistance creates a pressure differential across the resistive element. This pressure difference is easily measured with a sensitive differential pressure transducer. The resistive element can be either a fine mesh screen[21] or a bundle of small capillaries (Fleish type),[25,26] both of which produce a laminar flow that is directly proportional to the measured differential pressure and thus have a linear output over a specific range of airflow.
2. *Nonlinear flow resistive sensors*, such as variable orifice and pitot tube flow sensors. These flow sensors also

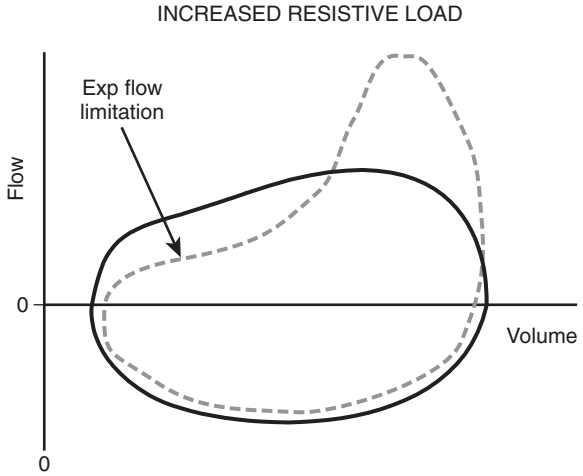

Figure 18-5 ■ Tidal flow–volume loop from a normal term neonate ("lemon-shaped") and a preterm neonate with high expiratory resistance (or compliant airways) illustrates a "ski-slope" effect during expiration.

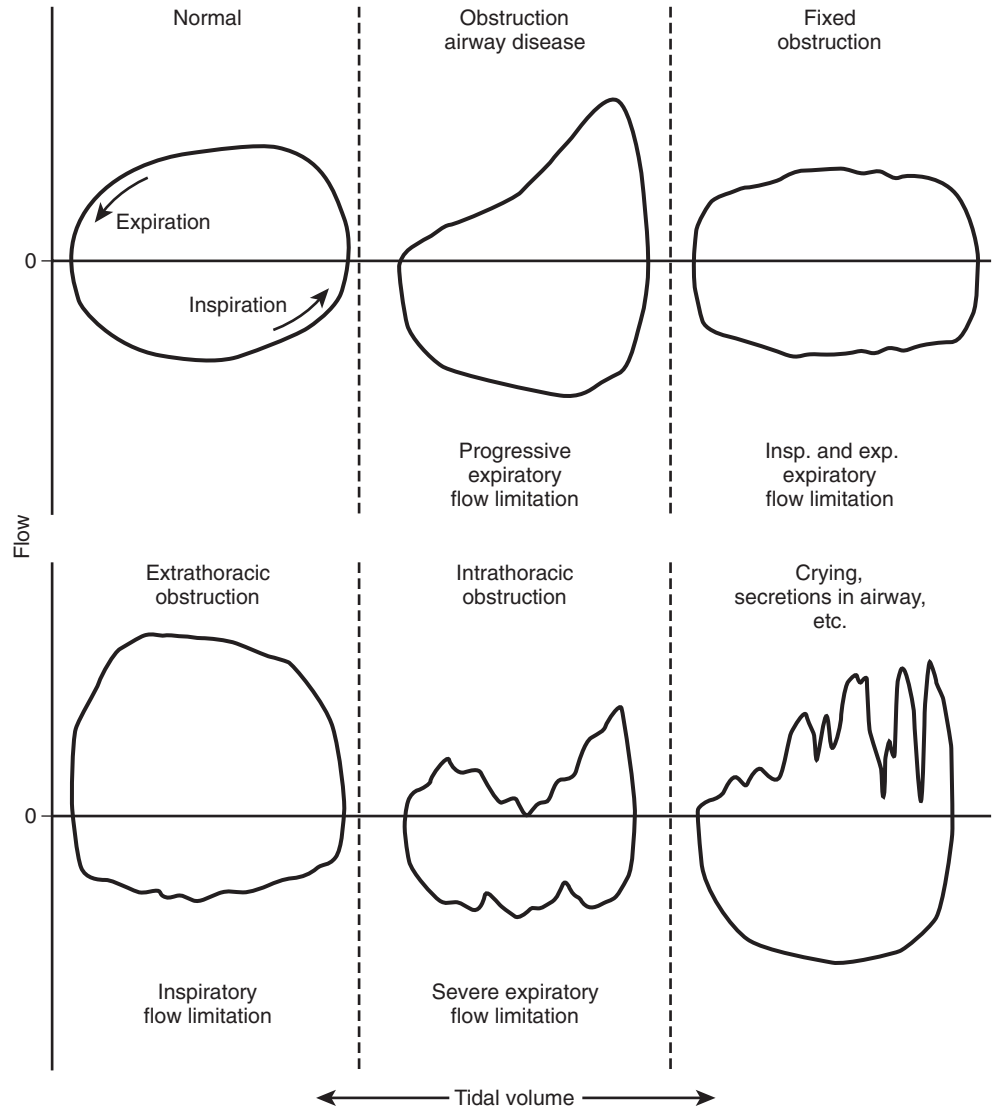

Figure 18-6 ■ Tidal flow–volume loops illustrating different manifestations of flow limitation that results from heterogeneity in airway resistance. **A,** Normal loop. **B,** "Ski-slope" loop observed with expiratory airflow limitation as seen in babies with bronchopulmonary dysplasia. **C,** Extrathoracic airway obstruction with inspiratory and expiratory airflow limitation as seen in babies with subglottic stenosis or narrow endotracheal tubes. **D,** Intrathoracic inspiratory airflow limitation as seen in babies with intraluminal obstruction (close to the carina) or an aberrant vessel compressing the trachea. **E,** Unstable airways or tracheomalacia. **F,** This type of loop usually is suggestive of an erratic airflow limitation, as seen with airway secretions.

require measurement of a pressure difference produced by gas flowing through a tube; however, the flow-pressure relationship for these devices is nonlinear.

3. *Flow sensors that use a piezoelectric film* to detect the turbulence produced in a gas stream. Vibration of the film results in an electrical output proportional to the flow.
4. *Anemometers.* These devices operate on the principle of measuring the amount of electrical current needed to maintain a given temperature in a fine heated wire suspended across an air stream. The added current increases as the airflow increases and more heat is dissipated, but the relationship is nonlinear as well as insensitive to flow direction.

The conventional pneumotachometer is a simple device having very linear input-output characteristics and can be easily and precisely calibrated. It may have a relatively significant dead space for a neonate's tidal volume. Thus the pneumotach is appropriate when performing discrete pulmonary function tests, but it is inappropriate for continuous airflow monitoring. The alternative flow-sensing devices mentioned earlier have the disadvantage of being either nonlinear, nondirectional, or both; thus they require more sophisticated signal conditioning and calibration techniques. Nonetheless, these sensors have the advantage of generally being lighter and smaller than pneumotachometers and have less dead space; thus they are more suitable for continuous monitoring of mechanically ventilated babies. In these infants, the airflow sensor is placed between the endotracheal tube connector and the ventilator circuit connection. Usually a heater is incorporated into the sensor to prevent condensation of water vapor, which can otherwise affect system response and accuracy. For

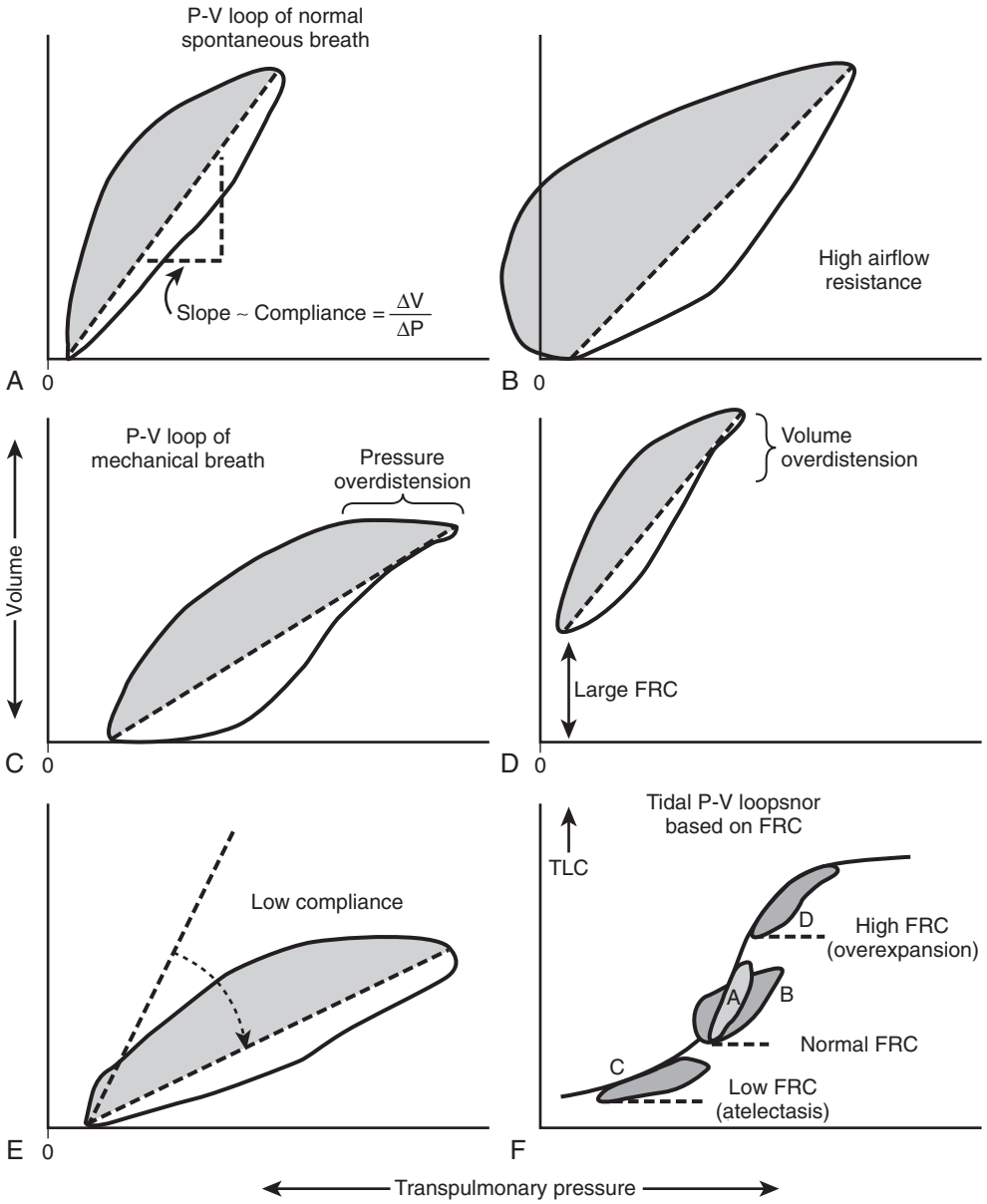

Figure 18-7 ■ Pressure-volume (P-V) relationships illustrations show components of inspiratory elastic work and inspiratory elastic and resistive work. **A,** a normal P-V relationship. **B,** Increased expiratory resistive work (such as, obstructive airway disease, meconium aspiration syndrome or bronchopulmonary dysplasia). **C,** Increased expiratory resistive work with excessive inspiratory pressure (such as overdistension due to high positive inspiratory pressure or high tidal volume). **D,** Increased expiratory resistive work due excessive functional residual capacity (such as overdistension, due to air-trapping, shortened expiratory time, etc). **E,** Decreased inspiratory elastic work (such as, respiratory distress syndrome, pneumonia, atelectasis, etc). **F,** Comparison of P-V relationships affected by the functional residual capacity.

spontaneous breathing measurements, the flow sensor is commonly attached to a snug-fitting face mask. To avoid tidal volume augmentation and changes in breathing pattern due to increased dead space and resistance, as well as the effect of facial stimulation[27] of the typical face mask and pneumotachometer apparatus, some investigators have used nasal prongs or nasal masks, although neonates are not necessarily obligate nasal breathers.[28] The specified measurement range of the flow sensor should be close to the expected flow range to be measured. Flow ranges can be as low as ±20 mL/sec for small prematures, up to ±400 mL/sec for ventilated infants depending on the ventilator waveform, and ±200 mL/sec for spontaneously breathing newborn infants.[29] To maintain accuracy, all flow sensors should be periodically checked for buildup of secretions and cleaned and recalibrated regularly. It should be noted that gas composition, temperature, and humidity can have significant effects on flow sensor accuracy if they are not properly corrected or compensated.[30-32]

Volume Measurement

For continuous monitoring, volume can be easily measured indirectly as the integral (i.e., area under the curve) of the flow signal. The integration can be performed electronically or digitally in computerized systems. The inspiratory and expiratory portions of measured tidal volume

signal will necessarily be different because inspiratory gas differs from expiratory gas in O_2 and CO_2 composition, water vapor, temperature, and viscosity.[31,32] In addition, flow sensors do not always have perfectly symmetrical inspiratory and expiratory response characteristics. Because of these reasons, the volume signal typically demonstrates a small baseline drift. However, differences in inspiratory and expiratory tidal volumes larger than 10% could be indicative of airflow leakage around the endotracheal tube. Large differences could indicate faulty flow sensor readings due to factors such as water vapor condensation, buildup of secretions, calibration drift, and integrator drift and should be investigated.

Signal Calibration

All monitoring or testing instruments require calibration for maintenance of accuracy and reproducibility. Reproducibility can be hampered by changes in the observed condition between tests, by errors of measurement, or by errors of calibration. Calibration, which determines the relationship between the output signal of a transducer and a known input signal, should be performed under both static and dynamic conditions and over the frequency and amplitude ranges of neonatal ventilation. For this purpose, only calibration reference standards that have certifiable accuracy should be used. In clinical practice, graduated or calibrated syringes, precise ball-in-tube flowmeters, water column manometers, and reference transducers are generally used. Linearity is a measure of how well the output-to-input ratio is maintained over a given measurement range for a transducer. Operation of an instrument outside its linear calibration range results in erroneous measurements. Use of the properly ranged flow sensor is crucial for accurate measurement of infant flow dynamics. Finally, it is important to carefully follow the manufacturer's procedures and guidelines for maintenance and calibration of a device or system.

Pulmonary Mechanics

Lung Compliance

If pressure is sequentially decreased (made more subatmospheric) around the outside of an excised lung, the lung volume increases. When the pressure is removed from the lung, it deflates along a pressure-volume curve that is different from that during inflation. The difference between the inflation and deflation levels of the pressure-volume curve is called *hysteresis*. The elastic behavior of the lungs is characterized by this pressure-volume curve (see Fig. 18-7, *A*). More specifically, the ratio of change in lung volume to change in distending pressure defines the compliance of the lungs. Although the pressure-volume relationship of the lung is not linear over the entire range, the compliance (of slope $\Delta V/\Delta P$) is linear over the normal range of tidal volumes beginning at functional residual capacity (FRC). Thus, for a given change in driving pressure, tidal volume will increase in proportion to lung compliance, or $\Delta V = C \times \Delta P$.

As lung compliance is decreased, the lungs become stiffer and more difficult to expand. When lung compliance is increased, the lung becomes easier to distend and is more compliant. Lung compliance and pressure-volume relationships are determined by the interdependence of elastic tissue elements and alveolar surface tension. Tissue elasticity depends on elastin and collagen content of the lung. A typical value for lung compliance in a young healthy newborn is 1.5 to 2.0 mL/cm H_2O/kg. This value depends on the size of the lung (mass of elastic tissue). As can be expected, the compliance of the lung increases with development as the tissue mass of the lung increases. Based upon where the driving pressure is measured, the compliance of that structure can be described as follows:

$$\text{Total Compliance (chest + lung)} = \text{Tidal Volume/Change in Driving Pressure} \quad (3)$$

where the change in driving pressure is the net driving pressure for the entire respiratory system.

In ventilated neonates the driving pressure can be measured as the airway pressure at the mouth while the infant is connected to a mechanical ventilator. During respiratory cycles of consecutive breaths, the equilibration of changes in pressure and volume may have yet to be completed at the termination of airflow. Thus the respiratory mechanics are probably still in a dynamic state. Therefore:

$$\text{Dynamic Lung Compliance} = \text{Tidal Volume/Change in Driving Pressure} \quad (4)$$

where driving pressure is the gradient between PIP and PEEP or the peak-to-peak pressure. This is the net driving pressure used to expand the lungs. The dynamic compliance overestimates the actual "static" compliance when the pressure measurements are underestimated. On the other hand, a slower equilibration of tidal volume may result in underestimation of dynamic compliance.

From a clinical perspective, the dynamic compliance is likely to be overestimated when there is an impaired surface activity, as with RDS. In babies with bronchopulmonary dysplasia (BPD), the associated resistive load may lead to underestimation of tidal volume and thereby of lung compliance. In both of these conditions, the baby has to generate a higher driving pressure to achieve a similar tidal volume, otherwise hypoventilation would occur. In assessing the elasticity of a "stiff lung," estimation of dynamic compliance can be erroneous. On the other hand, the dynamic compliance measurement may be useful because it provides the clinician with an index of the volume change that is likely to occur for every 1 cm H_2O change in driving pressure, provided the lungs are operating in a linear pressure-volume relationship. This assumption should be valid and anticipated during tidal breathing at optimal FRC.

Resistive Properties

Nonelastic properties of the respiratory system characterize its resistance to motion. Because motion between two surfaces in contact usually involves friction or loss of energy, resistance to breathing occurs in any moving part of the respiratory system. These resistances include frictional resistance to airflow, tissue resistance, and inertial forces. Lung resistance is predominantly (80%) attributed to

frictional resistance to inspiratory and expiratory airflow in the larger airways. Tissue resistance (19%) and inertial forces (1%) also influence lung resistance. Airflow through the airways requires a driving pressure resulting from changes in alveolar pressure. When alveolar pressure is less than atmospheric pressure (during spontaneous inspiration), air flows into the lung. When alveolar pressure is greater than atmospheric pressure, air flows out of the lung. By definition, resistance to airflow is equal to the resistive component of driving pressure (P_R) divided by airflow ($\dot{V}$). Thus:

$$\text{Resistance} = P_R \Big/ \dot{V} \quad (5)$$

When determining lung resistance, the resistive component of the measured transpulmonary pressure is used as the driving pressure (see Fig. 18-2). To measure airway resistance, the differential between alveolar pressure and atmospheric pressure is used as the driving pressure. Under normal tidal breathing conditions, there is a linear relationship between airflow and driving pressure. The slope of the flow versus pressure curve changes as the airways narrow, indicating that the patient with airway obstruction has a greater resistance to airflow. The resistance to airflow is greatly dependent on the size of the airway lumen. According to Poiseuille's law, the resistive pressure (ΔP) required to achieve a given flow ($\dot{V}$) for a gas of viscosity and flowing through a rigid and smooth cylindrical tube of specific length (L) and radius (r) is given as follows:

$$\Delta P = 8\mu L\dot{V} \Big/ \pi r^4 \quad (6)$$

According to this relationship, resistance to airflow increases by a power of four with any decrease in airway radius. Because the newborn airway lumen is approximately half that of the adult, the neonatal airway resistance is about 16-fold that of the adult. Normal airway resistance in a term newborn is approximately 20 to 40 cm H_2O/L/sec, which is about 16-fold the value observed in adults (1 to 2 cm H_2O/L/sec). Also, the hysteresis of the pressure-volume relationship represents the resistive work of breathing and can be separated into inspiratory and expiratory components.

In babies with obstructive airway disease, the expiratory component of resistive work of breathing is increased (see Fig. 18-7, *B* and *C*). Nearly 80% of the total resistance to airflow occurs in large airways up to about the fourth to fifth generation of bronchial branching. The patient usually has large airway disease when resistance to airflow is increased. Because the smaller airways contribute a small proportion of total airway resistance, they have been designated as the silent zone of the lung in which airway obstruction can occur without being readily detected. Unlike babies with RDS, babies with BPD (because of the associated airway barotrauma) have higher values of airway resistance with an associated increased resistive work of breathing.

Synchronous and Asynchronous Breathing

Real-time evaluation of synchronous respiratory cycles allows for visualization of successive P-V and $\dot{V}$-V loops as they superimpose neatly over each preceding loop. Asynchrony of respiratory cycles may be evident during airway obstruction (secretions, bronchospasm), "bucking" (during mechanical ventilation or involuntary Valsalva maneuvers), and during agitation (pain, excessive handling, impaired gas exchange). Objective evaluation of asynchrony is difficult to quantify. On the other hand, synchronous ventilation is easily observed.

Relationship of Oxygenation to Mean Airway Pressure

Other manifestations of pulmonary graphics include the visual interpretation of the relationship of arterial oxygenation to changes in mean airway pressure. Enhancements in bedside ventilatory software can easily provide the clinician with such data.

Relationship of Carbon Dioxide Elimination to Alveolar Ventilation

The relationship of arterial carbon dioxide tension to alveolar ventilation is feasible, provided no change in dead space has occurred during the phase of evaluation. The relationship between the driving pressure and alveolar ventilation and then to arterial carbon dioxide tension is feasible but requires a specially designed software program.

Role of Pulmonary Functions in Bedside Ventilator Management

Bedside evaluation of history, clinical assessment, blood gas, and acid-base profiles and the interaction of the baby with any supportive respiratory devices enhance the bedside application of pulmonary physiologic principles, especially for a neonate with respiratory distress. The noninvasive assessment of the three respiratory signals provides objective, valuable, online data that may be used in an adjunctive manner to monitor, interpret, and define the severity of dysfunction.[33] These data do not provide a clinical diagnosis, but they can be useful in the following situations: (1) evaluation of alteration and/or limitation in inspiratory/expiratory airflow; (2) evaluation of driving pressure, work, and effort to maintain minute ventilation; (3) evaluation and calculation of the elastic and resistive components of pulmonary dysfunction; (4) calculation of the inspiratory, expiratory, and total lung time constants; (5) evaluation of the interaction between spontaneous breathing and conventional mechanical ventilation, including continuous positive airway pressure (CPAP); (6) evaluation of the degree of response to a therapeutic intervention; and (7) evaluation of the evolution and resolution of the respiratory disease.

Optimizing Peak Inflating Pressure

If a baby is being managed on a pressure-limited ventilator, visualizing the concomitant tidal volume may corroborate the selection of a chosen PIP. A suggested goal would be to initially ventilate at the low "normal" value of tidal volume (such as 5 to 6 mL/kg). This provides for a more objective approach than choosing the PIP on the basis of auscultation for adequate breath sounds during manual ventilation. Similarly, the tidal volume actually delivered to a neonate can be measured when setting the volume support during volume-controlled ventilation.

Optimizing Positive End-Expiratory Pressure

It is feasible to define an optimal end-distending pressure using pulmonary graphics; however, the process is complex and at present not user friendly. Using a combination of the effects of driving pressure on tidal volume and visual changes in P-V relationships, one can ascertain whether incremental changes in PEEP lead to pulmonary overdistension or underdistension or moving to a linear component of the P-V relationship (see example in Fig. 18-3). Because the clinical goal is to ventilate at the linear portion of the P-V loop, bedside incremental changes in PEEP should only be done by experienced clinicians who can accurately assess the changes in measured data and thereby calculate the impact of PEEP manipulation. It is important to remember that at the end of passive expiration, the airway pressure equilibrates with the atmospheric pressure unless the infant exhales against a closed glottis.

Optimizing Expiratory Airflow

To better optimize FRC, defined by the volume and gas exchange surface area of the lung during expiration, the influences of time determinants for inspiration or expiration must be considered. Of these, adequate exhalation is important but is significantly affected by flow-resistive and elastic properties of the lung. Resistive loads would slow the equilibration time whereas elastic loads hasten the equilibration time. The key to successful ventilation is the delivery of the minimum level of ventilatory support to allow breathing at the baby's FRC.

The lung volume at which respiratory cycling occurs during spontaneous breathing, that is, the FRC, is about 40% of total lung capacity. Thus, for healthy term infants, a value of about 30 to 35 mL/kg represents the most linear component of the static pressure-volume (P-V) relationship of the lung. The challenge in caring for a sick newborn is that the FRC of a baby alters unpredictably with varying respiratory elastic and resistive loads. These phenomena are evident in infants with evolving BPD who manifest varying combinations of both elastic and resistive lung diseases. Resistive loads caused by mechanical ventilation–induced barotrauma further augment the fluctuations in FRC. Thus indirect estimates of FRC (other than chest radiographs) rely on interpretation of pulmonary graphics (identification of tidal P-V overdistension), tidal breathing flow-volume-loop described as the ratio of time to peak tidal expiratory flow and expiratory time (tPTEF/tE) (Fig. 18-8) and measures of tidal volume with incremental changes of driving pressure and online observations of flow-volume relationships. The decreased tPTEF/tE in BPD is suggestive of a lower compliance with increasing disease severity. As noted by the authors of this study,[34] tPTEF/tE reflects the neuromuscular response to respiratory mechanics. Thus, it is determined by the importance of establishing a stable FRC as defined by the underlying mechanical properties of the respiratory system and the interdependence between respiratory timing, modulation of expiratory flow, and dynamic elevation of lung volume.

Optimizing Circuit Airflow

Usually the setting of the circuit airflow of the ventilator has not been an active decision made by the clinician, but instead has been based upon manufacturer's guidelines. It is well known that excessive circuit airflow can lead to

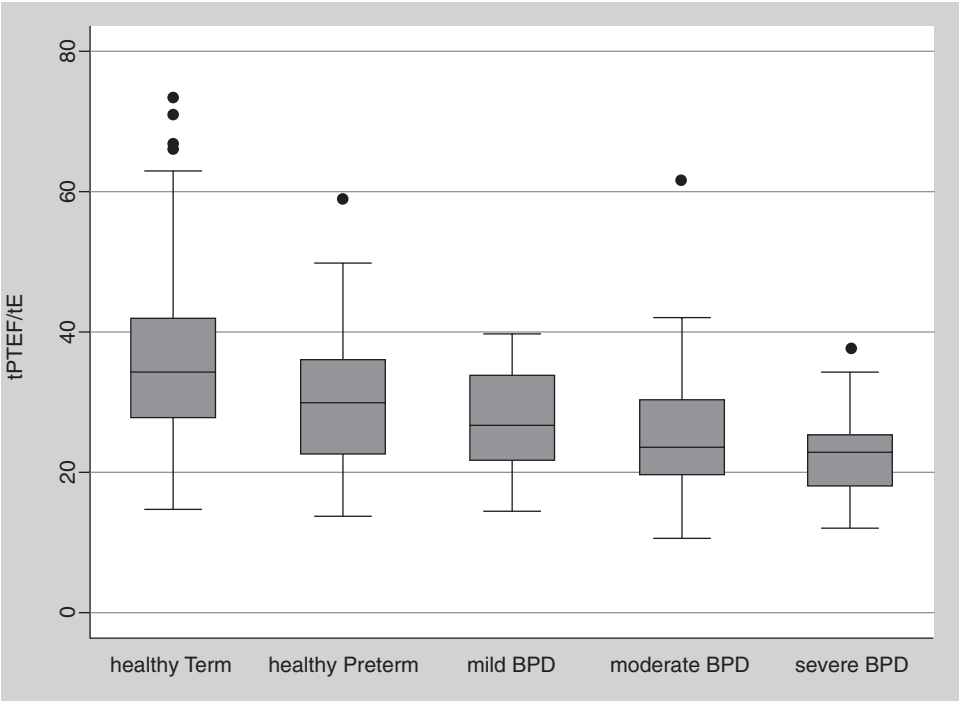

Figure 18-8 ■ The tidal breathing flow-volume loop described as the ratio of time to peak tidal expiratory flow (tPTEF) and expiratory time (tPTEF/tE). Box plots (median and the 25th and 75th percentiles) for subject groups for term and preterm infants using American Thoracic Society (ATS) definition of bronchopulmonary dysplasia (BPD). Outliers are shown as individual dots. *p*-value less than 0.001 for trend (by regression analysis). (Modified from Latzin P, Roth S, Thamrin C, et al: PLoS ONE 4[2]:e4635 [online journal].)

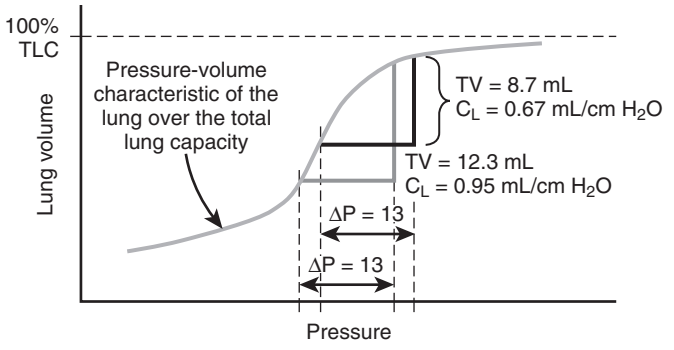

Figure 18-9 ■ Illustration of deflation pressure-volume (P-V) relationship over the total lung capacity (*shaded sigmoid line*) with superimposed demarcators of positive end-expiratory pressure and peak inflating pressure (delta pressure change), lung volume at end-expiration (functional residual capacity), and measured values of tidal volume and calculated dynamic lung compliance. Two scenarios are presented to show effect of ventilation at "flattened portion" of the P-V relationship with excessive ventilator circuit airflow settings.

overdistension and inadvertent excessive PEEP. Both of these effects would lead to hypoventilation and subsequent hypercapnia. The pulmonary graphic manifestations would be lower tidal volumes (Fig. 18-9), wider pulmonary hysteresis, pressure overdistension, and perhaps turbulence in the airflow signal. These would be immediately corrected by a bedside maneuver to reduce the circuit airflow. Another option for setting the circuit airflow is to base the setting on eightfold of the desired minute ventilation (tidal volume and respiratory frequency).

Optimizing Inspiratory Time

Inspiratory time can be increased or decreased (and thereby the expiratory time can be altered as well) by the physician as a response to change in the mean airway pressure and oxygenation. These clinical decisions usually are made based on the physiologic understanding of respiratory time constants (product of compliance and resistance). In addition to the impact on oxygenation, the concomitant and often indirect beneficial or deleterious effects of the new inspiratory time can be assessed by pulmonary graphics. These include the effects on tidal volume, inspiratory and expiratory hysteresis, pressure-volume relationship (such as overdistension from excessive mean airway pressure), and flow-volume relationships (such as expiratory flow limitation from excessive and inadvertent PEEP) as sequelae of shortened expiratory time. Infants with predominantly elastic loads need lower durations of inspiratory time (usually less than 0.4 sec). On the other hand, infants with resistive loads require longer duration of inspiratory time (usually greater than 0.5 sec). Acute changes in resistive loads, such as airway diseases, requires the bedside clinician to make dramatic manipulations in the level of inspiratory support. Remember, there are only 60 seconds in a minute. Because exhalation should ideally be longer than inspiration time, vigilance on respiratory rates (assisted and spontaneous) is essential during the management of these critically ill infants to avoid inverse inspiratory to expiratory ratios.

Optimizing Synchrony and Rate of Ventilatory Support

Real-time evaluation of synchronous ventilation on the graphic displays is helpful for nurses, respiratory therapists, and physicians to assess nonventilatory means to correct asynchronous ventilation. The clinical value of the visual display allows for early response to a neonate's discomfort. Babies who continue to "buck" the ventilator and are not amenable to bedside comforting and nursing measures may demonstrate their response to ventilatory technologies such as patient-triggered ventilation (see Chapter 12).

Optimizing Tidal Volume

The tidal volume is evident with placement of the pneumotachometer, and the digital readout provides the variability that is evident among spontaneous, mechanical, and augmented breaths. In fact, the optimal PIP can be ascertained by adjusting to appropriate tidal volume (thereby providing a more objective assessment to auscultation). In a clinical condition, when the baby is breathing synchronously with the ventilator or when spontaneous breathing has been diminished or abolished, the steady measures of tidal volume provide clinically useful information. First, when the tidal volume value is between 5 and 8 mL/kg and there are no signs of pressure-volume overdistension, the clinician may ascertain that ventilation is at optimal FRC. Incremental changes (by 1 cm H_2O) in PEEP and PIP (such that the driving pressure is unchanged) should not result in an appreciable change in tidal volume. The rationale for this observation is that if the baby is being ventilated at optimal FRC (at the linear component of the respiratory P-V curve: see Fig. 18-3), slight movements along the curve should maintain the tidal volume. Second, if the tidal volume is less than 5 mL/kg, the baby is being ventilated at either a low lung volume (increase in PIP would improve the tidal volume) or a high lung volume (decrease in PIP would actually improve the tidal volume). Finally, if the tidal volume is in excess of 8 mL/kg, both P-V and flow-volume curves should be evaluated for pulmonary overdistension and increased resistive work of breathing.

Optimizing Inspired Oxygen

The process of plotting serial arterial blood gases on the P_{O_2}-P_{CO_2} nomogram provides the clinician a perspective on the extent of variation induced by either the disease or the operator. Operator-driven swings in oxygenation may be minimized by prospective decisions (such as use of the alveolar gas equation) or by invoking changes in a cautious and incremental manner.

Optimizing Ventilatory Strategies for Permissive Hypercapnia

The relationship between alveolar ventilation and arterial carbon dioxide tension is incredibly linear and can be used as an advantage in defining desired goals for "permissive" hypercapnia. Selection of a P_{CO_2} value of 50 torr in lieu of the "normal" 40 torr is a choice of defining a 25% deviation; this may indicate hypoventilation by 25%. This decision could be an elective clinical maneuver, but the

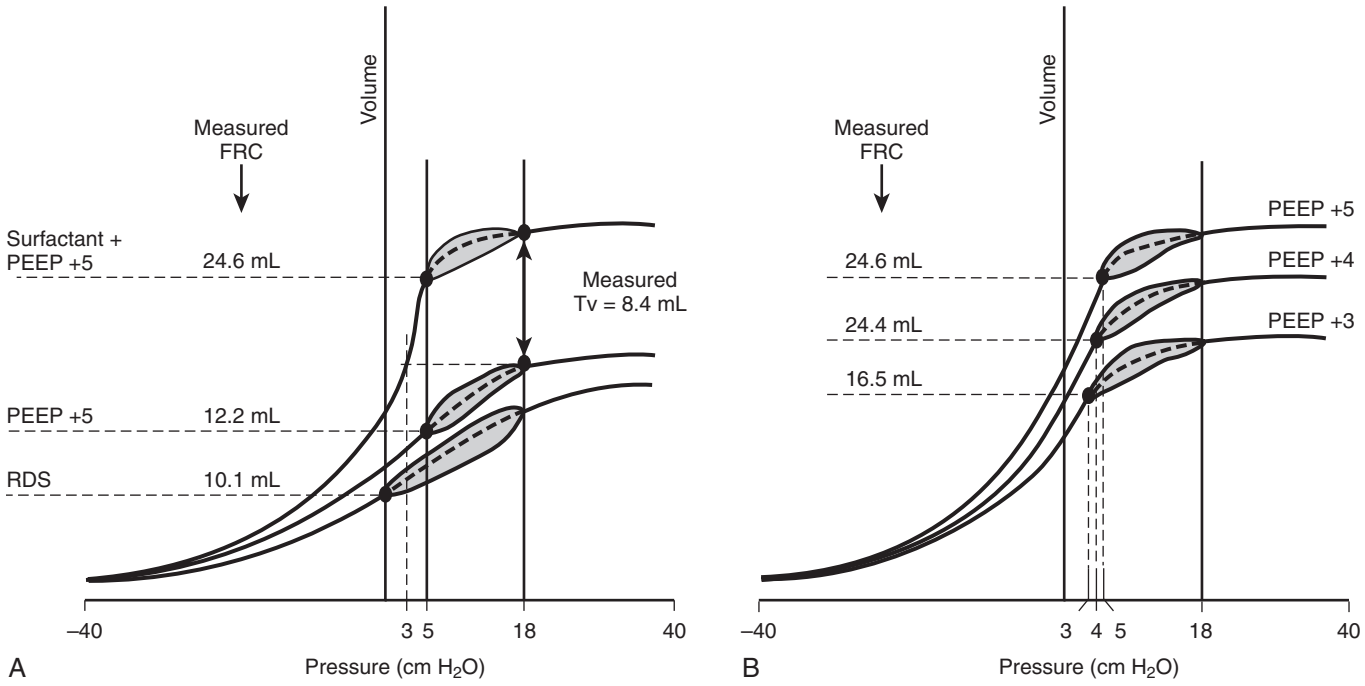

Figure 18-10 ■ Data obtained from a clinical case (birth weight = 980 g and GA = 27 weeks) to illustrate the interactions of incremental changes in PEEP, use of surfactant and combined effects of PEEP and surfactant on pressure-volume relationships and tidal volume while PIP is maintained at 18 cm H_2O. Each data set is illustrated by superimposing a theoretical deflation pressure-volume relationship over the total lung capacity. (Modified from Bhutani VK, Bowen FW, Sivieri E: Biol Neonate 887:323-331, 2005.)

clinician needs to ensure that the decision is not a passive one such that atelectatic lungs are being ventilated. Again, the plotting of serial blood gases on a P_{O_2}-P_{CO_2} nomogram provides the clinician with a direct visual impact of the recent gas exchange history such that prospective decisions are made consciously and conscientiously. Case 3, described below, suggests an alternate strategy by weaning from an overdistended lung volume and defining a lower driving pressure to achieve permissive hypercapnia.

Clinical Case Studies: Bedside Application of Pulmonary Graphics

Case 1 NEWBORN WITH RESPIRATORY DISTRESS SYNDROME TREATED WITH END-DISTENDING PRESSURE AND SURFACTANT

A male infant was born at 28 weeks of gestation with a birth weight of 980 g. He was delivered emergently by cesarean section because of placental abruption. Following resuscitation, the baby was placed on ventilatory support: PIP = 18 cm H_2O, PEEP = 5 cm H_2O, and synchronized intermittent mandatory ventilation (SIMV) = 40/min. Surfactant was administered at about 1 hour of age. Pulmonary graphics (P-V loops) were recorded and FRC measurements were made as the baby was placed on ventilatory support and prior to changes in PEEP at 3, 4, and 5 cm H_2O (Fig. 18-10). Pre-PEEP and presurfactant FRC = 10.1 mL (~11 mL/kg). Post-PEEP (5 cm H_2O) and presurfactant FRC = 14.2 mL (~14 mL/kg) with slight improvement in tidal volume and pulmonary compliance (steeper slope of the P-V loop). Postsurfactant FRC = 24.6 mL (~24 mL/kg), but the improvement in tidal volume and compliance were masked by the PEEP as evidenced by a flatter (overdistended) P-V loop. Serial reduction of PEEP to 3 and 4 cm H_2O showed FRC = 16.5 and 20.4 mL, respectively, and improvement in compliance (as evidenced by steeper and less overdistended P-V loops). Note that the selection of optimal PEEP value also depends on its effect on oxygenation.

Case 2 NEWBORN WITH BRONCHOPULMONARY DYSPLASIA AND AIRWAY INSTABILITY (POSSIBLE TRACHEOBRONCHOMALACIA)

A male infant was born at 26 weeks of gestation with a birth weight of 740 g. The mother delivered by cesarean section because of pregnancy-induced hypertension, and she was treated with one dose of

betamethasone. The infant had been treated with surfactant in the delivery room, with follow-up doses at 12 and 24 hours of age. Mechanical ventilatory support was initiated with PIP = 16 cm H_2O, PEEP = 4 cm H_2O, and SIMV = 40/min. The baby was extubated to CPAP at approximately 4 days of age and reintubated at day 7 for intractable apnea for 10 days. By 4 weeks of age, the baby was oxygen dependent and had increased work of breathing and radiographic changes of BPD. Serial pressure-volume loops at serial intervals over 4 weeks showed increasing expiratory resistive work with a widened pulmonary hysteresis. By 4 weeks of age, the baby had increased resistive work with both elastic and resistive loads (as illustrated in Fig. 18-7).

Case 3 STUDY OF WEANING STRATEGY IN A NEWBORN WITH RESPIRATORY DISTRESS SYNDROME ON VENTILATORY SUPPORT

At 6 hours of age, this 1350-kg male neonate with RDS was treated with surfactant and was placed on ventilatory support of PIP = 18 cm H_2O, PEEP = 5 cm H_2O, SIMV = 35 breaths/min, and F_{IO_2} = 0.55. Arterial blood gas was pH = 7.32, P_{aO_2} = 82 torr, and P_{aCO_2} = 54 torr. Measured tidal volume (by pneumotachography) = 8.7 mL (6.4 mL/kg). By calculation, driving pressure was 18 (PIP) – 5 (PEEP) = 13 cm H_2O; thus the effective compliance of the baby on a ventilator = ÄV/ÄP or 8.7/13 mL/cm H_2O = 0.67 mL/cm H_2O. Therefore, any 1 cm H_2O change in driving pressure leads to a change in volume of 0.67 mL. Bedsides weaning, theoretical options could include the following:

1. Make no changes.
2. Reduce PIP by 1 cm H_2O (to 17 cm H_2O) and the driving pressure (at 17 – 5) = 12 cm H_2O.
3. Reduce PEEP by 1 cm H_2O (to 4 cm H_2O) and the driving pressure (at 18/4) = 14 cm H_2O.
4. Change SIMV and thus alter minute ventilation and alveolar ventilation.

The impact on tidal volume can be calculated and confirmed by actual measurement. If the baby is being overventilated at the upper and flatter ends of the P-V slope (as shown in Fig. 18-9), the change in the actual tidal volume will be disproportionate to the expected change (as determined from the "effective compliance").

An alternative option could be a dual wean: reduce PIP/PEEP (wean both from 18/5 to 17/4 cm H_2O) such that the driving pressure is unchanged = 13 cm H_2O. If the baby is being ventilated at the upper and flatter ends of the P-V slope, a dual wean will result in "moving" down to a more linear part of the P-V slope and a marked improvement in the tidal volume, disproportionate to that anticipated because there is now a change in the driving pressure and no change in tidal volume is expected. Based on bedside calculations ("alveolar algebra" for pulmonary mechanics), the baby could be subsequently and effectively weaned to a lower driving pressure. Note that the weaning of PEEP may suboptimally decrease FRC. Thus any weaning of PEEP should be monitored for its effect on oxygenation.

Theoretical Alveolar Algebra: Pulmonary Mechanics (an example)

Compliance = Δ volume/Δ pressure
Δ of 1 cm H_2O leads to a Δ in volume
Compliance = 8.7 mL/13 cm H_2O = 0.67 mL/cm H_2O
Δ of 1 cm H_2O leads to Δ in volume = 0.67 mL
Δ of 1 cm H_2O to 16/4 will decrease tidal volume (TV) to ~8 mL
Δ of 1 cm H_2O to 15/4 will decrease tidal volume to ~7.3 mL
Δ of 1 cm H_2O to 14/4 will decrease tidal volume to ~6.6 mL

Thus effective driving pressure = 10 cm H_2O may deliver a theoretically lower tidal volume. Yet, if the actual measured tidal volume is disproportionately higher than calculated, it is possible the infant was being ventilated at an overdistended lung volume.

Case 4 VERY PRETERM NEWBORN WITH RESPIRATORY DISTRESS SYNDROME BEING VENTILATED WITH EXCESSIVE CIRCUIT AIRFLOW

Baby boy, a 540-g neonate, at 16 hours of age had received two doses of surfactant and was on ventilatory support for RDS with PIP = 20 cm H_2O, PEEP = 5 cm H_2O, SIMV = 60/min, and F_{IO_2} = 0.66. Arterial blood gases were P_{O_2} = 72 torr, P_{CO_2} = 58 torr, and pH = 7.29. Chest radiograph showed evidence of pulmonary interstitial emphysema. Clinicians were considering increasing the level of support or using high-frequency ventilation and an additional dose of surfactant. Another option would be to reduce the circuit airflow (which is generally adjusted to eightfold of minute ventilation). In this baby, a reduction of the circuit air flow from 8 to 4 L/min could lead to an appreciable reduction of the inadvertent PEEP such that subsequent reductions in PIP and PEEP (dual wean, as described earlier) would allow for lowered levels of driving pressure. The resultant reduction in volutrauma/barotrauma possibly was related to the "flow" overdistension (rheotrauma). In such a clinical situation, the hypercapnia and the pulmonary air leak may be iatrogenic.

Outcome Measures for Using Online Pulmonary Functions

Presently there are no evidence-based studies indicating that optimization of ventilatory support, reduction in pressure-related barotrauma, volume, or airflow overdistension, or reduction in alveolar hyperoxemia would reduce the severity or incidence of chronic lung disease. Even though this effect may be conjectured based on the

TABLE 18-3 Pulmonary Mechanics and Energetics at Term PMA of Surviving Infants with RDS Who Received Surfactant Replacement Immediately After Birth

Gestational age (weeks)	Term PMA week	Pulmonary Compliance (Cl) mL/cm H_2O/kg	Pulmonary Resistance (Rt) cm H_2O/l/sec	Tidal Volume mL	Flow-Resistive Work (g·cm/kg)
≤ 26 weeks (n = 25)	38.7	2.6 ± 0.09	61 ± 41	13.3 ± 4.1	29 ± 19
27-28 weeks (n = 35)	38.8	2.4 ± 0.08	59 ± 31	14.3 ± 4.2	29 ± 20
29-30 weeks (n = 38)	39.9	2.6 ± 1.3	57 ± 31	15.2 ± 4.4	30 ± 19
≥ 31 weeks (n = 59)	38.0	2.1 ± 0.6	40 ± 20	14.4 ± 4.7	25 ± 18

Data from Bhutani VK, Bowen FW, Sivieri E: Biol Neonate 87:323-331, 2005.
PMA, postmenstrual age (weeks)*; RDS,* respiratory distress syndrome.

fundamental principles of pulmonary physiology and clinical acumen, such evidence still needs to be gathered. Dysfunction in lung volume maturation, ventilation inhomogeneity, and tidal breathing parameters, as measures of lung function outcome, are influenced by intrauterine growth, maturity at birth, physical anthropometry, and disease severity after preterm birth (Tables 18-3 and 18-4). Contemporary concepts of disturbed lung growth after preterm birth suggest that a significant proportion of the abnormal lung function associated with chronic lung disease can be accounted for by the degree of prematurity and intrauterine growth.[34,35]

In view of disproportionate postnatal growth patterns, multivariable analyses are needed to account for the multiple complex and interacting determinants of lung function and to distinguish the effects of prematurity and lung disease from those of growth and development. Limitations in designing such studies may be attributed to ability to achieve clinical consensus, to define appropriate monitoring endpoints for respiratory and alveolar barotrauma, and to shift the emphasis from the ventilator (equipment) to the ventilator (the clinician at the bedside). In the meantime, a clinician needs to be guided to a fundamental principle of neonatal ventilation: use the least possible level of support to maintain adequate gas exchange in an expanded lung. Pulmonary graphics help to achieve this principle, serving as a road map and not as directives for neonatal ventilation.

TABLE 18-4 Lung Function Assessment Prior to Discharge in UK-Australian Study*

	Full Term	Preterm	RDS	BPD
Number of infants	64	59	54	42
PMA (weeks)	44.2 (1.4)	40.2 (4.1)	39.7 (4.3)	41.3 (3.8)
Length (cm)	54.6 (2.8)	48.7 (4.3)	47.8 (4.6)	47.5 (3.9)
FRC (mL/kg)	18.4 (3.6)	22.1 (6.0)	21.2 (5.4)	17.5 (4.8)
Vt (mL/kg)	6.8 (1.3)	7.2 (1.2)	6.6 (1.5)	6.0 (1.0)
RR (/min)	47 (12)	53 (13)	53 (14)	59 (16)
MV (mL/kg)	311 (57)	362 (87)	336 (74)	345 (83)

Data from Hüskamp G, Lum S, Stocks J, et al: Thorax 64:240-245, 2009.
*Results are expressed as mean (SD).
BPD, Bronchopulmonary dysplasia; *FRC,* functional residual capacity; *MV,* minute ventilation; *PMA,* postmenstrual age; *RDS,* respiratory distress syndrome; *RR,* respiratory rate; *UK,* United Kingdom; *Vt,* tidal volume.

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19 Quality Improvement in Respiratory Care*

Nathaniel R. Payne, MD

This chapter discusses quality improvement (QI) in respiratory care by addressing two daunting challenges: (1) identifying best practices and (2) implementing best practices. Public reporting of outcomes, "pay for performance," Medicare refusal to pay for complications, and the emergence of national centers of excellence have transformed QI from a desirable to a mandatory activity. However, improving respiratory care involves complex challenges. Best practices constantly evolve so that no one practice remains best forever. For example, early surfactant administration and mechanical ventilation for infants at risk for respiratory distress syndrome (RDS) was a best practice in the 1990s. Now, with increased use of antenatal steroids and delivery room nasal continuous positive airway pressure (nCPAP), it may no longer be best.[1-3] Furthermore, "best" practice is always contextual.[4-6] A practice producing superior results in one neonatal intensive care unit (NICU) may not produce similar results in another NICU. Thus clinicians must evaluate best practices as being "potentially best" practices within the context of their individual NICUs. After identifying a best practice, QI teams may encounter so much resistance to implementation, or best practice transfer (BPT), that care changes little. Thus quality improvement entails two challenges: first, identifying and then implementing best practices.

Why Improve Respiratory Care?

About two thirds of newborns admitted to a level III NICU require respiratory support (unpublished data). Respiratory care influences survival and short-term respiratory outcomes, which in turn affect long-term outcomes of very-low-birth-weight (VLBW)[7-13] and larger infants.[14,15] Bronchopulmonary dysplasia (BPD), a sequela of extremely premature delivery and respiratory support, increases length of stay, rehospitalization,[10,16-18] and treatment costs.[19,20] BPD may also cause emphysema in early adulthood.[21] Therefore, patients, clinicians, families, researchers, and health care administrators share a common interest in improving respiratory outcomes. Clinicians can improve their patients' respiratory outcomes, but it requires thought, planning, and considerable effort.[22,23] Successful QI teams generally follow 10 steps (Box 19-1).[22] Although seemingly obvious, failure to follow these steps jeopardizes success.

Step 1: Develop a Multidisciplinary QI Team

Whom to Include

Quality improvement (QI), like clinical care, requires contributions from many stakeholders. Excluded stakeholders inevitably refuse to endorse or may even oppose the QI team's efforts. Recruitment requires publicity, open discussions with all stakeholders, and *compensated*, nonclinical time to attend meetings and participate in QI team activities. This "paid time off" constitutes a major cost of QI projects (see below). Many QI project teams, such as those in the Vermont Oxford Network (VON)-sponsored NIC/Q Quality Improvement Collaboratives (QICs), also include parents. They bring a unique perspective and help the QI team keep interventions consistent with family-centered care.

QI Team Meetings

Meeting together as a multidisciplinary group accomplishes what cannot be achieved in any other format. Successful meetings require clear objectives, an agenda, a seasoned leader, a timekeeper, and considerable premeeting preparation. The QI team should delegate tasks to each attendee and enforce accountability for past assignments. Ineffective meetings waste time, dampen enthusiasm, and impede QI. Time spent improving meeting productivity accelerates QI efforts.

Step 2: Examine Outcomes to Identify High-Priority Goals

Outcome Measures

QI begins and ends with data on performance and outcomes. Without data from one's own NICU and other NICUs as a comparison, one cannot identify the outcomes that most need improvement. The advent of large databases of NICU outcomes has transformed quality improvement in neonatology. Participants in these databases can now compare their NICU's outcomes with the average and

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Box 19-1 STEPS IN DEVELOPING A SUCCESSFUL QI PROJECT*

1. Develop a multidisciplinary QI team.
2. Examine outcomes to identify high-priority goals.
3. Choose the "best" practices to transfer to your NICU.
4. Develop a plan to transfer (implement) best practices.
5. Create a mandate for change.
6. Implement the QI plan with iterative modifications.
7. Identify resistance to change and address the issues.
8. Monitor and analyze outcomes.
9. Report results to all stakeholders.
10. Maintain gains.

*Adapted from Bergman DA: Pediatrics 103:225-232, 1999; and Grol R: BMJ 315:418-421, 1997.
NICU, Neonatal intensive care unit; *PDSA*, plan-do-study-act.

best performers in the database. Many such databases now exist. The Vermont Oxford Network (VON), National Institute for Child Health and Development (NICHD), Pediatrix® Medical Group, National Association of Children's Hospitals and Related Institutions (NACHRI), California Perinatal Quality Care Collaborative (CPQCC), and many others maintain and periodically disseminate NICU outcomes to participants in their databases and in publications. For example, VON is a nonprofit collaboration of over 700 NICUs throughout the world that contribute their outcomes to the Network each year. VON provides an Annual Quality Management Report for each participating NICU that provides risk-adjusted outcomes and compares them against all other NICUs in the database.

For the sake of illustrating the QI process, this chapter focuses on reducing BPD (see Chapter 23, Complications). BPD is a clinical outcome, but related outcomes, such as pneumothoraces or inadvertent extubations,[24] and process outcomes, such as reducing time to achieve endotracheal intubation,[25] might also be appropriate goals. QI teams should choose an outcome that is important to them and their patients and that can be measured and compared to benchmark data. If the goal were to increase BPD-free survival, a QI team might start by reviewing current knowledge about BPD and their NICU's weight-specific BPD rates.

What Is BPD?

Early reports described BPD as a complication of RDS and emphasized the transition from RDS to BPD (see Chapter 23).[16] Improved respiratory care now results in excellent outcomes in most infants without the type of BPD described in Northway's original series. Today's BPD, found in extremely-low-birth-weight (ELBW) infants (birth weight [BW] less than 1000 g), differs from that originally described by Northway.[16,26] The "new" BPD occurs with little acute lung disease or after resolution of acute lung disease in up to 30% of cases.[27,28] Enlarged air spaces with impaired alveolarization, decreased and dysmorphic capillaries, variable alveolar wall cellularity, and variable fibrosis characterize this new BPD.[26] ELBW infants with BPD suffer more pulmonary and neurodevelopmental problems and have longer lengths of hospital stay compared to ELBW infants without BPD.[10,11,29,30] Therefore, BPD qualifies as a high-priority outcome. The pathophysiology and epidemiology of BPD should guide QI efforts and imply that preventing BPD requires more than just "gentler" ventilation. This basic understanding of BPD improves selection of potential best practices.

Variation in BPD Rates

Can QI teams really decrease BPD? BPD rates, and all other outcome measures, vary severalfold among NICUs within Europe and the United States.[31-33] League tables, raw percentages of BPD rates from multiple NICUs listed in tabular format, mislead as often as they inform.[34,35] League tables take their name from the tables used to track an athletic team's standing within a league. Risk adjustment for confounders often reduces the variation in outcomes among NICUs, altering the conclusions drawn from simple league tables.[35] Adding to risk adjustment the use of "shrunken estimates" adjusts for patient volume and random variation, removing more variation from comparisons of NICU outcomes.[35] The VON provides shrunken estimates of risk-adjusted outcomes, such as BPD, in each participating institution's Annual Quality Management Report. Despite all possible adjustments, residual interinstitutional variation in BPD rates remains so great that it must reflect varied clinical practice (Fig. 19-1). All QI rests upon this assumption.

Set Realistic Goals

Many QI teams overreach when setting goals. Achieving a 30% reduction in BPD or performance equal to the top 5th percentile within 2 years exceeds most QI teams' capacity. Published evidence suggests that QI teams can achieve process improvements more easily than outcome improvements (see below). QI teams without extensive QI experience might start with process improvement projects, moving on to more complex outcomes improvement projects as they gain experience. An alternative philosophy states that incremental improvement projects take no less time or effort than breakthrough projects.[36] Therefore, why not aim high? The author favors the latter approach, but with the understanding that changing a complex outcome like BPD requires years, not months.[1,2] Whatever the ultimate goal, QI teams need interim goals to measure progress during the project and provide feedback on the QI team's effectiveness.

Define an Outcome Measure

QI projects require consistent, relatively precise outcome measures. An NIH workshop in 1979 defined BPD as 28 days of oxygen therapy with radiographic changes.[37] Shennan et al.[7] proposed supplemental oxygen use at 36 weeks postmenstrual age (PMA) and showed that this definition more accurately predicted long-term outcome than did supplemental oxygen at 28 days. Since the1990s, supplemental oxygen at 36 weeks PMA has commonly defined BPD. Death competes with BPD as an outcome, leading many researchers to use BPD-free survival, rather than BPD rate, as the outcome measure.[38-40] This distinction acquires importance from the observation that some practices (e.g.,

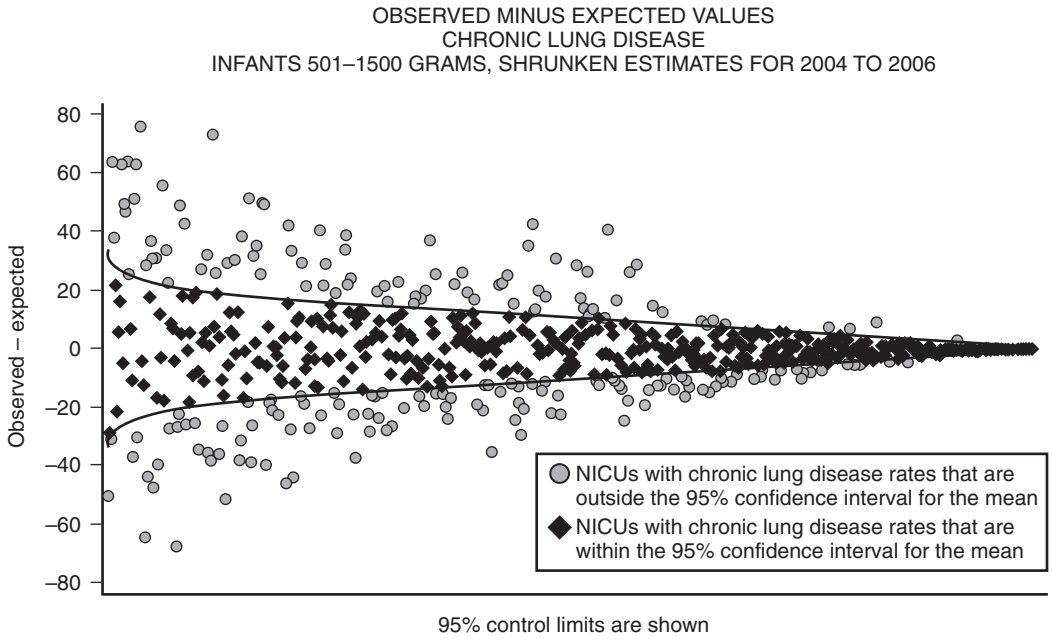

Figure 19-1 ■ Shrunken morbidity estimate for bronchopulmonary dysplasia (BPD) among the participating neonatal intensive care units (NICUs) in the Vermont Oxford Network in 2006. The Y-axis represents the observed-expected values. At zero the number of actual cases of BPD was equal to the number expected. NICUs with progressively fewer annual very-low-birth-weight (VLBW) infant admissions are represented progressively along the X-axis to the right. A positive number along the Y-axis represents the excess cases of BPD above those that would be expected on the basis of infant characteristics at birth (performance worse than expected). Negative numbers along the Y-axis represent the number of BPD cases that would have been predicted, but did not occur (performance better than expected). The parabolic curve indicates the 95% confidence limits. *Diamonds* represent NICUs within the 95% confidence limits and the *circles* represent performance either above or below the 95% confidence limits about the mean. This figure is part of the Vermont Oxford Network Annual Quality Management Report. Each member receives a version of the figure in which their own hospital is highlighted. (From unpublished data, provided courtesy the Vermont Oxford Network.)

antenatal steroids and surfactant administration) improve BPD-free survival, but not BPD rates (see Fig. 19-2).[41]

Problems with Measuring BPD

Imprecise diagnostic criteria confound outcome and process measurements. For example, clinicians use idiosyncratic criteria for administering supplemental oxygen. Ellsbury et al.[42] surveyed participants at a meeting of neonatologists and found that the percentage of oxygen saturation of hemoglobin (SpO_2) criteria for supplemental oxygen varied from less than 84% to greater than 96%, with only 41% of the respondents using the same criterion, less than 90%).[42] Walsh et al.[43] noted similar variation in criteria for supplemental oxygen and developed a physiologic definition of BPD, informally called the "room air challenge," that decreased interinstitutional variation in BPD rates.[43,44] Evolving definitions over the course of a QI project prevent meaningful assessment of the project. QI teams require an outcome measurement that is as precise and consistent among institutions and over time as possible.

Step 3: Choose the Best Practices to Transfer to Your NICU

Interventions That Matter

Published evidence validates few of the many potential interventions designed to reduce BPD.[10,47-50] Busy clinicians

Case Study 19-1 BPD CRITERIA

Using a physiologic definition of BPD, the room air challenge test, reduced the BPD rate by an average of 10%, range 0% to 44% at 16 of 17 hospitals participating in the NICHD Neonatal Network.[44] Some neonatologists prescribe supplemental oxygen to enhance growth and development, inflating the rates of supplemental oxygen use at 36 weeks postmenstrual age (PMA), independent of lung problems.

Many QI teams feel that they have reduced the severity of BPD, although the actual BPD rate might remain unchanged. Two published schemes exist for grading BPD severity. The National Institutes of Child Health and Development (NICHD) published consensus criteria for diagnosing and stratifying the severity of BPD (Table 19-1).[37] Two separate studies validated the new NICHD criteria.[18,45] Kaempf et al.[46] published capillary pCO_2 criteria that also stratify BPD by physiologic criteria. They began their study in frustration with the existing definition (supplemental oxygen at 36 weeks PMA) during their participation in a VON-sponsored QIC. They found a direct relationship between capillary pCO_2 and clinical severity of BPD, adding another variable that QI teams can employ to assess severity of BPD (Table 19-1).

TABLE 19-1 Criteria for Grading Severity of Bronchopulmonary Dysplasia

Patients	When Assessed	Mild	Moderate	Severe
Gestational age < 32 weeks (must receive FIO_2 > 0.21 for ≥ 28 days)*	36 weeks PMA *or* discharged home, whichever occurred first	RA	FIO_2 < 0.30*	FIO_2 ≥ 0.30, PPV (ventilator, HHFNC, or nCPAP)†
Gestational age ≥ 32 weeks (must receive FIO_2 > 0.21 for ≥ 28 days)*	Postnatal age 56 days *or* discharged home, whichever occurred first	RA	FIO_2 less than 0.30†	FIO_2 ≥ 0.30, PPV (ventilator, HHFNC, or nCPAP)†
Birth weight 501-1250 g	Within 72 hours of 36 0/7 weeks PMA *or* discharged home, whichever occurred first	RA $PaCO_2$ = 47 ± 6 (Mean ± SD)	FIO_2 < 0.30† $PaCO_2$ = 54 ± 7 (Mean ± SD)	FIO_2 ≥ 0.30, PPV (ventilator, HHFNC, or nCPAP)† $PaCO_2$ = 62 + 11 (Mean ± SD)

Adapted from NICHD criteria[37] and the work of Kaempf JW, Campbell B, Brown A, et al: J Perinatol 28:48-54, 2008.
*Day of treatment should reflect FIO_2 greater than 0.21 for more than 12 hours.
†Patient should not have had recent acute event that would increase required FIO_2. Actual FIO_2 for patients receiving oxygen by nasal cannula was calculated using data from Benaron DA, Benitz WE: Arch Pediatr Adolesc Med 148:294-300, 1994.[56]
HHFNC, Humidified high-flow nasal cannula; *nCPAP*, nasal continuous positive airway pressure; *PMA*, postmenstrual age; *PPV*, positive-pressure ventilation; *RA*, room air; *SD,* standard deviation.

Case Study 19-2 CONSEQUENCES OF BPD

Severe BPD, as measured using the NICHD criteria (Table 19-1) and compared to no BPD, doubles the odds of a patient requiring pulmonary medications at discharge and being rehospitalized for pulmonary problems.[18] Compared to mild BPD, severe BPD increases the risk of cerebral palsy from 11% to 27% and discharged home on oxygen from 3% to 67%.

do not need to become experts in all areas of respiratory care to reduce BPD. They can access numerous systematic reviews, guidelines, and other such resources to identify best practices. For example, the NICHD sponsors an Internet site with reviews of neonatal care practices from the Cochrane Collaboration.[51] This site contains over 200 systematic reviews, many relevant to respiratory outcomes. QI

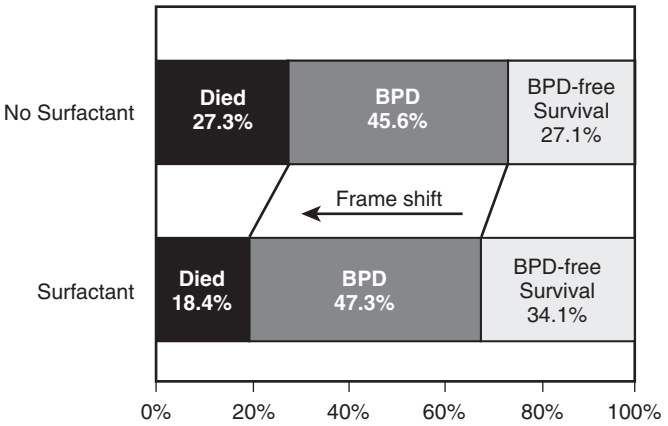

Figure 19-2 ■ Antenatal steroids and surfactant administration may cause a "frame shift" of patients from nonsurvival to survival, but at the cost of bronchopulmonary dysplasia (BPD) (see Fig. 19-1).[62] Patients who would have survived with BPD avoid BPD, but additional patients who would have died, survive with complicating BPD. This frame shift increases total survivors and survivors without BPD, but produces an inconsistent effect on BPD rates.[62] (Data from Liechty EA, Donovan E, Purohit D, et al: Pediatrics 88:19-28, 1991.)

TABLE 19-2 Muir Gray and Center for Evidence-Based Medicine Levels of Evidence

Muir Gray		Center for Evidence-Based Medicine (Therapy/Prevention)	
Level of Evidence			
1	Strong evidence from ≥1 systematic review of multiple, well-designed RCTs	1a	Systematic review (with homogeneity*) of RCTs
		1b	Individual RCT with narrow confidence interval
		1c	All patients previously died—now, with treatment, some survive, *or* some previously died and now all survive; no RCT
2	Strong evidence from ≥1 properly designed RCT of appropriate size	2a	Systematic review (with homogeneity*) of cohort studies
		2b	Individual cohort study (including low-quality RCT; e.g., <80% follow-up)
		2c	"Outcomes research"; ecological studies
3	Evidence from well-designed nonexperimental studies from more than one center or research group	3a	Systematic review (with homogeneity*) of case-control studies
		3b	Individual case-control study
4	Opinions of respected authorities, based on clinical evidence, descriptive studies, or reports of expert committees	4	Case-series (and poor-quality cohort and case-control studies)
5	Muir-Gray classification has only 4 levels	5	Expert opinion without explicit critical appraisal, or based on physiology, bench research, or "first principles"

Adapted from Muir Gray JA: Evidence-based healthcare. London, England, Churchill Livingstone, 1997, and Center for Evidence-Based Medicine (website): www.cebm.net/index.aspx?0=1025. Accessed May 25, 2008.
*Homogeneity means that the systematic review is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies.
RCT, Randomized controlled trial.

teams can also access The American Academy of Pediatrics' website for policies and guidelines,[52] NeoReviews,®[53] and frequently published topic reviews. A PubMed search on neonatal respiratory care identified over 30 such reviews from 2006 to 2007, many focused on BPD. QI teams will find much published evidence and must evaluate the reliability and value of that evidence.

Grade the Evidence

QI teams may choose from several systems for grading the level of evidence supporting a potentially best practice. Examples of published schemes are those of Muir Gray[54] and the Center for Evidence Based Medicine (Table 19-2).[55] The VON-sponsored QICs have generally used the Muir Gray classification scheme. Implementing best practices that are supported by high levels of evidence increases the likelihood of successful QI and broad-based clinician acceptance of proposed changes.[57]

One might assume that clinicians would quickly adopt practices supported by the highest levels of evidence. Experience contradicts this assumption.[58] For example, extensive evidence supports supplemental vitamin A to reduce BPD.[59] Yet, 4 years after the last published, randomized controlled trial (RCT), only 20% of NICUs in neonatology training programs and 13% of NICUs in nontraining programs administered vitamin A supplementation to 90% or more of eligible patients.[60] The following review of potentially best practices serves only to illustrate some of the issues. Please see other chapters for more complete discussion.

Specific Clinical Practices

Effective Practices

Vitamin A

Supplemental vitamin A administered (see Chapter 21) to ELBW infants (less than 1000 g birth weight) reduces the combined outcome of death or BPD at 36 weeks PMA (relative risk [RR] = 0.93; confidence interval [CI] = 0.88, 0.99).[59] Despite the modest effect of size, unambiguous evidence of effectiveness and ease of implementation recommend this practice.

Prophylactic/Early Surfactant

Surfactant administration (combining both prophylactic and therapeutic use) does not reduce BPD (see Chapter 22). Prophylactic surfactant (defined as administration in the first 15-20 min of life) improves BPD-free survival (RR = 0.85, 95%; CI = 0.76, 0.95), but not BPD (RR = 0.96, 95%; CI = 0.82, 1.12).[61] Prophylactic surfactant probably results in a "frame shift" with additional infants surviving, but at the cost of BPD (see Fig. 19-2), and in infants who previously developed BPD surviving without pulmonary compromise.[62] Neonatologists differ regarding the gestational age at which they administer prophylactic surfactant. Data from the original RCTs support a gestational age of less than 30 weeks.[61] However, evolving clinical practice such as greater use of antenatal steroids and delivery room nCPAP, have caused some to recommend a lower gestational age. Prophylactic surfactant does not decrease BPD, but it does increase BPD-free survival, making this an important strategy for improving respiratory care, especially in the smallest ELBW infants.

Early surfactant (as distinguished from prophylactic) administered within the first 1 to 2 hours in patients with RDS reduces the combined outcome death/BPD (RR = 0.84, 95%; CI = 0.75, 0.93) and BPD (RR = 0.70, 95%; CI = 0.55, 0.88).[63] However, this conclusion depends on two heterogeneous studies, the larger of which, the OSIRIS study, drives the RR estimate.[63] The OSIRIS study used a synthetic surfactant that does not contain surfactant proteins and is no longer used. Interestingly, some NICUs with low BPD rates administer surfactant only if infants fail nCPAP treatment.[64] Available evidence supports administering prophylactic or early (less than 2 hours) surfactant to improve survival and reduce severity of acute lung disease.[61,63]

Administering surfactant followed by extubation to nCPAP may also reduce lung injury.[2,65] Meta-analysis indicated that this approach reduced the need for mechanical ventilation (RR = 0.67, 95%; CI = 0.57, 0.79) and BPD (RR = 0.51, 95%; CI = 0.26, 0.99) as measured by need for supplemental oxygen at 28 days.[65] Unfortunately, many studies of this approach come from single institutions or use historical controls. These studies also tended to enroll larger infants (BW greater than 1250 g) and lack sufficient data to assess BPD as measured by supplemental oxygen at 36 weeks PMA.[65]

Postnatal Corticosteroids

Postnatal corticosteroids (see Chapter 21), primarily dexamethasone, given in the first 2 weeks after birth, increase BPD-free survival and decrease BPD,[66,67] but at the expense of neurologic injury[66,68,69] and worsened alveolar simplification.[37] Dexamethasone may cause hypertension, hyperglycemia, and when given with indomethacin, intestinal perforation.[70] However, relative risks and benefits vary by gestational age. Some believe that the highest-risk ELBW infants derive more benefit than harm from postnatal dexamethasone.[71] Current practice reflects this belief. Among NICUs reporting data to VON, 23% of infants with birth weight 501 to 750 g received postnatal steroids in 2006. This is about half of the rate of postnatal corticosteroid use in 2001 (23% vs. 41%).[72] Dexamethasone carries too much risk to warrant consideration as a best practice. The AAP recommends against the routine use of postnatal dexamethasone outside of research studies.[73]

In an effort to avoid the risks of dexamethasone, many clinicians have considered using hydrocortisone in physiologic doses to prevent BPD. Premature infants do not synthesize cortisol as well as older infants, and this relative adrenal insufficiency may increase BPD.[74,75] Watterberg et al.[70] studied hydrocortisone replacement therapy to prevent BPD in ELBW infants and found no reduction in BPD. However, the study ended before completing enrollment because of increased intestinal perforations in the treatment group. In post hoc subgroup analysis, hydrocortisone treatment did increase BPD-free survival in ELBW exposed to histologic chorioamnionitis.[70] Hydrocortisone did not adversely affect neurologic development,[76] but insufficient information exists to recommend its routine use.

Probably Effective Practices

Minimize Supplemental Oxygen

High F_{IO_2} injures lung tissues (see Chapter 15).[37] Exposure to excessive F_{IO_2} begins in the delivery room. Many NICU teams routinely resuscitate with 100% oxygen and do not have a blender in the delivery or resuscitation room with which to administer lower concentrations of oxygen. Resuscitation with room air may work just as well as resuscitation in 100% oxygen[77,78] with no apparent difference in long-term outcomes.[79] The American Academy of Pediatrics/American Heart Association's Neonatal Resuscitation Program (NRP) now recommends resuscitating premature infants with blended oxygen between 21% and 100%, but quickly decreasing the F_{IO_2} as soon as the patient achieves an acceptable Sp_{O_2}.[80] Alternatively, one could start with low F_{IO_2} (21%-30%) and increase as needed.[81] These approaches require blended oxygen and pulse oximetry in the delivery room, and the NRP now recommends these capabilities if routinely resuscitating infants less than 32 weeks' gestation.[80]

In both acute and convalescent care, high F_{IO_2} appears to injure neonatal lungs. The cross-sectional, retrospective study of Tin et al.[82] reported that patients (gestational age less than 28 weeks) treated with lower target Sp_{O_2} ranges (70%-90% vs. 88%-98%) required fewer ventilator days (13.9 vs. 31.4 days) and oxygen days (96 vs. 40 days). The BOOST trial randomized convalescing infants (greater than 2 weeks old) to standard (91%-94%) or higher Sp_{O_2} target range (95%-98%) to improve growth and development. This trial also reported more pulmonary sequelae with the higher target Sp_{O_2}.[83] The higher Sp_{O_2} target range did not confer a growth or development advantage. The STOP-ROP study, which randomized infants with retinopathy of prematurity (ROP) to one of two target Sp_{O_2} ranges (96%-99% vs. 89%-94%), found more pulmonary complications in those treated with the higher Sp_{O_2} target.[84] A post hoc analysis of baseline respiratory status showed that patients in the two treatment groups of the STOP-ROP study had similar pulmonary scores at randomization.[85] Taken together, the laboratory[86] and clinical evidence[77-79,82-85] implicate supplemental oxygen as a significant contributor to BPD. The higher the target Sp_{O_2}, the greater the concentration of oxygen required to achieve that target. Infants with lung disease require an even higher F_{IO_2} to achieve the target Sp_{O_2} than those with normal lungs.[87] Unfortunately, published evidence does not establish the "ideal" Sp_{O_2} target range.[88]

Avoiding Mechanical Ventilation

Avoiding mechanical ventilation likely explains at least some of the best performing centers' low BPD rates (see Chapter 8).[1-3,31,32,64] Substituting nCPAP for mechanical ventilation and allowing permissive hypercapnia, best performers report BPD rates almost an order of magnitude lower than comparable institutions.[1,31,32] Animal data also support the avoidance of mechanical ventilation to reduce ventilator-induced lung injury (VILI).[86,89-91] Although minimizing duration of ventilation may help, even brief mechanical ventilation injures neonatal lungs.[91] Intuitively, avoiding mechanical ventilation offers the best hope of preventing BPD.

Despite the logic of this practice, it has not become widespread nor been validated in RCTs. Small, single-center trials of nCPAP in place of mechanical ventilation showed mixed, but encouraging, results with regard to BPD.[92-95] In the largest RCT, the COIN trial, 46% of the nCPAP group required intubation in the first 5 days of age.[95] Death or oxygen requirement at 28 days was lower in the nCPAP group, as was the duration of ventilation. However, BPD did not differ in the two groups, and pneumothorax was higher in the nCPAP group.[95] nCPAP may reduce the need for mechanical ventilation, but it has not consistently reduced BPD.

Starting nCPAP in the delivery room, and thus avoiding mechanical ventilation, requires a major change in NICU care. A recent feasibility study showed 54% of infants born at less than 28 weeks gestation could be stabilized in the delivery room without tracheal intubation.[96] However, only 20% did not require intubation during the first postnatal week. Developing organizational capability to support ELBW infants without mechanical ventilation takes years, not months.[2,64] Aly et al.[64] reported that ELBW infants who started on nCPAP in the delivery room and required mechanical ventilation within the first week decreased from 38.5% to 7.4%, and BPD dropped from 46.2% to 11.1% over approximately a 4-year period in a single institution. The choice of which ELBW infants should receive only nCPAP is also not clear. There is a much higher failure rate in the most preterm infants (23-25 weeks) and the clinical conditions of maternal steroid administration, intrapartum asphyxia, and infection may have significant impact on the success of early nCPAP. Changing a complex outcome such as BPD requires major changes in treatment processes and personnel's attitudes and skills.

Preventing Volutrauma/Atelectrauma

Excessive stretching of the lung, or volutrauma, injures lungs. Mechanical ventilation injures neonatal lungs and incites an inflammatory response leading to BPD in experimental animals (see Chapters 9 and 10).[90,91] These reports suggest that end-inspiratory volume, more than pressure, mediates lung injury. Published studies of adult respiratory distress syndrome (ARDS) demonstrate a survival advantage with low tidal volume (V_T) ventilation.[98-100] ELBW infants are particularly vulnerable to volutrauma. Two studies found an association between hypocarbia, implying excessive V_T or volutrauma, and BPD.[101,102] Volume-targeted, as opposed to pressure-targeted, ventilation may reduce volutrauma (see Chapter 10).[103] Volume-targeted ventilation reduces duration of mechanical ventilation, severe intraventricular hemorrhage (IVH), and pneumothorax, but not BPD.[103] Delivery room resuscitation poses the greatest risk of volutrauma as clinicians vigorously ventilate bradycardic, cyanotic infants. Avoiding positive pressure ventilation and the use of a T-piece resuscitator when ventilation is necessary are two potential ways to prevent volutrauma.

Atelectrauma, or repeated atelectasis at end exhalation caused by too little positive end-expiratory pressure (PEEP), injures lungs.[97,104,105] This recruitment-derecruitment cycle occurs when infants are ventilated using self-inflating bags

without a PEEP valve. The T-piece resuscitator (Neo-Puff®) device limits peak inspiratory pressure and provides constant PEEP, thereby minimizing the risk of atelectrauma.[106,107] Devices or strategies that reduce volutrauma and atelectrauma should improve pulmonary outcomes, but little published evidence supports this assumption.

Caffeine Administration

Methylxanthines facilitate extubation and reduce apnea and hypoventilation,[108] which frequently prolongs the duration of mechanical ventilation or necessitates reintubation.[96] Recent evidence suggests that caffeine started in the first 10 days after birth also reduces BPD.[109] Infants received 20 mg/kg of caffeine citrate as an intravenous loading dose (or saline) and maintenance doses of 5 to 10 mg/kg daily. Those receiving caffeine required about 1 week less of positive airway pressure and less often were judged as needing patent ductus arteriosus (PDA) closure by drug or surgery. Routine caffeine treatment reduced BPD (adjusted odds ratio = 0.64; CI = 0.52-0.78) and improved neurodevelopmental outcome at 18 to 21 months.[110] Caffeine started in the first 10 days after birth appears to reduce BPD, as well as apnea.

Preventing Nosocomial Sepsis and Pneumonia

Nosocomial bacteremia increases BPD.[111,112] Bacteremia elicits a systemic inflammatory response that likely contributes to lung and brain injury. Reducing infection should not only reduce BPD, but also neurodevelopmental problems,[113] and should be a priority for every NICU. The prevention of ventilator-associated pneumonia (VAP) should also reduce time on mechanical ventilation and BPD, although evidence in this area is scant (see Chapter 24).

Antenatal Steroids

Antenatal steroids increase survival and decrease acute lung disease, but not BPD.[41,114,115] Antenatal steroids may cause a "frame shift" of patients from nonsurvival to survival, but at the cost of BPD (Fig. 19-2).[62] Patients who would have survived with BPD, avoid BPD due to maternal steroid treatment, but additional patients who would have died, survive with complicating BPD. This frame shift increases total survivors and survivors without BPD, but produces an inconsistent effect on BPD rates.[62] An alternative explanation posits that maternal antenatal steroids improve lung function, but initiate alveolar simplification.[116] Without additional insults, the lungs recover and develop normally. With exposure to mechanical ventilation, oxygen toxicity, or infection, alveolar simplification worsens. This theory potentially explains atypical BPD.[27,28,117] Although administering antenatal steroids may not reduce BPD, it improves survival (RR = 0.69; CI = 0.58, 0.81),[41] and should be considered by all perinatal QI teams, especially in NICUs with low administration rates (the 2006 VON database mean = 74%, interquartile range, 66%-82%).[72]

Possibly Effective Practices

Permissive Hypercapnia

Permissive hypercapnia should reduce the risk of volutrauma by reducing the target V_T and the risk of volutrauma.[100] Clinical reports indicate that permissive hypercapnia decreases the duration of mechanical ventilation, but without a significant decrease in BPD/death,[118] although BPD trends in the desired direction. Concerns about increased IVH with high $PaCO_2$ levels[119] have not been confirmed in most studies.[100,118] Permissive hypercapnia may play a role in an overall strategy to reduce volutrauma or avoid mechanical ventilation (see Chapter 15).

High-frequency Ventilation

Multiple trials have studied high-frequency ventilation (HFV) using different protocols for surfactant use and ventilator strategy (high- or low-volume), making interpretation complicated (see Chapter 11). By meta-analysis, it appears that high-frequency oscillatory ventilation may reduce BPD very modestly (RR = 0.93, CI = 0.86-1.00),[120] although another meta-analysis did not find a reduction in BPD.[121] Early reports noted an increase in IVH, but with the use of a high-volume strategy, HFV does not increase severe IVH. However, it does increase pneumothorax (RR = 1.19, CI = 1.05-1.34).[120] High-frequency jet ventilation may reduce BPD when used in conjunction with surfactant therapy (RR = 0.59; CI = 0.35-0.99).[122] In 2006, 58% of infants with BW of 501 to 750 g in the VON database received HFV.[72] Although HFV may have some utility in rescue situations, it does not reduce BPD when used electively. HFV requires considerable technical expertise, which likely determines the success of this practice.[123]

Inhaled Nitric Oxide—Level 2

Numerous studies with different entry criteria and study protocols have administered inhaled nitric oxide (iNO) to preterm infants with RDS to increase BPD-free survival with mixed results. As a rescue therapy, iNO does not improve pulmonary outcome or survival,[124,125] and trends toward an increase in severe IVH. Routine, early use in intubated preterm infants may decrease the combined outcome of death or BPD, but by meta-analysis, this effect is small (RR = 0.91, 95%; CI = 0.84-0.99).[124] Routine iNO treatment carries few side effects in premature infants and importantly did not increase severe IVH.[124-128] No studies report long-term effects of iNO treatment. Although iNO treatment looks promising, the optimal patient population, dose, duration of treatment, and time of initiation remain ill defined.

Extubation to nCPAP to Reduce Duration of Mechanical Ventilation

Extubation to nCPAP rather than oxygen or air alone reduces the duration of mechanical ventilation by reducing the need for reintubation after elective extubation (RR = 0.62; CI = 0.49, 0.77).[129] Unfortunately, published evidence does not clarify the most effective type of nCPAP or the criteria for identifying infants ready for elective extubation. Nasal intermittent positive pressure ventilation (NIPPV) appears more effective than nCPAP in preventing reintubation.[130] Neither postextubation nCPAP nor NIPPV

Case Study 19-3 INADVERTENT EXTUBATIONS

One QI team found that about a third of accidentally extubated patients did not need to be reintubated, if they were immediately placed on nCPAP. This suggested that many infants received mechanical ventilation when nCPAP would suffice.

reduce BPD, although the trend is favorable with NIPPV.[129,130]

Inositol

Nutritional supplementation with inositol may reduce BPD and severe ROP.[131] However, the studies occurred in the pre-surfactant era. Ongoing studies should help define the role of inositol supplementation.

Pentoxifylline

There is a single, randomized study reporting that nebulized pentoxifylline may reduce BPD.[132]

Ineffective (but potentially important) Practices

Fluid Restriction

Patients who develop BPD lose less weight and receive more intravenous fluid immediately after birth than those not developing BPD.[133,134] Excessive fluid administration increases the risk of BPD and PDA, but it is not clear that fluid restriction reduces BPD.[135] Patients destined to develop BPD may simply have greater capillary leakage and thus retain more fluid. Although judicious fluid administration appears to improve outcome, many factors likely influence fluid requirements in ELBW infants.

PDA Closure

In VLBW infants, PDA for greater than 6 days prolongs the need for supplemental oxygen or mechanical ventilation.[136] Pharmacologic closure of a PDA does not worsen BPD,[137] and in experimental animals prevents the arrest in alveolar development that characterizes the new BPD (see Chapter 26).[138] However, treatment of PDA has not been shown to reduce BPD. Prophylactic indomethacin reduces the risk of PDA,[139,140] but increases the risk of BPD, perhaps by increasing water retention during the first week of life.[140] Surgical ligation of a PDA clearly increases BPD[141,142] and worsens neurodevelopmental outcome.[142] Therefore, neither pharmacologic nor surgical closure of PDA reduces BPD.

Inhaled Steroids

Because systemic corticosteroids improve survival in those infants with BPD, it would seem logical that steroid delivery directly to the lungs might provide benefit without systemic complications. Unfortunately, the few studies examining this hypothesis have not shown an effect. It may be due to the difficulty of getting sufficiently small, aerosolized particles into small airways. Meta-analysis supports neither the prophylactic use nor treatment use of inhaled steroids to reduce BPD.[143-144]

Super Oxide Dismutase

Super oxide dismutase (SOD) reduces inflammatory changes and pulmonary vasconstriction and appears safe, but does not reduce BPD.[145-149] SOD did reduce respiratory illnesses (wheezing, asthma, pulmonary infections) severe enough to warrant treatment with bronchodilators or corticosteroids at 1-year corrected age.[149]

Thyroid Hormone Therapy

Although thyroid hormone treatment increases surfactant in animal models, it does not reduce BPD.[150]

How to Choose from Among the Many Alternative Practices

How does a QI team select practices from among all the evidence? They should prioritize their efforts to address safety, efficacy, and finally, efficiency of care. First, the QI team should identify and address safety issues, such as nosocomial bacteremias, pneumonias, inadvertent extubations, and atelectrauma. Second, the QI team should consider practices most likely to reduce BPD: vitamin A administration, prompt surfactant administration, avoiding mechanical ventilation, using caffeine to minimize apnea/hypoventilation, and minimizing exposure to supplemental oxygen. Third, practices without benefit or with potential harm should be eliminated, such as routine, open suctioning (disconnecting ventilator circuits for suctioning),[151] CPAP trial through an endotracheal tube prior to extubation,[152] and routine deep tracheal suctioning.[153] Whatever practices the QI team selects, implementation requires tailoring selected practices to their specific NICU.[4,6]

Best Practice Invention

Instead of mimicking best performers, why not just develop the best practices locally? Clinicians have always implemented physiologic principles of care differently. The array of ventilators, CPAP devices, and the methods of using them attest to this variation. Until recently, NICU personnel received little feedback on their performance relative to that of their peers. Almost all clinicians believe that their individual practices produce better outcomes than those of others. Without feedback on comparative performance, such an assumption goes unchallenged. The advent of large networks and databases enables feedback to NICU personnel as never before. As one might expect, random variation based on individual physicians' idiosyncratic practices uninfluenced by systematic feedback produces some very good, some very poor, and lots of mid-range outcomes. Feedback from databases and various consortia transform clinical practice by identifying the truly best outcomes and, potentially, the associated best practices. Benchmarking and BPT attempts to harvest the lessons learned from the identified best performers. Given enough time and feedback, individual NICUs could probably evolve their own best practices. However, for most NICUs, BPT improves outcomes more quickly than does individual experimentation.

Case Study 19-4 DISTINGUISHING QI FROM RESEARCH

A multicenter study assessed risk prediction for trisomy 21 by combining maternal age and nuchal translucency as measured by ultrasound at 10 to 14 weeks' gestation.[158] Women were offered the scan and provided a leaflet explaining the scan, other available procedures (e.g., chorionic villus sampling), and the risks of each procedure. Women also received a form to complete about the outcome of the pregnancy. The authors obtained neither consent nor Institutional Review Board (IRB) review because they thought this was an audit of clinical practice, not a study.[159] However, some patients thought they were unfairly recruited into a study without giving consent.[160]

Step 4: Develop a Plan to Transfer (Implement) Best Practices

Quality Improvement vs. Research: The Institutional Review Board

Issues

Before embarking on a major QI project, the implications of the change should be carefully reviewed, preferably by someone not involved in the project. QI and research projects differ (Table 19-3), but sometimes overlap and raise questions about patient protection.[154-157] Both expose patients to some risk by altering care. Most QI projects expose patients to no more than minimal risk, defined as the risk associated with current standard care and the use of confidential information. However, some QI activities indirectly expose patients to more than minimal risk and feel more like research than QI.

Differences

A Hastings Center report defined QI as "systematic, data-guided activities designed to bring about immediate improvements in health care delivery in a particular setting."[154] The Department of Health and Human Services defines research as "… a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge."[161] This definition separates research from QI based on intent and design. However, some QI teams publish their results and seek generalizable knowledge about BPT. Lo and Groman[155] argue that the balance of potential benefits and risks to patients, not the activity's structure, more properly differentiates QI from research.

Projects that alter care primarily for the benefit of providers or health care institutions provide no potential benefit to participants, involve randomization, implement untested interventions, receive funding from external sponsors, or breach confidentiality (Table 19-3) should undergo review by the IRB or some other oversight group. Projects intended to bring clinical care into compliance with best practice qualify as QI activity, and do not need review except by the managers who oversee clinical care in the NICU. Giving patients or their families general notice of ongoing QI activities at admission has also been recommended.[155,156]

Avoiding Controversy

Despite fulfilling the criteria for a QI project as defined by the Hastings Center report, controversy may still arise.[157] For example, researchers at Johns Hopkins conducted, and the Agency for Healthcare Quality and Reform funded, a multicenter study in Michigan ICUs to reduce nosocomial infections.[162] Interventions included (1) handwashing, (2) full-barrier precautions during insertion of central venous catheters, (3) chlorhexidine skin preparation before catheter insertion, (4) minimizing the femoral site for catheter

TABLE 19-3 Distinguishing Between Research and Quality Improvement Activity

Research	Quality Improvement Projects
Systematic investigation including hypothesis development, testing, and evaluation to contribute to generalizable knowledge	Systematic, data-guided activities designed to immediately improve health care in a particular setting
Start with hypothesis; equipoise about efficacy; go beyond current knowledge	Implement proven practices
Treatment determined by randomization and/or protocol	Treatment determined by attending physician
Participants often do not benefit	Participants likely to benefit
Federal or other external funding	Usually funded from operations
Risks often exceed those of routine, standard care	Minimal risk, usually same as routine care
Same protocol followed in multiple institutions	"Best" practice modified by adopting institution
Requires informed consent	Recommend general notice to families
Projects reviewed by IRB	Projects reviewed by clinical managers or IRB
Ignores the NICU culture—temporary protocol	Seeks permanent integration into NICU culture
Plan to publish results	Results occasionally published
Opinions of nonstudy personnel often irrelevant	Opinions of nonproject personnel crucial to success of project
Primary intent is knowledge	Primary intent is better local care
Delays feedback to prevent bias	Provides frequent feedback to modify behavior
Knowledge applicable to many other sites	Results mostly applicable to single site

Adapted from Lynn J, Baily MA, Bottrell M, eta; Ann Intern Med 146:666-673, 2007; Lo B, Groman M: Arch Intern Med 163:1481-1486, 2003; Nerenz DR, Stoltz PK, Jordan J: Qual Manag Health Care 12:159-170, 2003; Miller FG, Emanuel EJ: N Engl J Med 358:765-767, 2008, and the author's own experience.
IRB, Institutional review board; *NICU,* neonatal intensive care unit.

insertion, and (5) removing catheters as soon as possible. The researchers submitted the project to their IRB, which deemed the study exempt, which is "… research involving the collection or study of existing data, documents, records, pathologic specimens, or diagnostic specimens, if these are publicly available or if the information is recorded in such a manner that subjects cannot be identified."[163] Shortly after publication of the results, the Office for Human Research Protection (OHRP) contacted the researchers and issued an opinion that the research was not exempt from IRB review and that patient consent should have been obtained.

The OHRP subsequently relented on its demand for informed consent.[157] Consent may be waived if (1) research poses no more than minimal risk, (2) does not adversely affect the rights and welfare of the subject, (3) could not reasonably be conducted otherwise, and (4) when appropriate, the subjects receive additional pertinent information after participation.[155,156] This QI study qualified for a waiver of informed consent. However, this project appeared to be a research study that sought generalizable knowledge, received federal funding, prospectively implemented a study protocol to reduce infections, and submitted its results for publication (see Table 19-3). Although it is likely the research would have qualified for expedited review, it was not exempt research.[157] If in doubt, QI teams should discuss the project with their IRB, especially if planning to publish their results or implement interventions that may not qualify as minimal risk.

Health Care and Non–Health Care Industry Experience

Most quality improvement teams spend more preparatory time researching best clinical practices than they do researching best implementation practices. Although NICUs tend to be hierarchical organizations, merely sending out a memo or even writing an order will not generally effect successful implementation.[164,165] To improve quality, QI teams must cause a change in the behavior of caregivers. The *best practices*, or *potentially better practices* as the VON has called them, are "best" only in the context of the NICU implementing them.[4,6] Many best practices simply do not transfer well and do not produce the same results in the recipient organization as they did in the benchmark organization. The reasons for this may reside in the practice itself, the implementing organization, clinical differences in patient populations, or the method of transfer. Successful QI teams must understand BPT and how to effect change in their NICU.

Although devices and supplies matter, BPT mostly requires transferring knowledge from one organization to another.[4] Successful knowledge transfers combine mimicry and adaptation. For example, one QI team prepared a protocol to increase nCPAP use patterned after the benchmark site's protocol. They even purchased the same equipment as used by the benchmark site. A few weeks after implementation began, nasal septal injuries occurred and nurses actively resisted implementation. After considerable review, the QI team discovered the reason: they had modified their CPAP devices in a way they did not understand. Their oxygen tubing was more rigid than that at the benchmark site and they had varied their use of the Velcro® mechanism securing the nCPAP prongs.[166] Subtle differences in their adaptation derailed their efforts. Small changes in application of new technology dramatically change outcomes.

Process knowledge consists of two components, explicit and tacit. Explicit knowledge can be codified and communicated easily. QI teams share this at conferences, site visits, and in publications. Tacit knowledge resides within the minds of workers and by definition is not written and sometimes not even easily identified. Tacit knowledge, more than explicit knowledge, determines BPT success. Much of the knowledge critical to BPT may be tacit, which requires dialogue, mentoring, and interactive problem solving.[4,167] Some companies have concluded that only by transferring workers from the benchmark plant to the recipient worse performing plant, can they adequately transfer tacit knowledge. The more technologically complex the practice, the more likely tacit knowledge determines success.

Although unstudied, tacit knowledge transfer plausibly influences reports of respiratory care improvement. For example, one study found that HFJV decreased BPD and decreased IVH compared to conventional ventilation.[168] A separate but similar study reported that HFJV increased severe brain injury and offered no pulmonary advantage over conventional ventilation.[169] Such contradictory reports still occur and confuse clinicians. Although the two studies used different approaches, it is likely that tacit, technical details, not reported or perhaps not even recognized at the time by the researchers, also contributed to these contradictory reports.

Social Networks

Social networks facilitate sharing of both explicit and tacit knowledge. They encourage person-to-person contact, dialogue, and reduce geographic barriers to knowledge sharing. Networks of NICUs within the same hospital system, state, association, or other organization create a forum for information sharing. Professional networks, such as the Vermont Oxford Network, the California Perinatal Quality Collaborative Consortium (CPQCC), Pediatrix Medical Group, and the National Association of Children's Hospitals and Related Institutions (NACHRI) share protocols, best practices, and outcomes. Collaborative efforts naturally grow out of these networks.

Quality improvement collaboratives (QICs) bring together groups of clinicians from different hospitals to collaborate on QI. Typically, QICs include participants with multiple professional backgrounds, teach evidence-based practices and quality improvement concepts, and establish timelines and goals. The VON-sponsored NIC/Q series of QICs have transformed QI in neonatal care. Social networks establish professional relationships that last long after the QIC concludes.[170] QICs generally last for 18 to 24 months and meet 2 to 3 times per year to share implementation experiences and knowledge.[171] Published studies do not permit us to know which variations on the QIC method work best.[172,173] Whether or not participants realized improvements from QICs, most say that QICs provided professional stimulation and personal reward.[171]

The IHI Experience

In their Breakthrough Series collaboratives, the Institute for Healthcare Improvement (IHI) pioneered many methods now widely used by QICs.[174] The IHI model includes identifying a topic, recruiting and preparing participants, and developing a collaborative process for deploying the lessons learned during the collaborative. The VON-sponsored QICs largely followed the IHI Breakthrough Series' model, which emphasizes rapid, iterative change.[175] QI teams using the Breakthrough Series approach have improved cardiac surgery,[176] decreased cesarean section rates,[177] increased infant vaccination rates,[178] and improved the treatment of stroke[179] and chronic heart failure.[180] Despite successes, skeptics remain.[181] Results from cluster randomized trials using the QIC method have been mixed, but generally positive.[39,182-184] QICs seeking to change process succeed more easily than QICs seeking to change complex outcomes, which require changes in multiple clinical practices over an extended hospitalization.

VON

The VON has sponsored many QICs, modeled after the IHI series,[38,185] as well as Webcasts that do not require travel to semiannual meetings. Horbar et al.[182] reported that the original NIC/Q reduced BPD[38] overall, but with significant heterogeneity of outcome. The VON-sponsored Reduce Lung Injury (ReLI) group, a subset of the NIC/Q 2000, did not show improvement in BPD (unpublished data). A subsequent project, the Breathsavers group of the NIC/Q 2002, reported a 27% reduction in BPD.[40] In all reported QICs, individual NICUs' results vary, with some NICUs experiencing a paradoxical increase in the target complication rate and some showing a remarkable decrease.

The Breathsavers group's success may have been related to choice of best practices, which differed from those of the preceding, unsuccessful ReLI group's best practices.[186,187] Also, the Breathsavers group had greater experience in QICs. For some participants, the NIC/Q 2002 was the third consecutive QIC in which they had participated over a 7-year period. Experience improves a QI team's capacity for BPT.[64]

Plan-Do-Study-Act

QI is an iterative process. The plan-do-study-act (PDSA) cycle of iterative continuous quality improvement originated with Walter Shewhart in the 1930s[188] and undergirds most successful QI activities today. This cycle emphasizes inductive reasoning and continuous improvement through iterative change, analysis, and feedback. The IHI, VON, and others use the PDSA approach.

Step 5: Create a Mandate for Change

Without a mandate for change, QI teams encounter surprisingly stiff and, at times, unreasonable resistance to BPT. Caregivers actively resist change addressing a problem they do not believe exists. For example, at one NICU, tradition dictated that ELBW infants with respiratory distress in the delivery room receive quick intubation, surfactant, and mechanical ventilation. Caregivers dedicated enormous resources and effort over several years to systematize this approach. Attempts to implement nCPAP in the delivery room, contradicted established tradition or "the way we do things here." Clinicians did not believe the existing approach was flawed. They were uncomfortable with the new approach and frequently found reasons to skip nCPAP, moving directly to tracheal intubation. NICU personnel do not welcome unbidden change.

QI teams create a mandate by creating tension in the minds of caregivers between current and potential performance. Multichannel, educational campaigns that include case studies, outcomes measures, parents' stories, published clinical reports, meetings with groups and individuals all serve to increase this receptivity. No one channel works for all stakeholders.[189] Until QI teams have created this mandate, they create friction.

Step 6: Implement the QI Plan with Iterative Modifications

Analyzing the VON experience has enlightened BPT in NICUs.[57,190] Tucker et al.[57] surveyed NICU personnel from institutions participating in the VON-sponsored NICQ 2002 to assess the self-perceived implementation of best practices. They found a positive correlation between the quality and amount of supporting evidence for a best practice and its successful implementation. They also categorized QI activities into two types: those that identified best practices ("learn-what") and those that helped caregivers operationalize best practices ("learn-how").[57]

Learn-What and Learn-How

Learn-what activities included team meetings, site visits, and other activities that identified best practices. Although QI teams needed these activities to identify efficacious practices and to organize their efforts, learn-what activities were not directly associated with improvements in care or perceived BPT.[57,190] *Learn-how* activities taught frontline personnel how to integrate best practice into their daily work. For example, a pilot run of a new practice with a small set of patients or a dry run that mimics the best practice, but does not involve patients teaches participants how to operationalize new practices. *Learn-how* activities were associated not only with more effective implementation but also with improved clinical outcomes.[37,190] *Learn-how* activities depend on psychological safety and facilitate iterative modifications of the practice allowing smooth integration within the context of a particular NICU.[57] Organizational climate, and particularly psychological safety, influences QI and outcomes.[190-193] Staff must feel free to ask questions and raise difficult issues without fear of punishment or ridicule. Psychological safety also influences innovation,[192] making the organizational climate an important determinant of organizational change. These findings suggest that implementation poses the greatest challenge to QI teams.

Step 7: Identify Resistance to Change and Address the Issues

Cabana et al.[194] analyzed 76 studies of guideline implementation and identified major obstacles to BPT. The obstacles to BPT resemble those of guideline implementation. QI teams will confront all of these obstacles. Diagnosing the nature of the obstacle facilitates an appropriate solution. Most QI teams will encounter multiple obstacles and need multiple solutions.

Lack of Awareness

A meta-analysis of studies on compliance with guidelines found an average of 54% of physicians surveyed were not aware of the guideline to be implemented.[194] Despite memos, posters, emails, and journal reprints, some clinicians will remain unaware of the motivation, purpose, and mechanics of any proposed QI effort. The average practicing physician (and likely most other professionals) has only 1 hour per week available to read educational material relevant to their practice.[195] Complicated, new protocols can overwhelm busy physicians.[195] Simple messages presented repetitively in different formats succeed more often than a single message. However, even after clinicians become aware of a best practice, they do not necessarily agree with it.

Lack of Agreement

Physicians and nurses resist new practices that they do not believe will improve care. Physicians object to new practices on the basis of reduced autonomy, "cookbook" oversimplification, impracticality, and decreased flexibility.[194] Physicians must believe that the proposed practice is well supported by published evidence and can work in their setting. QI teams may need to show comparative data, evidence of successful implementation and improved outcomes at other institutions, or positive results from a pilot run of the practice. If just one clinician has a negative experience or outcome using the new practice, not only he or she but also others may refuse to adopt the new practice. Using the PDSA cycle of iterative modifications to address specific concerns mollifies this resistance. Enlisting the assistance of opinion leaders also improves acceptance.

Inability to Comply

Fear of failure also drives resistance to change. About two thirds of respondents from 19 studies of physician compliance reported that they could not reasonably comply with the practice they were asked to implement.[194] Clinicians may feel anxiety about using new technology (e.g., HFV) or practices (e.g., delivery room nCPAP for resuscitation) with which they lack familiarity. Without an environment of psychological safety, caregivers will not raise their concerns about ability to comply. Grol and Grimshaw[196] identified factors increasing compliance with a new practice: concrete description of the desired performance, few new skills required, required decision making that is simple, and minimal change to the organization overall.[196]

Inertia of Previous Practice

Clinicians who feel comfortable with traditional care feel little motivation to change. Change readiness begins with contemplation about an outcome that could be improved and the need for a new practice.[197] QI teams need first to create change readiness and then have a mandate for change, usually through unit-specific data that does not meet expected results. Virtually all professionals possess an innate desire to provide superb care. Demonstrating the potential performance improvement from compliance with new practices through benchmark data, case studies, and other NICUs' experiences help overcome inertia.

Behavior rarely changes without feedback. NICU care requires the contributions of many doctors, nurses, therapists, and others. This "group" care insulates individual clinicians from feedback about their specific performance. Individual feedback showing that a particular physician weans mechanical ventilation more slowly, uses surfactant later, or uses nCPAP less often than his or her peers overcomes inertia faster than group feedback. Without feedback, inertia often overpowers change efforts.

External and Environmental Barriers

Clinicians often describe new practices as cumbersome, confusing, and inconvenient.[194] QI teams must recognize and address the workflow implications of new practices. For example, infants on nCPAP require more nursing skill and time than sedated, mechanically ventilated infants. However, nurses with the most experience and skill are often assigned to intubated infants, and less experienced nurses are assigned to babies on nCPAP. The increased nursing requirements from expanded use of nCPAP can doom a QI team's efforts. Implementing new practices can place new demands on the NICU and hospital resources. The effectiveness of addressing these new demands often determines success.

Interventions to Overcome Resistance

Whatever obstacles a QI team confronts, they will need multiple interventions to overcome them.[198,199] Grol[201] has categorized interventions into seven groups: educational, epidemiological, marketing, behavioral, social, organizational, and coercive. A modification of his approach appears below.

Educational/Epidemiological Strategies

Educational and epidemiological strategies assume that if clinicians just knew the data and the evidence for a better practice, their drive for excellence would motivate them to adopt it. The published results of educational efforts suggests that QI teams occasionally succeed by educational efforts alone.[196] Educational meetings/seminars affect clinician performance modestly.[195] Adult learners benefit most from interactive educational sessions[196] that engage learners and relate the new practice to their daily practice. This approach addresses lack of awareness or lack of agreement, allowing participants to seek clarification and express doubt.[201] Educational efforts work best at the beginning of a project to build a desire for change and engage caregivers in the QI process.

Case Study 19-5 OVERCOMING LACK OF AGREEMENT

One QI team sought to reduce the fluids administered to ELBW infants to reduce BPD. Despite a well-prepared presentation and protocol, the neonatologists rejected the protocol as incomplete. Only when the QI team had addressed the special needs of infants with hypotension, renal failure, or high insensible water losses, did the neonatologists agree to the protocol.[167] Engagement of clinicians in protocol development greatly facilitates implementation of a new practice.

Marketing

Attractively and cleverly framed messages create a desire in caregivers to adopt a new practice.[201,202] QI efforts need to appeal to head and heart, both logic and caregivers' passion for helping patients. The new practice should be framed in fact and appearance as assisting caregivers achieve their goals of superb care. Clever bedside signs and project names, such as Oxygen With Love, or OWL (designated at each bedside with the picture of an owl to maintain oxygen saturations in the SpO_2 target ranges),[202] help caregivers connect the new practice with their desire to help their patients. Marketing requires multiple distribution channels for the message.[201] Marketing creates desire for the practice and builds on educational efforts that should create tension between current and potential performance. When coupled with learn-how activities, clever marketing can drive QI efforts beyond obstacles such as lack of awareness, inability to comply, and inertia.

Behavioral Interventions

Behaviorists view human behavior as being modifiable by external stimuli, such as feedback, incentives, reminders, and sanctions.[201] Rewards for compliance with the new practice and negative feedback for noncompliance help overcome inertia.[200,203] However, feedback does not appear sufficient to sustain change.[198] Feedback works best when the recipient agrees to receive it[204] and when it is continuous.[198] Case audits, computerized reminders, and checklists modify behavior.[200] Feedback changes behavior most effectively when given proximate to the behavior to be influenced[204] and to individuals, not groups.

Social Interventions

Each NICU constitutes a sort of social network. Caregivers look to this network for support and approval.[201] QI teams have used opinion leaders, expert consultants, and even patients' families to change caregivers' behavior. Opinion leaders also facilitate agreement, but each group (neonatologists, nurse practitioners, nurses, etc.) requires an opinion leader specific to that group. Furthermore, different practices require different opinion leaders.[195] QI teams have even enlisted parents by asking them to challenge caregivers who do not practice appropriate hand hygiene before touching their baby. Peer pressure, informal communication, and social interactions contribute to overcoming inertia.

Organizational Interventions

Many QICs view the NICU as a microsystem within a larger macrosystem (hospital or health network).[172] They approach care improvement from the systems perspective, recognizing the need to coordinate many different personnel, equipment, facilities, supporting activities, and working relationships to improve care. Emphasizing the role of systems, and particularly microsystems, forms a key part of recent VON and IHI QICs. This view of QI works better than many approaches and emphasizes the interdigitated roles of multiple caregivers in producing complex outcomes. This inclusive approach minimizes assignment of blame and encourages all stakeholders to collaborate to improve care. A systems perspective works especially well when addressing barriers to implementation. QI efforts always occur within a context of competing demands for fiscal and human resources. For example, conversion to an electronic medical record, computerized physician order entry, and staffing levels all impact the QI team's ability to transfer new clinical practices into the NICU microsystem. QI teams that recognize and adapt BPT to the demands of the whole microsystem and understand their role within the larger meso- and macrosystems overcome barriers more effectively than those that myopically focus on just the implementation of their proposed best practices.

Coercive Interventions

As a last resort, QI teams turn to coercion. Frustration with poor compliance leads to rules, complaints, and threats for noncompliance, such as the often heard "It's malpractice if you don't … ." Occasionally, inertia and resistance may be so fixed that organizational force is required to dislodge caregivers out of old habits. However, this approach damages relationships and engenders *sub rosa* resistance. It should be used sparingly, and only if all else fails.

Step 8: Monitor and Analyze Outcomes

Primary Outcomes

Monitoring and analyzing interim and final outcomes serves three purposes. First, without measuring process change, QI projects produce uninterpretable results. Improvements in outcomes could be due to chance, BPT, or a change in patient demographics. Second, interim goals allow a QI team to detect unintended consequences, and critical to the PDSA cycle, make iterative adjustments in implementation. Third, QI projects lose momentum without frequent assessment of progress and feedback to participants. Measures of process change (e.g., minutes after birth to surfactant administration, babies receiving postextubation nCPAP, percentage of eligible mothers receiving antenatal steroids, etc.) provide critical windows on the effect of BPT. Another reason to monitor outcomes and processes is that QICs sometimes cause unintended and unexpected consequences.

Subgroup Analysis

Infants with BW 401 to 750 g develop BPD more frequently than any other BW group. QI teams also have the

Case Study 19-6 UNINTENDED CONSEQUENCES

Even innocuous changes in care can injure patients. For example, efforts to introduce new guidelines for standardized monitoring of alcohol-withdrawal severity and a prophylactic, fixed-schedule benzodiazepine treatment of at-risk patients reduced clinical deterioration leading to a transfer to a higher level of care.[205] However, the new protocol was associated with a doubling of the risk of death and also increased the length of stay by 18%. Researchers could not identify the cause of the adverse effects.

most difficulty implementing change in this group. For example, the ReLI group successfully increased nCPAP use and decreased postnatal steroid use in infants with BW 750 to 1000 g, but could not make comparable changes in the smaller infants with BW 501 to 750 g (author's unpublished data). Other studies have found similar difficulty in changing the outcomes in this smallest group of ELBW infants.[122] Clinicians should be mindful of this subgroup influence without data torturing to discover a subgroup that improved.

Step 9: Report Results to All Stakeholders

QI teams must report interim and final results of QI projects to stakeholders. Too many teams fail to disseminate QI results to their peers and to others within their institution, such as administrators. Whether or not a new practice improves care, publicizing QI efforts to others within the larger organization garners administrative support, without which QI efforts cannot be sustained.

Step 10: Maintain Gains

QI projects have achieved performance gains; the approach works. However, these improvements often diminish over time. As the QI team turns its attention to other projects, previous gains can erode. Caregivers may simply return to previous practices or modify the newly implemented practices, thereby altering outcomes.

Practical Considerations

Costs of QI Projects

Quality improvement projects consume resources.[20,174] Individual hospital costs for participating in the VON-sponsored QIC, the NIC/Q, averaged about $126,181 in 2007 dollars.[20] Internal costs (staff time to participate) for the 2-year project were $60,353, with the remainder paying for staff to attend semiannual meetings of the collaborative. Rogowski et al.[20] also measured VLBW treatment costs (not charges) associated with participation in the NIC/Q. The six NICUs focusing on nosocomial bacteremias decreased the infection rate from 26.3% to 20.9% (p = 0.007) and decreased treatment costs 19%. The four other NICUs in the NIC/Q attempting to increase BPD-free survival did not show a significant costs savings, although the trend was favorable. Eliminating nosocomial infections saves money for a hospital. The marginal cost of nosocomial bacteremias in VLBW varied from $5875 to $12,480 (in 1999 dollars), depending on gestational age.[206] On the basis of these reports, quality improvement projects provide a return on investment that more than justifies their costs.

Criticisms of QI Projects

Some criticize QI projects and the QIC method as being ineffective. They attribute improvements to regression toward the mean by NICUs with high BPD rates or to the Hawthorne effect—a short-term improvement in performance caused by increased scrutiny. Others criticize QI projects as being unscientific, because they change many treatment processes simultaneously and usually rely on before/after comparisons. QI projects and scientific studies fundamentally differ in their purpose and structure (see Table 19-3). QI projects should be seen as embedding sound medical science into clinical care. The way in which new science becomes integrated into practice will vary at each NICU. QI teams could learn from the careful planning that goes into clinical trials. When they plan their QI projects with the same attention to detail used by clinical trialists, they are more likely to succeed. Caregivers also need more reports of effective BPT in NICUs.

Conclusions

Although our knowledge of the best respiratory practices and BPT remains incomplete, QI teams can improve respiratory care.[1,24,25,40,63,64,203,207] Improving respiratory care improves the lives of our patients forever. Horbar et al.[208] estimated that reducing all NICUs' CLD rate from the current mean to the 20th percentile would prevent over 2500 cases of BPD annually. Although QI teams may not consistently succeed in all of their objectives, they will succeed over time, if they persist in using evidence-based clinical practices and apply them using evidence-based BPT principles. Our patients and their families deserve this effort.

Case Study 19-7

One center developed a project to reduce BPD, which included reducing nosocomial infections. During and shortly after implementing multiple best practices, they saw a significant improvement that was maintained for about 8 months. As the infection rate began to rise again, an investigation of compliance showed that caregivers had reverted to the previous skin prep routine and abandoned the newer, more effective routine for central line insertions. New practices take many months or years to become part of the NICU culture and habitual practices of caregivers.

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20 Human Factors and Safety in Ventilator Management

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Mechanical ventilation in most situations is a life-saving intervention and is a central feature of neonatal intensive care. Unfortunately, in some situations it can also cause inadvertent harm (including death) to patients, through preventable events such as unplanned extubation, airway injury leading to subglottic stenosis, ventilator-induced lung injury, and ventilator-associated pneumonia. In one study of 10 Dutch neonatal intensive care units, 9% of patient safety incidents were related to mechanical ventilation. Of all recorded incidents, those related to mechanical ventilation and to blood products had the highest risk scores (an indicator of the likelihood of recurrence and likelihood of severe consequences).[1] In recent years, many publications and expert reports have emphasized that preventable harm to hospitalized patients from medical errors is frequent. A *medical error* is defined as failure of a planned action to be completed as intended, or the use of a wrong plan to achieve an aim.[2] An *adverse event* is defined as an injury resulting from a medical intervention.[2] *Patient safety* is defined as freedom from accidental injury.

Ensuring patient safety involves the establishment of operational systems and processes that minimize the likelihood of errors and maximizes the likelihood of intercepting errors when they occur.[2] It is crucial to ensure patient safety while providing mechanical ventilation to neonates. The complexity of mechanical ventilation, the number of health care providers who interact with the patient-ventilator interface, and the differences in experience and training of these providers, makes such an endeavor a prime source of potential medical errors.

This chapter describes some preventable adverse events related to mechanical ventilation, the potential causes of such events, and methods of preventing them. Although the primary focus is mechanical ventilation, many of the principles described also apply to ancillary equipment such as endotracheal tubes, monitoring probes, gas fittings, and heat-humidification devices. A key principle of improving patient safety and reducing medical errors is to focus not on individual health care providers as the cause of errors (the "person approach"), but to focus more broadly on the system of care (in which the provider is embedded) as the desired locus of prevention (the "system approach"). Optimal design of equipment, tasks, and the work environment can enhance error-free human performance and the use of principles of human factors engineering can successfully guide such optimal design. Rather than commenting on specific devices and equipment used for neonatal mechanical ventilation, this chapter describes some general human factors engineering principles that clinicians can apply to the selection and use of devices and equipment in their own institutions to ensure safe mechanical ventilation. Some evaluation and analysis tools are also provided.

Errors and Adverse Events Related to Mechanical Ventilation

A wide range of adverse events and errors may occur during mechanical ventilation. These are listed in Box 20-1. Many of these result paradoxically from the same features of ventilation that are usually life saving and beneficial. For example, oxygen is both a source of harm and a necessary component for life; positive airway pressure presents a similar challenge, and both too much and too little can cause harm (see Chapter 23 on Complications). An important scientific discipline that is a foundation of safety sciences is *human factors science*.

Human Factors Science and Patient Safety

Human factors science is a well-developed discipline with considerable application to patient safety[3]; it can be valuable in identifying the causal mechanisms leading to adverse events during ventilation, as well as in developing preventive strategies. Under the human factors approach, it is important to consider the ventilator and the associated equipment and monitoring devices as a *system*. This system serves to replicate respiratory function and involves a complex set of elements and processes, of which the operator is one variable. The inevitable presence of humans in this system makes things more complicated and complex. The integrity of this system depends on the design of the device and its interaction with other parts of the system. The concept of interface is integral to the consideration of human factors and safety and an ecological approach seems most appropriate.[4] The interfaces of concern are not just the displays and control of the various ventilators and ancillary devices, but also the interactions with a complex and central component of the system—the patient.

Although it is convenient to examine any device or interface in isolation, in reality, all such equipment is

Box 20-1 ERRORS AND ADVERSE EVENTS RELATED TO MECHANICAL VENTILATION

Endotracheal Intubation
- Use of wrong size of endotracheal tube
- Right main-stem bronchus intubation
- Unplanned extubation
- Obstruction of endotracheal tube due to inadequate suction
- Airway injury leading to subglottic stenosis
- Tracheal perforation from endotracheal tube suction catheter
- Kinking of endotracheal tube

Initiation of Mechanical Ventilation
- Improper setup of ventilator and accessories
- Failure to add water to humidifier
- Misconnection of ventilator tubings
- Omission of safety limits on ventilator settings
- Omission of alarm settings

Use of Mechanical Ventilation
- Delay in changing ventilator settings in response to blood gas results
- Inadvertent delivery of high or low ventilator pressures (e.g., auto PEEP)
- Failure to wean inhaled oxygen when oxygen saturation is high
- Ventilator associated pneumonia
- Inadequate drainage of condensate in ventilator tubing leading to inadvertent pulmonary lavage
- Ventilator failure due to poor maintenance by biomedical engineering
- Overriding ventilator alarms
- Ignoring ventilator alarms

PEEP, Positive end-expiratory pressure.

operated in conjunction with other devices in a constantly changing neonatal intensive care environment that is unique to each hospital, adding to the complexity of the system. Error management in such complex systems requires broad consideration of the mechanisms of error. Errors relating to device use often involve some aspect of device design, and the conditions for error are set in place by the way in which the device-operator interface is designed and functions in the variable contexts of use.

Task Hierarchy and Error Analysis

Hierarchical task analysis[5] provides a method to analyze the system associated with ventilation safety. This approach involves the identification of goals, tasks, and steps. Although a detailed hierarchical task analysis has not been reported for ventilation management, it would be a valuable tool. Such an analysis is partially completed in various forms when clinicians and administrators detail their procedures for standardization, education, and other purposes. A hierarchical task analysis applied to mechanical ventilation begins with an assessment of the goals of ventilation management.

These goals might be listed as follows:

1. To maintain adequate pulmonary gas exchange
2. To avoid causing harm to the patient's respiratory tract or to other organ systems

Next the task analysis would detail the various tasks involved in ventilator usage. These tasks may include the following:

- Identification of requirement for ventilation
- Selection of appropriate mode, settings, and parameters (ventilator breath settings, alarms, and safety limits)
- Monitoring of patient status and ventilator functioning
- Routine checks and preventive care (e.g., suctioning, draining of condensate from ventilator circuit)
- Responding to changes in the patient's condition, including changes in monitoring parameters

Human Error Taxonomy

When considering the safety implications of any process involving human performance, it is useful to take a systematic approach to enable a broad and thorough consideration of possibilities. One such systematic approach is SHERPA (Systematic Human Error Reduction and Prediction Approach; Box 20-2).[6]

Errors in perception lead to errors in action. The fidelity of the device's display in representing the patient's true state and the system's function (the veridical concept) can lead to appropriate or erroneous action. The format, that is, the kind of information displayed and its physical characteristics (e.g., graphic, numeric, complete, partial) will also affect the operator's responses and either promote or prevent errors. If the display provides information that is incomplete or not easy to integrate into a defined and known action response, the operator may commit an error, leading to potential harm. Operators may also act without full information or in haste due to situational factors such as urgency, distraction, or operator fatigue. Novel display design characteristics for ventilators have been the subject

Box 20-2 SHERPA—SYSTEMATIC HUMAN ERROR REDUCTION AND PREDICTION APPROACH

Action Errors	Operation too long/too short
	Operation mistimed
	Operation in wrong direction
	Operation too little/too much
	Misalign
	Right operation on wrong object
	Wrong operation on right object
	Operation omitted
	Operation incomplete
	Wrong operation on wrong object
Checking Errors	Check omitted
	Check incomplete
	Right check on wrong object
	Wrong check on right object
	Check mistimed
	Wrong check on wrong object
Retrieval Errors	Information not obtained
	Wrong information obtained
	Information retrieval incomplete
Communication Errors	Information not communicated
	Wrong information communicated
	Information communicated incomplete
Selection Errors	Selection omitted
	Wrong selection made

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of study. However, the optimal format of information presentation that leads to better qualitative decisions and respiratory control remains inconclusive.

Human Factors and Device Usability

With the advent of information technology and concomitant complexity in device-user interfaces, usability has become an important consideration in patient safety. The intravenous pump in particular has been the subject of the application of principles of usability in efforts to aid hazard analysis and evaluation for the purpose of procurement.[7,8] A similar analysis has not been reported for the use of neonatal mechanical ventilators. However, the following principles will enable analysis and consideration of error potential relating to usability.

Nielsen[9] has reported extensively on the topic of usability and his framework has been used by others as the starting point for applying heuristics to usability evaluation. Usability engineering should be applied in the design phase of device development, at which point the greatest opportunity exists to avert potential usability-related problems. The practice involves a variety of techniques in which potential users are given realistic use situations and the user experience is evaluated through simulation and observation.[10] This approach has been applied to various medical device evaluations, primarily infusion pumps.[7,8,11] For the purpose of understanding potential human factors and patient safety of ventilator management, a typical set of usability heuristics are illustrated here (see below). It is important to recognize that thorough and comprehensive human error identification would involve systematic application of task analysis and human error tools such as SHERPA, which have been shown to improve the effectiveness of error reduction potential beyond that of heuristic usability evaluation alone. In general, usability testing involves a combination of *evaluation* using heuristics to direct attention to specific potential user problems and *testing* using simulation and observation with potential users.

Human factors engineering methods are described by Gosbee[12] and include field observations, simulation, heuristic analysis, and cognitive walkthroughs. Each method has advantages and application through the design process. Usability evaluation and testing have been the subjects of review from the practical standpoint of those involved in device selection and procurement. Both approaches have demonstrated value in aiding decisions; enabling the systematic identification and articulation of user experience in terms that can be considered and compared.[13] The knowledge gained by conducting this kind of evaluation also enables heightened awareness of error potential and consequently should have value in improving hazard control. The precise manner and extent to which user difficulties so identified would be significant clinically in the case of ventilators are unknown.

Usability Evaluation and Error Potential

The following is a review of typical heuristics used in the evaluation of device usability with consideration of some potential implications for ventilator management.[7] Although the application of usability heuristics such as these is considered cursory compared with full usability testing from concept through prototyping and design, it is a method of recognized validity and utility for practitioners and it informs the discussion of human factors and ventilator safety in this chapter.

Consistency with Standards

Each device should have a unique sequence of actions in order to perform common tasks. In the case of ventilators, the sequence to set one parameter should not be radically different than that of another, to enable skill acquisition and ease of use. A consistent standard can also be the use of color for categorization or display readability; for example, the provision of warning or alarm messages might always be outlined in red at the top right of the display. Similarly, all ventilation parameters might be displayed on the bottom of the screen in the same sequence in all cases. In cases for which an operator must use a hierarchical task sequence, display characteristics such as font differentiation or color might be used to indicate the operator's location in the hierarchy or sequence. Operational terminology such as *Delete, Escape* or *Enter* must be consistently used in all instances.

Visibility of System State

During the use of a device, clear visibility of its current mode and settings in response to an operator's input is essential if the operator is to remain aware of his place in the input sequence and of the performance of the device. This is also relevant to the indication of other conditions affecting performance such as when a ventilator has switched to battery mode—to indicate remaining battery life.

Match Between System and World

An important concept in cognitive engineering is mapping; the device control or display maps must project onto the real world exactly or with symbolic congruence. For instance, on the ventilator control, if a value is "turned up," a corresponding display should illustrate an increase. This is a difficult principle to follow because parameters such as pressure, flow, and rate are not easily illustrated except by numerical surrogates.

Minimalist

With advances in technical capability, devices are able to accrue and display an increasing amount of information in a complex fashion. A control and display should provide only the information required for the task and for safe performance and not superfluous information. A display or control should not be provided just because it is technically possible. Display information and control sequences should enable the operator to access increasing levels of detail as required rather than default to display all information for all tasks.

Minimize Memory Load

Task sequences should be designed into the user interface in a way that does not demand that information be remembered. Sequences and routines should remain the same across all tasks to enhance the ability of users to learn and follow standard use procedure. A device can be designed, when prudent, to provide prompts and choices rather than user-recalled variables.

Informative Feedback

The performance of task steps that are critical to safety should provide feedback to confirm that they have been performed correctly and to illustrate the effect of action taken. On the ventilator this may be an immediate display of the parameter or value; with other associated equipment this feedback may be something as simple as a confirmatory 'click' sound when tubing is properly connected or a temperature probe has been inserted to the appropriate depth for monitoring accuracy.

Flexibility and Efficiency

Flexibility is important for usability in ventilators because of the range of ventilation modes and settings. If a particular setting sequence can be safely provided as a selectable choice, avoiding the unique entry of all parameters for each instance of use, it can reduce the possibility of operator error and improve efficiency. This capability should be weighed against the possibility that an easily selected choice may result in an inappropriate variable.

Prevent Errors

A device can be designed to help prevent errors through mechanisms based on known hazards. A simple example is the structural differentiation of anesthetic gas and oxygen tubing fittings through unique shapes that are incompatible with each other to prevent the misconnection of oxygen and anesthetic gas tubing. The strongest hazard control will make the error impossible. Other mechanisms include affordances such as color matching and visibility of error or alarms and warnings that display to indicate inappropriate choices or to specify a hazard prior to execution. Another example relates to the increasing use of ventilators designed to accommodate all ranges of patient populations for neonates; a neonatal setting should be selectable that locks-out adult or pediatric parameters to make this dangerous range of parameter values inaccessible.

Meaningful and Effective Messages

Early devices faced the limitation of primitive display technology and resulted in limited information at any one step in a procedural sequence. It is now possible for devices to display complex information with symbols and color. This has resulted in a surge of information that is available "on-screen." More is not necessarily better, and in the case of ventilators, the messages must carry meaning that is easily interpreted and acted upon. Messages provided to supplement default displays may carry error information; when this requires action, the message should be delivered visually and with an auditory alarm. The message must provide information about the system state and ideally the action to be taken to restore a safe condition.

Clear Confirmation and Closure

The final step in a set-up procedure should provide a clear indication of the action about to take place and confirm with the operator that the action is correct. The confirmation step affords a natural redundancy in performance, and verification is an opportunity to avert an overlooked error that occurred during the procedure. This may be a step that is routinely acknowledged without verification, but the opportunity for a check is provided. For example, after adjusting a flow rate, the ventilator may present a confirmation message stating the new flow rate and requiring the operator to push a button to confirm the new rate as correct. The inclusion of a confirmation step in some instances and an instant change on other settings can create confusion for operators. This confirmation step is a feature that should be standardized to minimize confusion when changing ventilator settings.

Reversible Actions

When an individual step or series of task steps have been performed and an error is discovered, the operator should be able to learn that an error has occurred and then correct the error without necessarily first completing the whole task sequence.

Use Users' Language

Respiratory care has a set of definitions and terminology that must be adhered to in device displays and controls. Variation would set up opportunity for error and misunderstanding.

Users in Control

The feeling of being in control, having the capability to perform action, and respond to system information with confidence when required are important factors in usability. Operations should not have tedious sets of actions, surprising results, or unexpected outcomes.

Help and Documentation

Extra help is valuable for novice operators or in situations where a device is being used in a nonroutine manner. Increasingly this is available in the context of a task being performed. Some entry sequences for devices have implicit help in that they "walk the user through the steps."

Displays

Visual displays associated with medical devices have advanced considerably with the advent of new processing and screen technology. A recent review of research found that physiologic monitor display design can positively influence speed of response to adverse events, facilitating an accurate diagnosis, clinical decision making, and perceived workload and that novel designs improve performance over numerical displays in most cases. However, what designs are optimal and why they work is unclear.[14]

In addition to the usability features discussed above, one should consider other factors as part of a thorough analysis of safety. The proximity compatibility principle is concerned with both display proximity—how close together two display components are and processing proximity—the extent to which two information sources are used in the same task.[15] If a task requires high processing proximity, there should be high display proximity. The need to integrate, compare, or optimize more than one parameter is inherent to respiratory care tasks involving ventilator settings. This has implication for the device display design and, to a lesser extent, the position of complementary displays such as cardiorespiratory monitors whose display information may be involved in task steps involving the ventilator. An experimental display design

for a ventilator integrated the peak airway pressure, positive end-expiratory pressure, minute volume, respiratory rate, fraction of inspired oxygen, and end-tidal carbon dioxide into a circular graphic format.[16]

Each wedge of the circle graph showed the upper and lower alarm limits for each parameter and the current state value. The authors hypothesized that this would make the detection of deviation easier and, consequently, would improve response and correction actions. The study found this display format had a positive effect on ability to detect the meaning of parameter deviations and was subjectively preferred by the test group (nurses) over a more conventional numbers-only display. The study is important because it indicates a move toward scientific study of alternative design of displays.

Alarms

Auditory alarms in ventilation devices can carry a range of information from simple confirmatory feedback for an operation, such as a single tone associated with an entered parameter through to a warning announcing an abnormal critical physiologic measurement such as low or high oxygen saturation. The neonatal intensive care unit (NICU) can present a cacophony of auditory information for which providers develop a tolerance. Indeed, the adaptive responses associated with alarms follows a predictable pattern. The phenomenon associated with perceived need and response rate is called *probability matching*.[17] The higher the reliability of the alarm, the greater the compliance in response. A ventilator disconnect alarm is often much louder and persistent than a high or low oxygen saturation alarm and usually generates a quicker response from the bedside caregiver. This has led to a call for fewer but more reliable auditory alarms to improve patient safety.[18]

Procurement

A review of device usability should be a routine part of product evaluation. This has been reported by Zhang[7] and Ginsburg[8] using a heuristic approach as outlined above.In addition, the Federal Drug Administration (FDA) requires application of human factors engineering approaches as part of the design process and refers to the International Organization for Standardization (ISO) standard (ISO 14971:2007).[19,20] Furthermore, the Association for the Advancement of Medical Instrumentation (AAMI) is preparing a new standard: AAMI/CDV-2 HE75, Human factors engineering—Design of medical devices.

Beyond the device characteristics in isolation, one should also consider how a device's operational characteristics may vary from other devices in operation in the same unit. Despite the FDA general requirement to address human factors and safety associated with medical devices, there is no rigid standard. Variation in specific control, display, and operational sequences suggest a review of how these may conflict in any unique clinical context. There may be error-provoking nuances in operation that at the very least should be identified and included in operator instruction and training. If conflicts have severe consequences, the risk should be carefully considered.

Device procurement decisions are influenced by cost and hospital standards. In some cases ventilators are not specific to the neonatal population. How this decision may affect safety warrants careful review and analysis. The capacity to program, set, and lock devices in neonatal mode with fail-safe mechanisms is one alternative for controlling this hazard.

Training is a final preventative approach that should be deployed as part of implementation. Programs should include a review of any potential usability difficulties and specific safety concerns associated with the use of devices.

Procedural Control

Consider the following examples:

1. A premature baby was admitted with respiratory distress, requiring hood oxygen, which was set-up by the respiratory therapist, and documented. The unit policy was to run oxygen into an oxyhood from a blender and wean via the blender, monitoring O_2 concentration with an analyzer. In this case, the oxygen was inadvertently run into the hood from an oxygen flowmeter attached to the wall oxygen outlet, not from a blender. The baby was treated with oxygen through the hood for 48 hours without an oxygen analyzer in line. No pulse oximetry or blood gas analysis was performed.
2. A premature infant in an incubator has been weaned from oxygen to room air, but now has a continuous oxygen saturation of 100%. The nurse noticed that the oxygen flowmeter was left running at 6 lpm with oxygen tubing inside the incubator, contrary to policy. The position of the flowmeter made identification of air/oxygen difficult.

These two cases are examples of "rule violations" in which the health care providers failed to follow the unit's policy or procedure. The use of ventilators and associated equipment invariably becomes the subject of operational rules or protocols that would ideally integrate the practice that has been standardized along with relevant supplementary direction on how equipment is deployed. Although this is an important component of effective hazard control, one must be clear about the limitations and fallibility of this approach.

The conscious and deliberate migration from rules has been identified as a common behavioral outcome of working in complex environments that require ingenuity to get the work done.[21] In many cases the deviation becomes the norm and de facto standard, despite contrary "official" rules. Extreme cases of violation must not be tolerated, but there are what Amalberti calls *borderline tolerated conditions of use*—those situations when a variation from standards is accepted and socially sanctioned.[21] In this category, variation can be a signal that something is not working—the proverbial "work-around" should be an alert to health care providers of the potential for hazardous situations in need of some form of remediation beyond the creation of new or reminder of old (ineffective) rules.

In addition to the deliberate variation from accepted standards, there are also practical limits to the effectiveness of operational procedures due to errors such as lapses in attention, memory failure, and distraction. Omission of a procedural step or steps is one of the most common errors of procedure compliance.[22] Consequently, it is important to error-proof procedures with redundant safeguards for procedural steps that may be left out. Reason has classified

omission affordances—conditions that promote the likelihood that a step will be omitted (Box 20-3).[22] These factors provide clues on how to modify conditions to reduce the likelihood of omission. Additionally, there are two strategies with demonstrated success in health care procedures: checklists and reminders.

A checklist provides a procedure-following aid that helps to ensure standards are followed every time. This strategy has been used to improve safety in the ICU[23] and for distinct procedures associated with infection prevention practices.[24] The mechanism of checklists is likely to have a beneficial effect for some procedures associated with ventilation, especially procedures that are infrequent or complex.

Reminders are often used in a make-shift manner to assist with prospective memory for tasks or steps that need to be performed or checked or as safety warnings. Characteristics of effective reminders are outlined in Box 20-4.

Other methods of ensuring that procedures are followed include visual cues and affordances such as inspiratory and expiratory tube color differentiation. Visibility provides a form of redundancy following the performance of a task; even if the operator does not catch his or her own error, if it is visible, it is more likely to be detected by someone.

Fatigue and Error

Finally, there is the operator's state that can compound any human factors design weaknesses. Fatigue has a predictable effect on performance, and the prospect of fatigue-proofing practice or device design is appealing. For instance, fatigue causes a reduction in memory performance; the need for devices whose operation does not overly rely on memory becomes more important under conditions of sleep debt. Fatigue also reduces auditory attention, which may lead to missing subtle alarms or auditory feedback.

Box 20-3 OMISSION AFFORDANCES

Information Load
- High demand on short-term memory for this step may lead to part of the step's omission.

Functional Isolation
- No prior step cues the action involved in this step or the step does not follow as part of an easily recognized succession. No subsequent step requires this step's completion.

Repeated Step
- The same or similar step is repeated. If steps must be repeated, one or more of the iterations may be missed.

Necessary Step After Main Goal
- Steps near the end of procedure after the main goal has been achieved. May be a routine action that is omitted while preoccupied with the next step or finishing the procedure.

Item Acted on Hidden or Not Obvious
- The step requires an item that is not visible or conspicuous.

Departure from Standard
- The step is different than standard procedure; habit may result in substitution of standard step instead.

Weak or Ambiguous Signal
- The step must be triggered by a signal that is easily missed (not heard, not seen, not recognized)

Unexpected Interruption Likely
- The procedure is likely to be interrupted at or just before this step.

From Reason J: Quality and Safety in Health Care 11(1):40-44, 2002.

Box 20-4 CRITERIA FOR GOOD REMINDERS

Conspicuous	Able to catch attention.
Contiguous	As close as possible in time and space to the necessary action.
Context	Provides information about the *when* and *where* of the item to be remembered.
Content	Provides sufficient information about *what* has to be done.
Count	Allows a count of the number of actions that need to be done.

From Reason J: Quality and Safety in Health Care 11(1):40-44, 2002.

Conclusion

Ensuring that patients are not harmed as a result of mechanical ventilation is an important aspect of providing respiratory care. Using a combination of knowledge from the fields of engineering, psychology, and design and applying that knowledge to the purchase and use of respiratory equipment, to the training of health care providers, and to the design of health care providers' work will undoubtedly maximize the benefits of respiratory care and minimize the potential for caregiver errors.

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21 Pharmacologic Adjuncts I

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Pharmacologic agents are frequently used as adjuncts to therapy with mechanical ventilation. Neonates present a special challenge in this regard because knowledge of drug dosage, distribution, metabolism, and side effects for them is often incomplete. Reported experience is frequently anecdotal, and extrapolation of information from adults or older children to the neonate may be inappropriate. Furthermore, many agents must be used off-label because they have not undergone the rigorous testing in this age group required by the United States Food and Drug Administration (FDA) for inclusion in the package insert. The following discussion is limited to those commonly used drugs not discussed elsewhere in this text, and it is not intended to be a complete reference work.

Sedatives and Analgesics

In a survey published in 1997, neonatologists and neonatal nurses rated the pain associated with intubation and with endotracheal suctioning at approximately 2 on a scale of 0 to 4 (not painful to very painful). Yet, depite their beliefs that infants experience significant procedural pain, the use of techniques to manage pain were suboptimal.[1] Infants with pain and discomfort may struggle against the ventilator, thereby decreasing the effectiveness of ventilation. This often is referred to as *agitation.* Under such circumstances, sedation and analgesia not only improve ventilation but also may make patients more comfortable, hasten recovery, and even decrease the risk of complications such as pneumothorax and intraventricular hemorrhage.[2-4] Evidence suggests that pain experienced in the neonatal period carries long-term consequences[5,6]; therefore, one should consider use of analgesics in all ventilated neonates. Anand et al. in a pilot study[7] found that morphine administered prophylactically reduced the incidence of poor neurologic outcomes from 24% in preterm, ventilated, nontreated patients to 4% in the morphine group.

However, the beneficial findings in the Anand study were later refuted in the group's larger randomized trial,[8] and in fact, the use of morphine was found to be deleterious to long-term outcomes. This has led clinicians to reevaluate their practice of using analgesics in premature infants. Nevertheless, a recent review[9] and statements by the American Academy of Pediatrics (AAP)[10,11] recommend strategies about pain management in neonates that includes pharmacologic therapy. The Committee of the Fetus and Newborn of the AAP is presently developing a statement on the use of premedications (to include analgesics) for nonemergent intubation of neonates. Environmental strategies such as swaddling, containment, facilitated tucking, and decreasing ambient noise and light may attenuate physiologic responses to ventilation and endotracheal suctioning and should be attempted as a first measure.[12] Typical dosages for sedatives and analgesics are listed in Table 21-1.

Morphine

Morphine is a well known opium alkaloid whose major effects act on the central nervous system (CNS) and organs containing smooth muscle, such as the gastrointestinal and urinary tracts. Its mechanism of action as an analgesic agent is the stimulation of opiate receptors in the CNS that mimic the effects of natural endorphins.[13] Sedation, analgesia, and respiratory depression and reduction in body temperature are all produced by the administration of morphine in conventional dosages. Respiratory depression, which is due to effects on respiratory centers in the brainstem, may be marked but is not usually of clinical significance in ventilated infants unless weaning from the ventilator is anticipated.[14]

Morphine may cause a reduction in peripheral resistance with little or no effect on cardiac index that could lead to hypotension, but usually is well tolerated in neonates. In a secondary analysis of the NEOPAIN Study,[15] Hall et al. found that morhine was associated with hypotension, but the adverse outcomes of intraventricular hemorrhage or death were associated with preexisting hypotension, not the use of morphine. The authors concluded that morphine infusions can be used safely for most preterm infants, but needs to be used with caution in infants of 23 to 26 weeks' gestation and especially in neonates with preexisting hypotension.

Histamine release is common; bronchoconstriction may occur either as an idiosyncratic reaction or from large dosages. Morphine decreases gastric motility and, at the same time, increases anal sphincter tone and urinary tract smooth muscle tone. In a randomized trial, Menon et al.[16] showed that morphine delays the attainment of full feeds but did not lead to major gastrointestinal complications.

Morphine is well absorbed by all routes, including the oral route, but it is usually given parenterally to sick neonates. The onset of action is prompt and peaks at about 1 hour after injection.[17] The duration of action in neonates

TABLE 21-1 Sedation and Analgesia for Neonates

Agent	Bolus Dose	Dose Frequency	Infusion Dose
Sedation			
Lorazepam	0.05-0.1 mg/kg	4-12 hr	Not recommended
Midazolam	0.05-0.15 mg/kg	2-4 hr	10-60 mg/kg/hr
Analgesia			
Morphine	0.05-0.2 mg/kg	2-4 hr	10-15 mg/kg/hr
Fentanyl	1-4 mg/kg*	2-4 hr	1-2 mg/kg/hr

*Slowly, over approximately 5 minutes.

may be 2 to 4 hours. Morphine is primarily detoxified by hepatic conjugation with glucuronide, which is then excreted in the urine and bile. Morhine pharmacokinetics vary with age, both gestational and chronological. In neonates less than 1 week, estimated clearance is 9 mL per min per kg but by 2 months is at adult values (20 mL/kg/min).[18] There is an average elimination half-life of approximately 9 hours in preterm infants.

The usual dose of morphine sulfate in neonates is 0.05 to 0.2 mg/kg. Repeat doses of the same magnitude may be given as necessary, usually every 2 to 6 hours. Morphine can also be given by continuous intravenous infusion at a rate of 10 to 15 mcg/kg/hr after an initial loading infusion of 100 mcg/kg over the first hour,[19] but some authors suggest that a dosage of 5 mcg/kg/hr in term newborns would give adequate morhine concentrations for effective pain relief.[20] With prolonged administration, some degree of tolerance develops, necessitating an increase in dosage. Following extended use, a weaning regimen that reduces the dose by 10% to 20% per day is recommended to prevent withdrawal symptoms.

Respiratory depression, decreased gastric motility, and urine retention must be anticipated and considered in the management of infants receiving morphine. Morphine effects can be reversed by naloxone 0.1 mg/kg.

Fentanyl

Fentanyl is a synthetic opioid that has been used for anesthesia and is a popular analgesic agent in neonates. It is 80-fold more potent than morphine on a weight basis but has fewer respiratory depressant and cardiovascular effects. The latter characteristics are considered to be a result of its lesser effect on histamine release.[21] It also has been shown to have less gastrointestinal side effects.[22] Disadvantages of fentanyl, with respect to morphine, include a lack of sedative properties and the risk of chest wall rigidity.[23,24] Fortunately, this as well as its other adverse effects can be reversed by naloxone administration. In addition, there is some evidence for a lower incidence of withdrawal after fentanyl therapy compared to morphine.[25] Fentanyl decreases the stress response to surgery and inhibits certain reflexes such as the baroreflex control of heart rate and the irritant receptors in the airway.[26]

Fentanyl has a rapid onset of action; however, it has a shorter duration of effect compared to morphine (1 to 2 hours).[27] Tolerance occurs more readily with fentanyl than with morphine, and a weaning regimen similar to that described for morphine is highly recommended for infants treated for more than a few days.[28] In one study,[29] a fentanyl total dose greater than 415 mcg/kg predicted withdrawal with 70% sensitivity and 78% specificity whereas a fentanyl infusion duration greater than 8 days predicted withdrawal with 90% sensitivity and 67% specificity.

Fentanyl can be given periodically by intravenous bolus, 1 to 4 mcg/kg, when short-term analgesia is desired and repeated as required every 2 to 4 hours. If prolonged use is anticipated, infusion is begun at a rate of 1 to 2 mcg/kg/hour and is increased according to symptom relief. Apnea is much less common when fentanyl is administered as an infusion compared to a bolus; however, its use may prolong duration of mechanical ventilation.[30]

Clearance is directly related to gestational age and birth weight, so adjustment of the infusion should be individualized in preterm infants.[31] Care should be used in neonates with increased intra-abdominal pressure as may be seen after repair of abdominal wall defects or with necrotizing enterocolitis because elimination is prolonged.[32] This is thought to be due to decreased hepatic circulation and thus clearance of the drug.

Diazepam

Diazepam has anxiolytic, hypnotic, anticonvulsant, muscle relaxant, and amnesic effects that are characteristic of benzodiazepines and, like other benzodiazepines, has no analgesic properties. Diazepam is absorbed rapidly after oral administration but irregularly after intramuscular administration. The elimination half-life approximates 75 hours in premature newborn infants and 30 hours in full-term infants.[33] It is metabolized in the liver and, along with its metabolites, is slowly excreted in the urine. No simple correlations exist between plasma level and clinical response. Diazepam can cause respiratory depression, which may actually help infants to "settle" on the ventilator. This agent can be useful as a long-acting sedative when given in doses ranging from 0.10 to 0.25 mg/kg every 6 hours.

Midazolam

Midazolam is a benzodiazepine that is water soluble at acid pH. It has a rapid onset of action (5 to 6 min) because at physiologic pH it is lipophilic. It is about twice as potent as diazepam, and it has a more rapid onset and shorter duration of action.[34] Because of this, midazolam has become a popular sedative, especially as a continuous infusion. It is metabolized in the liver, and the metabolites are excreted in the urine. Rapid injection may produce apnea and a decrease in blood pressure; however, with slower infusions, these side effects are less pronounced than with diazepam.[35] In adult patients, midazolam has more amnesic properties than other benzodiazepines. It is not clear what impact the prolonged administration of midazolam has on neonatal development.

Using the Premature Infant Pain Profile scores, neonates treated with midazolam tolerate painful procedures (such as endotracheal suctioning), as do neonates treated with morphine, and both groups tolerate these interventions better than untreated controls.[7] And, in a randomized placebo-controlled trial,[36] patients receiving midazolam infusions had a better sedative effect than placebo, as estimated by the behaviour score, along with a reduction in heart rate and blood pressure, although it remained within

the normal range for gestational age. No effect on ventilatory indices were seen and complication rates were similar. No midazolam-related side-effects were noted. However, in the original study by Anand et al.,[7] infants treated with midazolam showed a higher incidence of adverse neurologic events (death, grade III to IV intraventricular hemorrhage, periventricular leukomalacia) compared with infants not sedated or sedated with other drugs, particularly morphine. In addition, the midazolam group had a statistically significantly longer duration of neonatal intensive care unit stay compared to the placebo group.

With the perceived confounding results of studies of midazolam in neonates, Ng et al.[37] performed a systematic review and concluded there was insufficient evidence to support the use of midazolam as a sedative for neonates undergoing intensive care and that more definitive studies were needed. Babies receiving midazolam stayed in hospital longer and had more adverse effects.

Midazolam usually is given intravenously or intramuscularly in a dose of 0.1 mg/kg (range 0.05-0.15 mg/kg), which is repeated every 2 to 4 hours as needed or as a continuous infusion.[38] Clearance is directly related to birth weight,[39,40] and the dose should be titrated to desired effects. In seriously ill neonates, the terminal elimination half-life of midazolam is substantially prolonged (6.5 to 12.0 hours) and the clearance reduced (0.07 to 0.12 L/hr/kg) compared to healthy adults or other groups of pediatric patients.[39] It cannot be determined whether these differences are due to age, immature organ function or metabolic pathways, or underlying illness or debility.

Toxicity caused by overdosage is unusual and would likely present as excessive somnolence. Poor social interaction and dystonic movements have been reported in some infants after 4 to 11 days of sedation with a combination of midazolam and fentanyl. Symptoms resolve after discontinuation of use of the medications.[41] Some concern exists regarding possible withdrawal following prolonged use.[42] New onset of seizure-like activity has been seen with midazolam use in premature infants.[43,44] Finally, the usual parenteral preparation contains 1% benzoyl alcohol as a preservative; this may need to be taken into consideration when dosing this drug.[34] Use of the more concentrated 5 mg/mL preparation will reduce exposure to benzoyl alcohol per milligram of midazolam used. Newer preparations of midazolam are preservative free.

Lorazepam

Lorazepam is a benzodiazepine with potent anticonvulsant activity, and because it is lipophilic, it has a rapid onset of action.[45] The sedative effects of lorazepam are variable in duration (3 to 24 hours). It is conjugated in the liver to an inactive glucuronide, which the liver excretes. Apnea, somnolence, and movement disorders may occur.[46,47] The parenteral preparation contains 2% benzoyl alcohol and 18% polyethylene glycol. Propylene glycol has been implicated in serious toxicity when lorazepam was given as a continuous infusion[48,49]; therefore, we do not recommend use in neonates.

Chlorpromazine

Chlorpromazine is a dimethylamine derivative of phenothiazine. It has variable absorption when given orally, reaching peak plasma concentration within 2 to 4 hours after administration. Absorption is greater after intramuscular injection, which results in a fourfold to tenfold greater plasma concentration.[50] Frequently, it is used in combination with meperidine and promethazine, the so-called lytic cocktail or DPT (demerol, phenergan, and thorazine). As a single agent, chlorpromazine has little if any sedative or analgesic properties,[51] and toxicity is common, with its antiadrenergic and anticholinergic properties predominating. Because of lack of efficacy, unacceptable complications, and better alternatives, we do not recommend chlorpromazine, or DPT, as a sedative for ventilated newborns.

Chloral Hydrate

Chloral hydrate is a hypnosedative with actions similar to those of the barbiturates. It does not significantly depress respiratory drive;[52] however, it has no analgesic properties and it is a gastrointestinal tract irritant. Chloral hydrate is well absorbed from the gastrointestinal tract and is converted to trichloroethanol by the liver. Both trichloroethanol and an inactive metabolite, trichloroacetic acid, are conjugated and excreted as glucuronides, primarily in the urine and, to some degree, in the bile.[9]

The half-life of trichloroethanol is 9 to 40 hours and that of trichloroacetic acid is even longer, with no appreciable clearance over a 6-day period after a single 50 mg/kg dose of chloral hydrate.[53] With repeated and prolonged use, trichloroethanol can accumulate to toxic levels and cause paradoxical CNS stimulation, cardiac arrhythmias, and hypotension.[54] Although published documentation of clinical toxicity is limited to a few case reports, the prolonged clearance of these metabolites and potential accumulation make repeated dosing of chloral hydrate in neonates undesirable.

Trichloroacetic acid may displace protein-bound drugs and bilirubin in the newborn. Increased incidence of direct hyperbilirubinemia from chloral hydrate also occurs;[55] therefore, it should be used with caution in jaundiced infants.[21] Dosage of 25 mg/kg every 6 hours has been reported to be effective, but caution is warranted if administration is prolonged beyond a few days.[56] Larger, single doses for one-time sedation appear to be well tolerated.

Propofol

Propofol is an intravenous, nonbarbiturate anesthetic that is chemically unrelated to other intravenous anesthetics. Propofol is used to induce anesthesia that can be maintained by continuous infusion or with inhalation anesthetics. Propofol induces anesthesia as quickly as thiopental, but emergence from anesthesia is 10-times more rapid than with thiopental and is associated with minimal postoperative confusion.

Based on the reduced clearance of propofol, a longer recovery time is more likely to occur in neonates.[57] In a clinical trial,[58] propofol was more effective than the morphine, atropine, and suxamethonium regimen as an induction agent to facilitate neonatal nasal endotracheal intubation. Importantly, hypoxemia was less severe, probably because of the maintenance of spontaneous breathing. The authors concluded that the shorter duration of action would be advantageous in a compromised infant.

However, there are important reasons to avoid using propofol in neonates until more information on it's safety is available. The administration of propofol for sedation has been associated with the so-called propofol infusion syndrome[59] characterized by acidosis, bradyarrhythmia and rhabdomyolysis. This complication is rare but frequently fatal and has been reported in 21 children and 14 adults. It appears that the main complications arise with prolonged infusions,[60] as would be needed for sedation for mechanical ventilation, and its use in this respect is strongly discouraged.[61]

Muscle Relaxants

Use of muscle relaxants is not routinely indicated during mechanical ventilation of neonates, although it seems to be popular in certain patient populations such as infants with persistent pulmonary hypertension of the newborn (PPHN).[62] Although paralysis may improve oxygenation and ventilation of severely hypoxemic term infants with persistent pulmonary hypertension, it may have adverse effects on premature infants with respiratory distress syndrome (RDS).[63] Use of synchronized ventilation using ventilator rates above the spontaneous rate of the patient frequently will accomplish the goals of paralysis (see Chapter 12).[64] It may be useful in selected premature infants whose own respiratory efforts interfere with ventilation and may reduce the incidence of pneumothorax in this group of infants.[65]

Perlman et al.[66] demonstrated that the elimination of fluctuating cerebral blood flow velocity by muscle paralysis reduced the incidence of intraventricular hemorrhage in selected preterm infants with RDS. It has also been suggested that muscle paralysis may reduce oxygen consumption;[67] this would be advantageous to infants with compromised oxygenation.[68] Prolonged paralysis of 2 weeks' duration has been associated with disuse atrophy and subsequent skeletal muscle growth failure.[69] Importantly, in terms of pulmonary mechanics, Bhutani et al.[70] have shown a decrease in dynamic lung compliance and an increase in total pulmonary resistance after only 48 hours of continuous paralysis with pancuronium. Both parameters improved by 41% to 43% at 6 to 18 hours after discontinuation of paralysis.

Spontaneous respiratory efforts appear to contribute very little to minute ventilation in the severely ill premature infant with low lung compliance.[68] These infants are at risk of dropping their functional residual capacity after paralysis, possibly through loss of upper airway braking mechanisms.[63] In infants with lung compliance that is less compromised and in larger infants, spontaneous respiratory efforts contribute significantly to total ventilation. Thus ventilator adjustments (usually increases in rate) are necessary to prevent significant hypoventilation when paralysis is instituted. Monitoring of blood gases, end-tidal carbon dioxide tension, or both, is recommended. Although loss of intercostal muscle tone may lead to an increase in intrathoracic pressure, this does not appear to cause an increase in respiratory resistance.[71]

The primary hazard during paralysis appears to be accidental inconspicuous extubation. The paralyzed neonate is entirely dependent on mechanical ventilation, and careful observation is required. Also, paralysis obscures a variety of clinical signs whose expression depends on muscle tone and movement, such as seizures. Finally, paralysis does not alter the sensation of pain; thus analgesics should be administered under circumstances in which their use would be indicated in a nonparalyzed infant.

In practice, the decision to administer a muscle relaxant is most often based on clinical observation of an infant in combination with arterial blood gas measurements. Muscle relaxants are used frequently to facilitate hyperventilation therapy (see Chapter 15 and the section entitled Persistent Pulmonary Hypertension of the Newborn in Chapter 26). Analysis of ventilator or esophageal pressure waveforms is a more objective method of assessing whether an infant is in phase with the ventilator and whether mean intrathoracic pressure is increased.[65] However, there is no reliable way of predicting which infants in this circumstance will benefit from paralysis. Thus muscle relaxants should be administered as a therapeutic trial and their use continued if arterial blood gas values improve during the trial, if nursing care is greatly simplified, or if there is obvious improvement in patient synchrony with the ventilator and comfort. If the complications of prolonged paralysis are to be prevented, periodic assessment of the infant in the nonparalyzed state is essential.

The short-acting depolarizing muscle relaxant succinylcholine is infrequently used in the care of neonates, except when paralysis for intubation is necessary; therefore, only the commonly used nondepolarizing agents are discussed in this section. Recommended dosages are listed in Table 21-2.

Pancuronium

Pancuronium bromide, a long-acting, competitive neuromuscular blocking agent, is the muscle relaxant most frequently used in neonates. Gallamine and D-tubocurarine are seldom used because of significant cardiovascular effects, sympathetic ganglionic blockade, and, in the case of the former, obligatory renal excretion. All of these agents block transmission at the neuromuscular junction by competing with acetylcholine for receptor sites on the postjunctional membrane.[72] Pancuronium has vagolytic effects, and an increase in heart rate is commonly observed during its use. Administered intravenously, pancuronium produces maximum paralysis within 2 to 4 minutes. The duration of apnea after a single dose is variable and prolonged in neonates and can last from one to several hours. Incremental doses increase the duration of respiratory paralysis. In addition, the duration of paralysis is prolonged by acidosis, hypokalemia, use of aminoglycoside antibiotics,

TABLE 21-2 Neuromuscular Blocking Agents for Neonates

Agent	Initial Dose (mg/kg)	Dose Frequency	Infusion Dose (mg/kg/hr)
Pancuronium	0.04-0.15	1-4 hr	Not recommended
Vecuronium*	0.03-0.15	1-2 hr	0.05-0.10

*Incremental doses, 50% to 100% of the initial dose.

and decreased renal function. Alkalosis can be expected to antagonize blockade. Although renal excretion is the major route of elimination of pancuronium, hepatobiliary excretion and metabolism may account for the elimination of a significant portion of an administered dose.[17]

The recommended dosage in neonates varies from 0.06 to 0.10 mg/kg (see Table 21-2).[72] Although it is customary to administer repeat doses that are of the same magnitude as the initial dose, subsequent doses of half the initial dose may be effective in prolonging paralysis when muscular activity or spontaneous respiration returns. Continuous infusion of pancuronium in neonates is associated with the potential for accumulation because of these patients' slow rate of excretion; thus this method of administration is best avoided unless electrophysiologic monitoring is available.

The long-term benefits of respiratory paralysis need to be balanced with potential complications. Prolonged use of pancuronium bromide has been implicated in sensorineural hearing loss in childhood survivors of congenital diaphragmatic hernia (CDH).[73,74] In a pediatric intensive care unit setting, head trauma patients treated with and without paralysis were compared.[75] In the 15 patients with isolated intracranial pathology who received continuous paralysis, compliance progressively dropped by 50% over 4 days. This improved to normal after discontinuation of paralysis. No changes in compliance were measured in the 15 patients with isolated intracranial pathology who were ventilated but not paralyzed. The paralyzed patients required mechanical ventilation longer than the nonparalyzed patients, and 26% of these patients developed nosocomial pneumonia, a complication that was not seen in the nonparalyzed patients. Prolonged use of pancuronium has also been associated with weight gain and third space accumulation from lack of movement and urinary retention.

Despite the reported complications, pancuronium is still frequently used in the NICU population.[76] A recent systematic review[77] summarized the literature by stating that in ventilated preterm infants with evidence of asynchronous respiratory efforts, neuromuscular paralysis with pancuronium seems to be associated with a decrease in the incidence of intraventricular hemorrhage and possibly in pulmonary air leak. The authors went on to stress that long-term pulmonary and neurologic effects are uncertain.

The effects of pancuronium can be rapidly reversed with the use of the anticholinesterase agent neostigmine 0.08 mg/kg intravenously, preceded by the administration of glycopyrrolate 2.5 to 5 mcg/kg, which blocks the muscarinic side effects. Although rapid reversal is seldom needed for medical reasons in neonates receiving assisted ventilation, it may occasionally be useful diagnostically in infants considered to have suffered a CNS insult during paralysis.

Vecuronium

Vecuronium is a short-acting nondepolarizing muscle relaxant that is structurally related to pancuronium. Its onset of action is 1.5 to 2.0 minutes after intravenous bolus infusion, but its duration is only 30 to 40 minutes.[72] It has few cardiovascular side effects and is cleared rapidly by biliary excretion. Thus it is safer than pancuronium in the presence of renal failure. Interference with excretion or potentiation of effect has been suggested when used in combination with metronidazole, aminoglycosides, and hydantoins. However, no problems have been observed in infants receiving these agents and vecuronium in its usual dosage.[72] Acidosis can be expected to enhance the neuromuscular blockade provided by vecuronium and alkalosis to antagonize it.[17]

Vecuronium usually is given by continuous intravenous infusion at a rate of 0.1 mg/kg/hr after an initial paralyzing bolus dose of 0.1 mg/kg.[78] Intermittent bolus dosing would need to be so frequent (i.e., every 30 to 60 min) that this type of regimen usually is impractical (see Table 21-2). Continuous infusion is preferred for certain postoperative cardiac patients whose respiratory or other muscular movement may jeopardize the success of the repair. The effects of vecuronium can be reversed by neostigmine administration, as described earlier for pancuronium.

Cardiotonic Agents

Hypotension is common in premature neonates with RDS. In neonates 23 to 27 weeks of gestation, the frequency of interventions to improve blood pressure can range as high as 98%,[79] and between 47% and 67% will require inotropic support for hypotension.[80] In the low-birth-weight infants, the hypotension that is associated with early postnatal adaptation to transitional circulation is also frequently associated with decreased blood flow to organs.[81] Signs of cardiogenic shock and its precursors also may be recognized in term newborns after perinatal asphyxia, during severe hypoxemia or metabolic derangements, in certain types of congenital heart disease, and as a consequence of sepsis. When other attempts to reduce oxygen demand and to support the circulation are inadequate, use of cardiotonic agents may prove life saving.

Because there is a poor relationship between systemic blood pressure and end organ tissue perfusion in preterm infants, and reliable methods to measure continuous tissue perfusion in NICU patients is lacking, the optimal management of hypotension in the preterm infant can be difficult for caretakers in the NICU setting. Clinicians should employ proven reliable monitoring techniques available to reasonably gather data about the patient while developing a rational individual therapeutic plan for a given hypotensive infant in their care. Central venous filling pressures and cardiac output can be difficult to determine in neonates and are not routinely measured. When available, these measures should be considered in conjunction with the usual heart rate, systemic blood pressure, urinary output, and blood gas measurements and can provide a more objective basis for the selection and manipulation of inotropic agents. Recently, more neonatologists have turned to echocardiography to provide several indices of cardiac function that may be useful in guiding therapy with inotropes (see Chapter 26).[82,83] Other measures, such as superior vena cava blood flow, which reflects cerebral perfusion, have been used more in a research setting.[84,85]

The developmental status of the cardiovascular system and the transition from the fetal to the newborn state

further complicate decisions about therapy in newborns, particularly those born prematurely. The immature myocardium has more noncontractile elements than that of the adult, and the orientation of the contractile elements does not appear to be as well organized.[86] Also, cardiovascular receptors for sympathomimetic amines may differ in number, distribution, and sensitivity from those of the adult.[87] Normally, the heart of the newborn appears to function at near-maximum contractile levels; thus reserve and inotropic response may be limited.[88,89] Afterload appears to be an important determinant of cardiac output in the newborn state.[90] In addition, the reactive pulmonary circulation of the newborn and the potential for shunting via fetal pathways can compromise oxygen delivery and increase the demands placed on the myocardium.

Attempts to increase the cardiac output pharmacologically should be preceded by strategies to correct hypoxemia, acidosis, hypoglycemia, hypocalcemia, and hypovolemia and to reduce metabolic demands. Cardiac output is the product of left ventricular stroke volume and heart rate (cardiac output = stroke volume × heart rate). The latter can be temporarily augmented by vagolysis with atropine or, more commonly, with chronotropic agents such as isoproterenol, dobutamine, or epinephrine administered continuously. An increase in heart rate of 30% usually can be obtained with similar increases in cardiac output. Stroke volume can be increased by increasing the preload (venous return), reducing the afterload (lowering systemic vascular resistance), or increasing myocardial contractility. Drugs that have the ability to increase contractility (positive inotropic effect) include certain sympathomimetic amines, cardiac glycosides, glucagon, and xanthines. Only the first of these currently has practical clinical importance in the treatment of shock.

Sympathomimetic amines are the most potent positive inotropic agents available. These agents have complex actions, depending on their interaction with specific receptors and the distribution of these receptors in the host. Extensive studies have led to the classification of receptors as alpha-adrenergic, beta-adrenergic, or dopaminergic. These receptors are located in the heart and blood vessels, as well as in liver, kidney, pancreas, and nerve terminals.[91] Dopaminergic receptors, which mediate dilation of renal, mesenteric, coronary, and cerebral arterioles, have also been characterized.[92] The receptor actions related to sites in the cardiovascular system are listed in Table 21-3.

TABLE 21-3 Cardiovascular Actions of Adrenergic Receptors

Adrenergic Receptor	Site	Action
$Beta_1$	Myocardium	Increase atrial and ventricular contractility
	Sinoatrial node	Increase heart rate
	AV conduction system	Enhance conduction
$Beta_2$	Arterioles	Vasodilation
$Alpha_1$	Peripheral arterioles	Vasoconstriction
Dopamine	Renal, cerebral, mesenteric, and coronary arterioles	Vasodilation

TABLE 21-4 Selectivity of Catecholamines for Adrenergic Receptors

	RECEPTOR			
Catecholamine	$Alpha_1$	$Beta_1$	$Beta_2$	Dopamine
Epinephrine	+++	+++	+++	–
Norepinephrine	+++	+++	+	–
Isoproterenol	–	+++	+++	–
Dopamine*	– to +++	– to +++	++	+++
Dobutamine	– to +	+++	+	–

Adapted from Zaritsky A, Chernow B: Catecholamines, sympathomimetics. In Chernow B, Lake CR (eds): The Pharmacologic Approach to the Critically Ill Patient. Baltimore, Williams & Wilkins, 1983, p. 483.
*Variable, dose-dependent effects. High doses produce predominant $alpha_1$-adrenergic effects.
+, Relative degree of stimulation; –, no stimulation.

The available therapeutic agents have a range of activity from almost pure alpha activity to almost pure beta activity. The pharmacologic actions of the catecholamines epinephrine, norepinephrine, dopamine, dobutamine, and isoproterenol are related to their selectivity and potency with regard to the stimulation of adrenergic receptors, as summarized in Table 21-4.

The metabolism of all of the catecholamines is similar. Catechol-*O*-methyltransferase (COMT) is responsible for the degradation of most exogenously administered agents and monoamine oxidase participates to a lesser degree. COMT activity has wide interpatient variability and increases twofold to sixfold during dopamine treatment, but it may not be the rate-limiting step in catecholamine clearance.[93] All catecholamines are thought to have short half-lives of approximately 2 minutes; therefore, continuous infusion is necessary for attainment of prolonged effect. However, in sick premature infants, half-life and clearance can be prolonged and may explain the enhanced responsiveness to the infusion.[94,95] Metabolites, and perhaps 20% of unchanged substances, are excreted in the urine.

The recommended dosages of these agents for neonates are listed in Table 21-5.

Dopamine

Dopamine is a naturally occurring catecholamine. Administered exogenously, it has complex cardiovascular effects that are dose related (see Table 21-5).[92,96] In low doses (less than 4 mcg/kg/min), it has primarily vasodilator effects on renal[97,98] and perhaps mesenteric, coronary, and cerebral arterioles. However, in premature infants, dopamine at doses of 2.5 to 7.5 mcg/kg/min has been shown to cause selective renal but not mesenteric vasodilation with an overall increase in the peripheral vascular resistance and an enhanced pressor response, possibly due to decreased clearance.[95] Larger doses (5-10 mcg/kg/min) exert a positive inotropic effect on the myocardium via the release of norepinephrine from nerve terminals and through a direct effect on $beta_1$-adrenergic receptors in the myocardium.[99] Decreases in norepinephrine stores secondary to

TABLE 21-5 Inotropic Agents for Shock in the Neonate

Agent	Dosage (mcg/kg/min)	Receptor Affected	Action
Dopamine	2-4	Dopaminergic	Increased renal and mesenteric blood flow
	4-10	$Beta_1$	Increased myocardial contractility
	>10	$Alpha_1$ + $beta_1$	Peripheral vasoconstriction accompanies cardiac effect
Dobutamine	<10	$Beta_1$	Increased myocardial contractility
	>10	$Alpha_1$ + $beta_1$	Peripheral vasodilation accompanies cardiac effect
Norepinephrine	0.1-1	$Alpha_1$	Peripheral vasoconstriction and peripheral vasodilation
Milrinone	0.5-0.75	cAMP PDE inhibitor	Increased myocardial contractility and peripheral vasodilation
Levosimendan	0.05-0.1	Troponin C sensitiser	Increased myocardial contractility and peripheral vasodilation
Vasopressin	0.035-0.36 units/kg/min	AVPR1A and AVPR2	Peripheral vasoconstriction
Isoproterenol	0.05-0.50	$Beta_1$ + $beta_2$	Tachycardia usually accompanies contractility and vascular effects

cAMP, Cyclic adenosine monophosphate; *PDE,* Phospoodieasterase inhibitor; *AVPR,* Arginine vasopressor receptor.

immaturity, heart failure, or both could be expected to limit the inotropic response to dopamine.[94] This has been found to be true in most studies on immature animals.[100] Dosages greater than 10 mcg/kg/min cause increases in systemic vascular resistance through stimulation of alpha-adrenergic receptors. Dosages greater than 20 mcg/kg/min may increase pulmonary vascular resistance.[101]

Dopamine is effective in treating hypotension in premature infants with RDS.[102-108] In this population, doses as low as 2 mcg/kg/min tend to increase blood pressure,[95] although studies show a median effective dose range of 7.5 to 12.5 mcg/kg/min for treatment of hypotension.[104,108] One should realize that the improvement in blood pressure with dopamine infusion may come at the expense of left ventricular output, which drops about an average of 14%.[108] Intestinal perfusion also may be compromised,[109] but this has not been universally found.[97,106]

Because myocardial dysfunction has been shown as having an important role in the etiology of hypotension in preterm neonates, particularly during their first few hours of life,[110] consideration of dopamine as a first-line therapy when managing a hypotensive very-low-birthweight (VLBW) infant is reasonable.[104] Dopamine is frequently used in the treatment of neonates with myocardial dysfunction, even though its efficacy in these patients has not been well documented.[111,112] It is commonly used in neonates with renal insufficiency to improve urine output.[113] Studies conducted to document a decrease in the renal side effects of indomethacin have reported conflicting results,[114-116] and therefore dopamine is not recommended for this purpose.[117] Complications such as arrhythmias and gangrenous skin sloughs (due to infiltrated intravenous infusions of dopamine in peripheral sites) are infrequently observed.

In summary, the rate of dopamine infusion must be individually determined for each patient depending on changes in cardiac output, urine output, blood pressure, and peripheral perfusion desired. In premature infants, even low doses of dopamine probably will affect blood pressure through increasing afterload and thus may compromise left ventricular output.

Dobutamine

Dobutamine is a derivative of isoproterenol and has a structure similar to that of dopamine. However, it does not have dopaminergic properties, does not increase systemic vascular resistance, and appears to stimulate the heart primarily via $beta_1$-receptors. In larger doses (greater than 10 mcg/kg/min), stimulation of vascular receptors occurs, with $beta_2$-stimulation predominating over $alpha_1$-stimulation.[118] Peripheral vasodilation occurs, which is in contrast to the vasoconstriction that results from the use of similar doses of dopamine.

The inotropic effect of dobutamine appears to be similar to that of dopamine in neonatal animals[99] and, probably, in human infants.[119,120] However, in small preterm infants, dobutamine appears to be more effective in increasing left ventricular output, whereas dopamine appears more effective in raising the mean blood pressure.[105-108,121] Therapy combining dobutamine with low doses of dopamine has been tried and appears more promising than treatment with either agent alone.[121,122] Arrhythmias appear to be an infrequent side effect, but apparently, increased intrapulmonary shunting of blood can occur with dobutamine as well as with dopamine and isoproterenol.[123] If the short-term goal of therapy is raising blood pressure without the means of assessing end-organ perfusion, then dopamine appears to be a better choice than dobutamine.[124]

Isoproterenol

Isoproterenol is a synthetic catecholamine with nearly pure beta-drenergic actions. Because $beta_1$- and $beta_2$-adrenergic receptors are stimulated, both increased myocardial activity and peripheral vasodilation occur.[96] Marked tachycardia and low blood pressure have accompanied its use in neonatal animals.[125] As heart rate increases, so does myocardial oxygen consumption; simultaneously, myocardial oxygen delivery may decrease in the presence of hypotension.[91] Because the use of isoproterenol can blunt hypoxic pulmonary vasoconstriction, it can lead to increased pulmonary shunting and increased hypoxia in patients with pulmonary disease secondary to increases in ventilation perfusion mismatch.[126]

For the neonate, isoproterenol appears to be a secondary agent for the treatment of shock. It may have application when afterload reduction is desirable and when an increase in heart rate can be tolerated. It may be of short-term benefit in patients with complete heart block[127] and has been used to lower pulmonary artery pressure in a patient with Ebstein anomaly.[128] Dosage varies between 0.05 and 0.5 mcg /kg/min.

Tachycardia and hypotension are the most common adverse effects of isoproterenol administration. Careful monitoring of central venous pressure and attention to circulating blood volume should accompany its use.

Epinephrine

Epinephrine is an endogenous catecholamine with both alpha- and beta-adrenergic action.[96] The relative actions are dose dependent. At low doses, beta-adrenergic activity predominates, resulting in increased cardiac contractility and output.[129] At higher doses, alpha-adrenergic effects develop, and the resultant peripheral vasoconstriction may offset the desired beta-adrenergic effects.[130] Dosages range from 0.05 to 0.50 mcg/kg/min.

For inotropic support when pulmonary blood flow is excessive, epinephrine infusion may be beneficial. In a newborn piglet model of first-stage repair of hypoplastic left heart, Riordan et al.[131] showed epinephrine 0.1 mcg/kg/min decreased the ratio of pulmonary-to-systemic blood flow and improved oxygen delivery compared to dopamine and dobutamine. Although not a first-choice drug when treating hypotension, it may be useful when dopamine and dobutamine have not been successful at providing adequate cardiac output and perfusion.

Norepinephrine

A recently published prospective study[132] performed on term neonates to evaluate the efficacy of norepinephrine in the management of septic shock showed it to be effective in increasing systemic blood pressure and urine output while it decreased the infant's lactate levels, suggesting improved cardiac function and tissue perfusion was achieved. The infants in the study had been fluid resuscitated and were on high doses of dopamine/dobutamine at the time that noerpinephrine was initiated. Doses used were 0.5 ± 0.4 mcg/kg/min.

Other Inotropes

Other positive inotropic agents have been used clinically in neonates, including cyclic adenosine monophosphate (cAMP) phosphodiesterase inhibitors such as amrinone and milrinone. These agents increase cardiac contractility and decrease systemic vascular resistance and have been used in volume-resuscitated patients with septic shock to improve their cardiovascular function. Milrinone has been used successfully in neonates with low cardiac output after surgery to achieve an increment in their cardiac index without increasing their myocardial oxygen consumption.[133] Milrinone has also been used successfully in the management of neonates with severe PPHN who have been nonresponders to inhalation therapy with inhaled nitric oxide (iNO).[134] In this group of infants, oxygenation improved without compromising systemic blood pressure. Milrinone typically is administered as a loading dose of 75 mcg/kg over 1 hour, followed by 0.5 to 0.75 mcg/kg/min. Caution should be exercised in premature infants by administering the loading dose over 3 hours and beginning maintanence infusions at 0.2 mcg/kg/min.

Calcium Sensitisers

Because desensitization to calcium (Ca^{++}) in the myocardium during septic shock can lead to myocardial depression, use of a troponin C sensitiser to calcium, levosimendan, has been successful in the treatment of septic myocardial depression in animals[135] and in a premature infant who developed postoperative myocardial stunning after arterial switch surgery.[136] The infant subsequently developed "low cardiac output syndrome" (decreased arterial oxygen saturations, systolic blood pressure and left ventricular function, increased lactate and left atrial pressure) despite therapy with milrinone, dobutamine, and epinephrine. The dose used in this case was 0.05 mcg/kg/min increased to 0.1 mcg/kg/min and infused continuously for 24 hours.

Arginine Vasopressin

In a case series[137] of VLBW neonates, arginine vasopressin, at doses of 0.035 to 0.36 units/kg/hr, was shown to resolve systemic hypotension and improve urine output in the group with septic shock but not in patients with nonsepsis-related hypotension.

The long-acting vasopressin analogue terlipressin has been used as rescue therapy for an 8-day-old neonate with refractory vasodilatory septic shock,[138] but extreme caution should be advised because of the longer half-life and inability to rapidly reverse the medications effects.

Summary

Myocardial dysfunction resulting in a decrease in cardiac output may be accompanied by a combination of increases or decreases in peripheral resistance, hypovolemia, or hypervolemia, and by increases or decreases in metabolic rates. Thus sound clinical judgment and hemodynamic measurements are essential for the selection and dosage of cardiotonic agents. The cause of the myocardial dysfunction should play a role in the selection of the appropriate inotropic agent. A summary of inotropic agents used in the treatment of shock is given in Table 19-5.

Pulmonary Vasodilators

Persistent pulmonary hypertension of the newborn (PPHN) with right-to-left shunting of blood through the ductus arteriosus, foramen ovale, or both can cause severe hypoxemia in newborn infants, both with and without lung disease.[139,140] The diagnosis, clinical course, and causes of PPHN are all discussed in detail in Chapter 26. Although PPHN has numerous etiologies and some of these etiologies, such as congenital diaphragmatic hernia (CDH), premature closure of the ductus arteriosus, and chronic intrauterine hypoxia, exhibit structural changes in the pulmonary vascular smooth muscle, the common endpoint of increased pulmonary vascular resistance is universal. Agents that decrease pulmonary vascular resistance may be useful therapies for treating PPHN when hypoxemia proves refractory to mechanical ventilation and O_2 therapy.

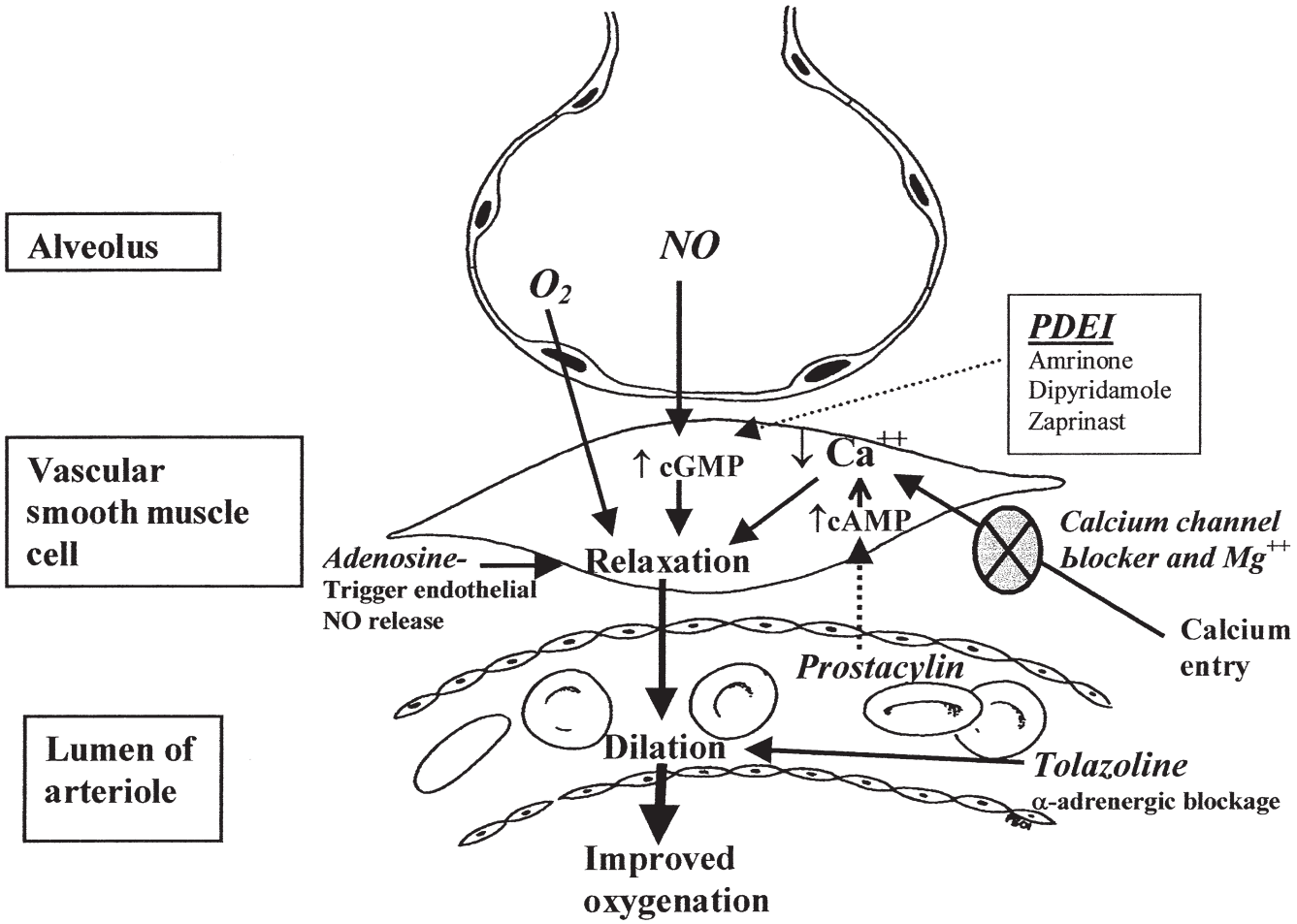

Figure 21-1 ■ Various substances that decrease pulmonary vascular resistance are illustrated graphically. Nitric oxide and phosphodiesterase inhibitors (PDEI) mediate vasodilation by an increase in the amount of cycle guanosine monophosphate (cGMP). Calcium channel blockers and magnesium (by competitive inhibition) block the entry of calcium into the vascular smooth muscle, which decreases the intracellular stores of calcium and leads to vasodilation. Prostacyclin produces a decrease in the amount of cyclic adenosine monophosphate (cAMP), which also decreases intracellular calcium. Adenosine, tolazoline, and oxygen (O_2) mechanisms of action leading to vasodilation also are described.

Substances that decrease pulmonary vascular resistance are shown graphically in Figure 21-1. Clinical experience with adenosine,[141] magnesium sulfate,[142] calcium channel blockers,[143] prostaglandin E_1,[144] prostaglandin D_2,[145] and prostacyclin[146] is limited. Tolazoline[140] has historical interest only in that it nonselectively acted as an alpha-blocker, and the nonspecific nature led to many untoward side effects such that it is no longer available. The use of high concentrations of oxygen and alkalizing agents to increase the blood pH, sometimes combined with hyperventilation, remains a vasodilator strategy in neonates with documented PPHN, but has now fallen into disfavor with the advent of less toxic pharmacologic treatment.[62] Since the approval of inhaled nitric oxide (iNO) by the FDA for the treatment of PPHN, iNOhas found rapid acceptance in the neonatal community. The addition of iNO to the ventilating gas has added a selective pulmonary vasodilator to the clinician's armamentarium[107,108] and is discussed in detail in Chapter 14.

Alkalosis

Prior to the approval of iNO, alkalosis in conjunction with oxygen to produce a blood pH of 7.50 to 7.60 or higher was the most common vasodilatation therapy used for treating PPHN.[62] The mechanism is not clearly established but appears to depend directly on the pH of the blood and not on the release of endogenous nitric oxide.[147-149] No critical partial pressure of arterial CO_2 ($PaCO_2$) exists, as once thought. Thus respiratory alkalosis, metabolic alkalosis, or a combination of the two can be used to produce the desired elevation in pH. Although this therapy is still used, the degree of alkalosis achieved is much less than was the goal prior to the use of iNO and newer ventilator strategies.

Sodium bicarbonate, sodium acetate, and tromethamine (THAM) have all been used to produce alkalosis, with similar results,[150,151] but there are no randomized trials to determine relative efficacy or safety of these

alkalizing agents. When significant elevation of $PaCO_2$ or sodium overload is a concern, some clinicians prefer to use THAM. THAM binds with hydrogen ions, resulting in an increase in bicarbonate ions without production of carbon dioxide. In the process, NH_3^+ is generated that must be excreted by the kidneys; therefore its use is not indicated in anuric or hypoglycemic patients.[152] THAM may cause hyperkalemia and hypoglycemia.

Although THAM can change intracellular pH faster than sodium bicarbonate, this characteristic does not appear to be a significant factor in its pulmonary vasodilator effect.[148,149] Treatment usually is initiated with bolus infusions of 1 to 2 mEq/kg of sodium bicarbonate or 1 to 2 mmol/kg of THAM.[152] A continuous infusion is then begun to obtain a desired pH level. Although each infant may have a particular pH at which he or she responds, that pH is routinely between 7.50 and 7.60.[153] After the desired pH has been achieved, it usually is possible to decrease the alkali infusion rate. Often the infusion can be stopped after approximately 48 hours, and the infant remains alkalotic for several more days as the bicarbonate, or THAM, is slowly cleared by the kidneys.

The adverse effects of alkalosis, including an increase in the affinity of hemoglobin for O_2, a decrease in the concentration of ionized calcium, and a decrease in cerebral blood flow, have not been reported to be problems during the treatment of infants with PPHN. A low incidence of neurosensory deafness has been observed in survivors of PPHN, and concern has been raised regarding the role of alkalosis in this sequela.[154] Rapid infusion of hypertonic sodium bicarbonate may play a role in causing intracranial hemorrhage in premature neonates,[155] and it is recommended that the concentration of sodium bicarbonate not exceed 0.5 mEq/mL and that it not be infused at a rate greater than 1 mEq/mL/min. An infusion of bicarbonate will transiently raise $PaCO_2$ but appears to be clinically unimportant in infants receiving effective mechanical ventilation.

All alkalinizing agents, especially THAM, should only be given intravenously, because intra-arterial administration of these solutions has been associated with significant vascular complications. Infusion of THAM through an umbilical venous catheter into the portal system of the liver has been reported to cause hepatic necrosis.[156]

The data supporting alkalosis for dilation of the pulmonary vascular bed is not from randomized trials and is based on a very small population of patients without controls.[153] Some centers have found success in treating these patients without inducing alkalosis.[157] Walsh-Sukys et al.[62] found that systemic alkalosis was not equivalent to respiratory alkalosis in the treatment outcomes of neonates with PPHN. Neonates who were treated with alkali infusions did not show a decrease in mortality and had an increased risk for the use of extracorporeal membrane oxygenation (ECMO) and prolonged oxygen dependency. This is in contrast to neonates treated with hyperventilation who showed a decrease in the use of ECMO without increasing pulmonary morbidity as measured by the use of oxygen at 28 days of age. These same concerns about alkalosis have been raised in particular patient populations, such as neonates with CDH. Based on historical controls, Kays et al.[158] demonstrated decreased mortality in the management of PPHN in neonates with CDH who did not have rigorous management of acidosis or hypercapnia with exogenous alkali infusions or ventilator adjustments. These concerns hopefully will generate a carefully controlled clinical trial of the best management strategy involving alkalosis. Until then, because of the lack of better initial treatment options, mild alkalosis combined with oxygen may remain as an initial therapy for the treatment of PPHN.

Nitric Oxide

Nitric oxide therapy has given the clinician a powerful selective pulmonary vasodilating agent for the treatment of PPHN. The topic of inhaled NO (iNO) is discussed in Chapter 14.

Other Agents

Other agents have demonstrated therapeutic value in the treatment of PPHN in small clinical trials. In light of large randomized trials of iNO not showing definitive improvements in mortality or a reduction in length of hospitalization, many of these agents are being tried in combination with nitric oxide[159] or alone if there is a complication with nitric oxide. This section briefly reviews some of these agents.

Adenosine

Adenosine is a purine nucleoside with a short half-life (less than 10 sec) and causes vasodilation by the stimulation of theophylline-sensitive A2 receptors on vascular endothelial cells and subsequent release of nitric oxide by endothelial cells.[141] Endogenous adenosine has been shown to play an important role in facilitating the decrease in pulmonary vascular resistance after birth.[141]

Two small studies examined the effects of adenosine infusion on neonates with PPHN. In a randomized, placebo-controlled, masked trial, Konduri et al.[160] infused adenosine at a dosage of 25 to 50 mcg/kg/min over a 24-hour period and compared the effects on PaO_2 in neonates infused with saline. The results demonstrated an improvement of PaO_2 levels from a baseline of 69 ± 19 to 94 ± 15 mm Hg. The arterial blood pressure and heart rate did not change during the adenosine infusion. Patole et al.[161] used adenosine to treat six neonates with PPHN who did not respond to conventional therapy. A rise in PaO_2 greater than 20 mm Hg occurred in 5 of 6 cases within 30 minutes of commencing infusion. No side effects (bradycardia, hypotension, prolonged bleeding time) were noted. Given the success of these two studies and absence of side effects, larger trials would be of benefit to determine whether adenosine alone or in combination with other agents has any bearing on the mortality and/or need for ECMO in neonates with PPHN.

Magnesium Sulfate

Magnesium is a therapeutic drug that produces vasodilation by antagonizing the entry of calcium into smooth muscle cells. It also may act by its effects on the metabolism of prostaglandins, suppression of the release of catecholamines, activation of adenyl cyclase, and reduction of smooth muscle to vasopressors.[162] Magnesium has other potentially desirable effects, including antithrombosis, sedation, muscle relaxation, and the alleviation of oxidant-mediated tissue injury after hypoxia-ischemia.[162]

Several groups have reported beneficial effects of magnesium sulfate therapy in patients with PPHN.[142,162-164] These studies have been small, nonrandomized series of patients. Tolsa et al.[142] administered a loading dose of 200 mg/kg of magnesium sulfate over 20 minutes, followed by an infusion of 20 to 150 mg/kg/hr to maintain a serum concentration between 3.5 and 5.5 mmol/L to neonates with PPHN. Oxygen index and mean airway pressure were significantly reduced after 72 hours of therapy, with no systemic hypotension or other side effects noted. The other studies had similar findings.[162-164] Prospective, randomized controlled studies of magnesium sulfate therapy for PPHN have not been performed and have been recommended by a recent Cochrane review.[165] Further studies may reveal that magnesium sulfate is a valuable adjunct to other drug therapies for PPHN.

Calcium Channel Blockers

Although many clinicians who treat adults[166] and children[167] with pulmonary hypertension believe that calcium channel blockers are standard of care therapy, the lack of pulmonary specificity, the high incidence of adverse effects, and the absence of a predictable response in adults suggest caution should be exercised in using calcium channel blockers in newborns with PPHN and related disorders.[143] In spite of these concerns, calcium channel blockers may have a role in certain subsets of patients with PPHN. Islam et al.[168] administered diltiazem hydrochloride to five neonates with recurrent pulmonary hypertension associated with pulmonary hypoplasia refractory to maximal conventional therapy. These neonates demonstrated a significant reduction in right ventricular pressure without overt side effects or systemic hypotension.

Calcium channel blockers may have a therapeutic value in patients with long-standing pulmonary hypertension, and in the neonatal intensive care unit (NICU), this probably would include neonates with severe chronic lung disease. Because of their effects on contractility, caution should lead the clinician to assure normal cardiac function prior to instituting this class of drugs, and potentially repeating echocardiographic studies while the infant is on treatment.

Prostacyclin (Prostaglandin I_2) and Prostacyclin Analogues

Prostacyclin (PGI_2)is an important mediator of pulmonary vasodilation.[169] Increased production of prostacyclin at birth occurs as a result of rhythmic distention of the alveoli.[170] Increased production of prostacyclin results in pulmonary vasodilation, which is an essential element in the normal transition to extrauterine life. Importantly, the mechanism is through cAMP, which may prove to be beneficial to patients not responsive to nitric oxide, which works through cyclic guanosine monophosphate (cGMP).[171] Patients with severe pulmonary hypertension have demonstrated a deficiency in prostacyclin synthase in pulmonary precapillary vessels.[143] Similarly, transgenic mice overexpressing prostacyclin synthase do not exhibit vascular smooth muscle hypertrophy or pulmonary hypertension when exposed to hypobaric hypoxia.[172]

In adults, prostacyclin analogues hold tremendous promise in the treatment of chronic pulmonary hypertension,[173] including intravenous (epoprostenol), subcutaneous (treprostinin) inhaled (iloprost), and orally (beraprost)[174] administered forms.

Intravenous PGI_2 is approved to treat pulmonary hypertension in children and adults. Its use in infants with PPHN has been limited by systemic hypotension.[175] In human neonates, a small nonrandomized trial of repeated or continuous instillation of prostacyclin via an endotracheal tube to four preterm infants with PPHN demonstrated an improvement in oxygenation.[146] No overt side effects were noted. Another trial using inhaled nitric oxide in combination with inhaled prostacyclin[176] delivered the treatment by aerosolizing the intravenous formulation.[177] All four patients had acute improvement in oxygenation and three of them survived. Interestingly, all four infants were also treated with milrinone, which inhibits the enzymatic hydrolysis of cAMP, which may have augmented vasodilation through increasing cAMP availability in smooth muscle cells. Iloprost is a new inhaled prostacyclin analogue formulation and has been reported to have benefit in small case studies.[171,178] Because of its site of action being on cAMP rather than cGMP, prostacyclin is a promising modality to be used as a rescue treatment of PPHN in neonates.

Endothelin-Receptor Antagonists

Endothelin-1 is a potent endothelium-derived peptide that has been proposed to contribute to the pathogenesis of heart failure and pulmonary hypertension. Endothelin-1 is one of the most powerful pulmonary vascular constrictors known,[179] and its concentrations are elevated in plasma and lung tissue of adult patients with pulmonary arterial hypertension, suggesting a pathogenic role for endothelin-1 in this disease.[180] Two types of endothelin receptors have been identified on vascular smooth muscle cells: A and B; only type B receptors have been found on endothelial cells. Stimulation of type A endothelin receptors mediates vasoconstriction wheres type B receptors mediate both vasoconstriction and vasodilation.

Bosentan is a specific and competitive antagonist at both type A and B endothelin receptors. Bosentan has a slightly higher affinity for endothelin-A receptors than for endothelin-B receptors.[180] In adults with pulmonary hypertension, bosentan lowers systemic vascular resistance, pulmonary vascular resistance, and mean pulmonary arterial pressure, with a small increase in cardiac output. The increase in cardiac output is likely due to decreased vascular resistance.[181] In two clinical trials in adults, bosentan significantly improved exercise ability.[181,182]

Adverse events associated with endothelin-receptor antagonists include an increase in liver function studies, teratogenicity, and possibly irreversible male infertility. In children, it is not well established whether the addition of endothelin-receptor antagonists to chronic oral calcium channel blockade therapy, continuous intravenous epoprostenol, or a prostacyclin analogue will increase the overall efficacy and risk/benefit profile for treating pulmonary arterial hypertension. Therefore, at this point its use in neonatal medicine must be done only after exhaustion of other possibilities. In adults, the newer, experimental selective endothelin-1–receptor antagonists sitaxsentan and ambrisentan show promise as having equal efficacy but a better safety profile.[183]

Phosphodiesterase-5 inhibition

Pulmonary vascular dilation with nitric oxide works through increasing cGMP. cGMP is metabolized by phosphodiesterase-5. Sildenafil is a phosphodiesterase-5 inhibitor and thus will increase the local concentration of cGMP and potentially potentiate vasodilation, either in conjunction with nitric oxide or without. Baquero et al.[184] used sildenafil 2 mg/kg orally in seven infants where nitric oxide and ECMO were not available. Six infants received placebo. Sildenafil was reported to be well tolerated and six of seven infants survived, compared to one of six controls. Noori et al.[185] used sildenafil in conjunction with nitric oxide in seven patients with diaphragmatic hernia and PPHN and found echocardiographic evidence of improvement in pulmonary hypertension, an improvement in cardiac output, and a small drop in systemic blood pressure. Further trials for safety are warranted because Stocker et al.[186] showed in neonates after heart surgery that although pulmonary vascular resistance dropped with sildenafil, systemic hypotension and a drop in systemic oxygenation also occurred.

Bronchodilators and Mucolytic Agents

The impetus for a timely management regimen with pharmacologic bronchodilator agents of premature infants who may have chronic lung disease (CLD) or be at risk to develop CLD stems from the physiologic responses observed. For many years, premature infants were thought to have too little bronchiolar smooth muscle to experience bronchospasm. This misconception has been disproved. Subsequently, bronchodilators have been shown to decrease airway resistance and increase compliance in neonates as premature as 28 weeks of gestation with bronchopulmonary dysplasia (BPD), as well as in other infants as young as 2 days of age with respiratory distress syndrome.[187] The bronchodilators used have been administered parenterally, enterally, or in aerosol form. In addition to effecting bronchodilation, some agents such as aminophylline have been shown to improve diaphragmatic and inspiratory muscle contractility,[188,189] which may result in both improved ventilation and a greater likelihood of successful and earlier extubation, the goals for which the clinician should be striving. Methylxanthines such as theophylline and caffeine effect the relaxation of bronchiolar smooth muscle, which increases vital capacity in patients; in therapeutic concentrations, these agents improve diaphragmatic contractility, decrease respiratory fatigue, and increase the medullary response to CO_2 leading to increased minute volumes for any given alveolar PCO_2.[190] Typical dosages for commonly used aerosolized medications are listed in Table 21-6.

Albuterol (Salbutamol)

Albuterol (also known as *salbutamol*) is a selective $beta_2$-adrenergic agonist. It promotes the production of intracellular cyclic adenosine monophosphate (cAMP), which enhances the binding of intracellular calcium to the cell membrane. This action decreases the calcium concentration within cells and results in the relaxation of smooth muscle and bronchodilation.[191]

Studies to evaluate lung function in premature infants with chronic lung disease have demonstrated that these infants have significant pulmonary function abnormalities, specifically moderate air trapping and obstruction when compared to the normal infant cohorts. Approximately 35% of the infants in one study group with CLD demonstrated significant bronchodilation in response to albuterol.[192] Of these, infants who were noted to have wheezing showed the most significant expiratory flow limitation and airway hyperinflation, but also the greatest airway response. Denjean et al.[193] studied the effects of albuterol on pulmonary mechanics in premature infants with a mean postnatal age of 13.3 ± 4.9 days and with subacute BPD. Albuterol 100 mg, administered via metered-dose inhaler with a spacer device, resulted in significant improvement in both resistance and compliance in approximately 65% of the infants studied; the remaining patients required 200 mg. The peak responses occurred at 30 minutes and were sustained for approximately 3 hours. Some systemic effects were present as evidenced by an increase in heart rate. In another study involving ventilator-dependent neonates weighing less than 1500 g at birth and between 1 and 4 weeks of age, albuterol improved compliance; however, airway resistance did not change significantly.[194]

Controversy has arisen over long-term beta-agonist stimulation of nonpulmonary tissues, possible adverse effects of long-term bronchodilation on healing lung tissue, and theoretical concerns over the development of tolerance. Therefore, most authors would advocate using beta-agonists in acute symptomatic situations for short periods of time.[195]

TABLE 21-6 Aerosolized Medications for Neonates

Agent	Dose	Dose Frequency	Comments
Salbutamol	0.20 mg/kg	Every 3-6 hr	With 0.5% solution, dilute 0.04 mL/kg in 1.5 mL NS
Ipratropium bromide	0.025 mg/kg	Every 8 hr	18-mg/puff, 1-2 puffs/dose with metered-dose inhaler*
N-Acetylcysteine	10-20 mg	Every 6-8 hr	Add bronchodilator if bronchospasm occurs; restricted use advised in view of undesirable effects
Cromoglycic acid (cromolyn sodium)	10 mg	Every 6 hr	Dilute 1 mL of 10 mg/mL solution up to 1.5 mL NS

*Only available metered-dose inhaler in the United States.
NS, Normal saline.

Acetylcysteine

Mucolytic agents usually are not required for airway maintenance during mechanical ventilation in the neonate. However, acetylcysteine, a free radical scavenger[196] and potent mucolytic agent, has been useful in some centers. *N*-acetylcysteine (NAC), which has a free sulfhydryl group, liquefies mucus by opening the disulfide bonds in the mucoproteins. It does not affect fibrin, blood clots, or living tissues. At one center, 0.1 or 0.2 mL of acetylcysteine was introduced into the endotracheal tube hourly to maintain airway patency; this was followed by aspiration of the secretions 30 minutes later. No histologic effects were observed on the tracheas or bronchi evaluated on postmortem examination.[197] Bibi et al.[198] showed in 10 ventilator-dependent infants (gestational age 27 weeks; postnatal age 22 days) that treatment with intratracheal NAC *increased* airway resistance significantly. Thus use of this agent should be undertaken cautiously because its adverse effects may outweigh its benefits. When administered for mucolytic actions, it often is combined with other bronchodilators so that the undesirable effects are offset.

NAC is used parenterally in the management of acetaminophen overdose to diminish hepatic injury. When administered parenterally to premature patients, no adverse effects were noted after receiving NAC for up to 6 days.[199] Because oxygen toxicity plays such a direct role in the subsequent development of CLD in neonates who require ventilator support, NAC therapy was evaluated as a possible way to enhance the role of glutathione in the antioxidant defense system in the premature infant. However, when given to premature infants in the first week of life, no significant improvement in the lung function was found.[200]

Cromoglycic Acid

Cromoglycic acid (cromolyn sodium) prevents the release of inflammatory mediators from mast cells, inhibits the influx of neutrophils, and inhibits the assembly of an active nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in the neutrophil, thereby preventing tissue damage induced by oxygen radicals.[201] In one study of former premature neonates born at 29 weeks of gestation with recurrent respiratory symptoms, including coughing and wheezing, prophylactic cromoglycic acid aerosol resulted in improvement in both functional residual capacity and "symptom score."[202] Kassur-Simienska et al.[203] reported significant differences in regression of obturative bronchitis and normalization of capillary blood gases in premature infants whose management for CLD included cromolyn sodium and inhaled steroids versus steroids alone. Although the results from both The Neonatal Cromolyn Study Group[204] and a Cochrane review[205] did not show a reduction in BPD in the neonates treated with cromolyn sodium, a decrease in inflammatory markers associated with BPD can be demonstrated when sodium cromolyn is used in conjunction with surfactant, diuretics, and steroids.[201,204] Sodium cromolyn may be an important adjunct therapy when used with other agents such as steroids and warrants further clinical trials.

Racemic Epinephrine

The subglottis is the narrowest portion of the airway in neonates. The presence of a foreign body, as occurs with prolonged intubation, produces edema in the subglottic region, which can produce further narrowing of the airway when the neonate is extubated. Racemic epinephrine stimulates both alpha- and beta-adrenergic receptors. It acts on vascular smooth muscle to produce vasoconstriction, which markedly decreases blood flow at the capillary level. This shrinks upper respiratory mucosa and reduces edema.[206] Racemic epinephrine is a useful agent in patients with established postextubation stridor; however, its efficacy for prevention of postextubation stridor has not been proven.[206] Racemic epinephrine may also be considered as an adjunct to therapy for pulmonary hemorrhage.[207] When using racemic epinephrine, one should be aware of the side effects, which include tachycardia, arrhythmias, hypertension, peripheral vasoconstriction, hyperglycemia, hyperkalemia, metabolic acidosis, and leukocytosis.[206]

Ipatropium Bromide

A synthetic congener of atropine is often used individually or combined with albuterol in the management of CLD. The rationale for the use of ipatropium bromide (IPB) in neonates who have CLD is due to the presence of functional muscarinic receptors in premature neonates. Fisher et al.[208] showed a dose-dependent bronchodilation when nebulized IPB was used in infants with BPD. A 20% decrease in respiratory resistance was noted at doses of 175 mcg. When Salbutamol (0.04 mg) was combined with IPB, the response increased in magnitude and duration, and a 20% increase in airway compliance was also observed. Similarly, the combination of IPB and salbutamol at doses of 175 mcg and 0.04 mg, respectively, achieved the greatest decrease in respiratory system resistance and increases in compliance in a group of ventilated infants with BPD.[209]

Diuretics

Diuretics are used to treat systemic fluid retention and to decrease edema in the pulmonary interstitium; the latter may cause both oxygenation and ventilation abnormalities and is implicated in the pathogenesis of BPD.[187] Diuretics may help clear the pulmonary interstitial fluid by shifting this fluid into the plasma space after diuresis of intravascular water. However, chronic use of loop diuretics may have the paradoxical effect of raising pCO_2 because they work by retaining bicarbonate at the expense of the excretion of chloride.

Furosemide

Furosemide is the most common diuretic used in sick neonates. The usual dosage is 1 to 2 mg/kg intravenously, but it may also be given intramuscularly or orally. The mode of action is inhibition of chloride reabsorption in the ascending limb of the loop of Henle.[210] The major hazards are electrolyte imbalance, including hyponatremia, hypokalemia, hypochloremia, and alkalosis, as well as dehydration and reduction in blood volume. In

addition, hypercalciuria leading to nephrocalcinosis can occur.[211,212] Furosemide is potentially ototoxic and should be used with caution in patients receiving aminoglycosides.[152]

Furosemide therapy has resulted in short-term improvement in airway resistance and dynamic pulmonary compliance in infants with BPD.[213] Furosemide has also been shown to improve lung compliance in infants recovering from RDS. The latter effect appears to result from direct pulmonary effects and is independent of the drug's diuretic actions.[214] In patients with BPD, prolonged therapy has resulted in improvement in mechanical properties of the lung without significant change in gas exchange.[215]

When inhaled, furosemide may have a direct effect on the lung, because the pulmonary effects can occur in the absence of diuresis. In a small series of neonates with BPD treated with inhaled furosemide, compliance and resistance improved.[216] A subsequent study in preterm neonates who required ventilator support showed improved compliance and tidal volumes in the group treated with furosemide, with no difference noted between infants who received 1 mg/kg/dose versus those who received 2 mg/kg/dose; also no effects on airway resistance were detected.[217] This mode of delivery offers the advantage of possibly decreasing systemic side effects while maintaining desired pulmonary effects. However, in view of the lack of data from randomized trials on the effects of aerosolized loop diuretics on important clinical outcomes, routine or sustained use of this mode of delivery cannot be justified based on the current evidence.[218]

Furosemide may decrease transvascular fluid flux in the interstitium via nondiuretic mechanisms. These changes may be mediated by prostaglandin E release, which has bronchodilator and pulmonary vasodilator action.[219] The release of prostaglandin E may explain the association of furosemide therapy resulting in an increased risk for patent ductus arteriosus.[220]

Bumetanide

Bumetamide is a potent loop diuretic used principally in the treatment of edema and congestive heart failure. This diuretic can be administered orally, intramuscularly, or intravenously and leads to a marked diuresis, usually within 30 minutes. Pharmacologically it is considered approximately 40 times more potent than furosemide but is less ototoxic and kaliuric than furosemide.[221] Thiazide diuretics can be used adjunctively with bumetanide when enhanced clinical responses are needed. A comparison of mineral excretion in premature neonates after therapy with single doses of bumetanide and furosemide showed that sodium loss per unit volume was lower with bumetanide use than with furosemide, but calcium losses were higher.[222] Parenteral doses of bumetanide in criticaly ill pediatric patients of 0.1 mg/kg every 12 hours produced beneficial effects in clearing edema and apperared to be well tolerated.[223]

Thiazides and Potassium-Sparing Diuretics

Chlorothiazide, a potent oral diuretic, has its major site of action in the proximal portion of the distal tubule[210]; it acts by inhibiting chloride reabsorption.[219] In addition, it decreases renal calcium excretion compared to loop diuretics.[210] Spironolactone, a potassium-sparing diuretic, competes with aldosterone in the distal convoluted tubule.[219] Because of the nature of aldosterone's mode of action, which is dependent on protein synthesis, the onset of action of spironolactone is delayed. In combination, these agents increase urinary excretion of sodium, potassium, and phosphorus while decreasing urinary calcium excretion. The usual dosages of chlorothiazide and spironolactone are 10 to 20 mg/kg and 1 to 2 mg/kg, respectively. This combination, given orally, results in improved lung function in infants with chronic lung disease (CLD).[224] Potential electrolyte imbalance (particularly potassium and phosphorus depletion) may occur; thus monitoring of these electrolytes is necessary.

Because of reports of serious neurologic complications with systemic steroid use, diuretic therapy should be strongly considered as a first-line therapy for early CLD. Chronic administration of thiazide-spironolactone leads to improved lung function and reduces the need for furosemide in neonates older than 3 weeks of age with CLD.[225] Further, thiazide-spironolactone may decrease the risk of death and decrease the incidence of continued intubation beyond 8 weeks in neonates who do not receive corticosteroids, bronchodilators, or aminophylline.[225]

Nesiritide-Recombinant Brain Natriuretic Factor

Nesiritide is approved for treatment of decompensated congestive heart failure in adults, and has been studied in pediatric-aged patients as well.[226,227] Preliminary reports suggest that natriuretic hormone infusions may improve patients with heart failure and acute lung injury but not in those with acute renal failure. Although some clinicians are currently using Nesiritide in postoperative heart patients, no reports of efficacy or safety are currently available.

Steroids

Corticosteroids have been tried in three distinct respiratory entities in neonatal medicine: acute RDS, postextubation stridor, and developing CLD. They have not proved useful in treating RDS in the newborn.[228]

Steroids may be helpful in reducing glottic and subglottic edema during trials of extubation in these infants. The Cochrane Collaborative Review concluded that dexamethasone reduces the need for endotracheal reintubation after a period of mechanical ventilation.[229] However, the review also warns that given the side effects of the medication, dexamethasone usage should be restricted to infants at increased risk for airway edema and obstruction, such as those who have undergone repeated or prolonged intubations or failed previous extubation attempts.[229]

Despite the use of antenatal corticosteroids and postnatal surfactant treatment, the incidence of CLD has increased. Two associated points may offer a partial explanation for the increase in the incidence of CLD: the incidence of CLD has an inverse relationship with birth weight and gestational age,[230] and survival of extremely-low-birth-weight (ELBW) neonates has increased.[231] Steroids have been widely used in the treatment of CLD of prematurity, also known as BPD.[232-235] CLD is a common complication seen in survivors of neonatal intensive care, and inflammation

plays an important role in its pathogenesis.[236] Treatment with corticosteroids is a potentially attractive therapy because of its powerful antiinflammatory properties.

Glucocorticoids have relatively long half-lives (cortisol 8 to 12 hours; prednisone 12 to 36 hours; dexamethasone 36 to 72 hours). These agents are metabolized in the liver to inactive compounds that are excreted by the kidney. High-dose therapy with dexamethasone or prednisone has resulted in rapid reduction in O_2 requirements and ventilator settings[237] and in improvement in lung compliance and gas exchange[238] in over half of the infants treated. In most cases, any improvement occurred during the first 5 days of therapy. The major positive effect has been a shortening of the time to extubation by 1 to 3 weeks.[232-235]

Systemic corticosteroids have potent acute side effects that include hyperglycemia, hypertension, hypertrophic obstructive cardiomyopathy, gastrointestinal hemorrhage and perforation, growth failure, and hypothalamic-pituitary-adrenal suppression.[239] Animal studies have also demonstrated that steroids can permanently affect brain cell division, differentiation, and myelination, as well as ontogeny of cerebral cortical development.[239] Follow-up studies in humans have added further cause for alarm. Neonates given dexamethasone 12 hours after birth showed a twofold increase in neuromotor impairments compared with controls at 2 years of age.[239,240]

The timing of initiation of therapy has been the subject of analysis in the Cochrane Collaboration, which performed a set of meta-analyses on corticosteroid therapy instigated at three different time points: early (less than 96 hours in at-risk neonates), moderately early (7 to 14 days in at-risk neonates), and delayed (greater than 3 weeks). At the early time point, the meta-analysis[241] demonstrated benefits with regard to early extubation, decreased risks of CLD, death or CLD at 28 days, patent ductus arteriosus, and pulmonary air leaks. Gastrointestinal bleeding and intestinal perforation were significant adverse effects at this time point. Importantly, several adverse neurologic effects were found at follow-up examinations of neonates treated with early steroid therapy: abnormal neurologic examination, cerebral palsy, and developmental delay.

Results for the administration at the moderately early time point (7 to 14 days)[242] demonstrated most of the positive effects seen in the early time point. There were no significant differences between steroid and control children assessed in the rates of cerebral palsy, blindness, deafness, or major neurosensory disability. However, because of the short-term gastrointestinal, metabolic, and infection-related side effects of steroids, and the less-than-ideal study design for seeking long-term complications, the authors suggest reserving corticisteroid treatment in this age group to infants who cannot be weaned from the ventilator and to minimize the dose and duration of therapy.[242] At the later time point (greater than 3 weeks), steroids did not reduce mortality, but did reduce chronic lung disease at 36 weeks. Similar reservations concerning patient selection and dosing were given by the authors.[243] At both the moderately early and delayed times, it appeared that trends toward higher neurodevelopmental complications from steroids were counterbalanced by a trend in decreased mortality.[242,243]

In 2002, because of the concerns of poor neurologic outcomes with less than convincing evidence for benefit, the American Academy of Pediatrics Committee on Fetus and Newborn stated that the *routine* use of systemic dexamethasone for the prevention or treatment of chronic lung disease in infants with very low birth weight is not recommended[244] and then reaffirmed the statement in 2006. Our present policy is to reserve steroid therapy for neonates 12 to 14 days of age on moderate to high ventilator settings and an F_{IO_2} of 0.6 or greater. A short course of 7 days is given, consisting of 0.25 mg/kg/dose every 12 hours for 4 days followed by 0.05 mg/kg/dose every 12 hours for 3 days. The therapy is then stopped. If the patient experiences a marked increase in ventilator settings after steroid therapy is stopped, the therapy is restarted and a longer weaning course is begun. Other centers reserve the use of steroids in patients who are still requiring mechanical ventilation at 1 month of age and are not weaning despite aggressive therapy including diuretics, adequate nutrition, bronchodilators, and appropriate weaning strategies. In these situations it is recommended that parental consent be obtained prior to the institution of this potentially harmful therapy.

Inhaled steroids offer an attractive way to interrupt the inflammatory cascade of CLD while minimizing potential side effects and long-term morbidity. To date, inhaled steroids have shown a reduction in the need for systemic steroids but have not demonstrated a reduction in the incidence of CLD or death (Table 21-7).[245] Although no particular study shows a clear benefit over systemic steroids, inhaled steroids offer an attractive therapy for CLD for the reasons stated, and the lack of conclusive evidence for efficacy may be related to drug delivery and dosing.

Respiratory Stimulants

Respiratory stimulants can be useful in the treatment of neonates with apnea of prematurity.[187,246,247] After the evaluation and treatment of these infants for specific, treatable underlying conditions such as infection or hypoglycemia, therapeutic regimens for apnea often include tactile stimulation, reduction in ambient temperature, continuous positive airway pressure, or intermittent mandatory ventilation. Some infants respond favorably to respiratory stimulants as separate or adjunctive therapy. In practice, the decision to administer a respiratory stimulant is dependent on the severity of the apnea and the patient's response to other interventions. If the apnea is severe and frequent, assisted ventilation usually is instituted first. When the apnea is less severe, the stimulant can be used without resorting to mechanical ventilation (see Chapter 3).

Occasionally, babies with severe RDS have recurrent apnea during attempts at weaning from assisted ventilation. Some have been effectively weaned more rapidly while being treated with respiratory stimulants.[248] Weaning from ventilatory support with the use of respiratory stimulants has been reported in a small series of infants with BPD[249] and in infants on low ventilatory settings.[214] The benefit of using theophylline prophylactically to reduce the incidence of postextubation respiratory failure and the need for reintubation was shown in an earlier study,[201] but a more recent meta-analysis of the literature could not prove efficacy in this regard.[250] However, in postoperative premature patients,

TABLE 21-7 Published Randomized, Placebo-Controlled Trials of Inhaled Steroids

Reference	Sample Size	Dosage	Recruitment Criteria	Delivery Method	Placebo	Positive Results in Steroid-Treated Infants
Laforce et al	13	Beclomethasone 3 × 50 mg for 28 days	>14 days, CXR BPD, VLBW	Nebulization through ventilator circuit or face mask	No blinded placebo	CRS; R(aw); no difference in infection
Geip et al	19	Beclomethasone 1000 mg daily for 7 days or until extubated	>14 days, VLBW CXR BPD	MDI + spacer	Double blind	Extubation
Arnon et al	20	Budesonide 600 mg twice daily for 7 days	14 days, BW <2000 g, IPPV	MDI + spacer	Double blind	Significant PIP; no difference in serum cortisol levels
Ng et al	25	Fluticasone propionate 1000 mg per day for 14 days	First 24 hours, <32 weeks' GA, VLBW	MDI + spacer	Double blind	Basal and poststimulation plasma ACTH and serum plasma cortisol concentrations significantly suppressed
Kovacs et al	60	Dexamethasone 0.5 mg/kg/day for 3 days, then nebulized budesonide 1000 mg for 18 days	>7 days, <30 weeks' GA, VLBW, IPPV	Nebulization	Not double blind	7/30 vs 17/30 required rescue dexamethasone; CRS; similar cortisol levels
Fok	53	Fluticasone 500 mg bid for 14 days	<24 hours, VLBW MDI + spacer IPPV		Double blind	17/27 vs 8/26 extubated at 14 days; CRS
Cole et al	253	Beclomethasone 40 mg/kg/day, decreasing to 5 mg/kg over 4 weeks	3-14 days, <33 weeks' GA, ≤1250 g, IPPV	MDI + spacer neonatal anesthesia bag + ET tube (even when extubated)	Double blind	Rescue dexamethasone,RR 0.6 (0.4-1.0); IPPV at 28 days, RR 0.8 (0.6-1.0) at 28 days

From Greenough A: Neonat Respir Dis 10:1-7, 2000.
ACTH, Adrenocorticotropic hormone; *CRS,* compliance; *CXR BPD,* chest radiograph appearance consistent with bronchopulmonary dysplasia, *ET,* endotracheal; *GA,* gestational age; *IPPV,* ventilator dependent (intermittent positive-pressure ventilation; *MDI,* metered-dose inhaler; *PIP*, peak inspiratory pressure; *R(aw)*, airway resistance; *VLBW*, very low birth weight.

TABLE 21-8 Methylxanthines for Neonatal Apnea

Drug	Loading Dose (IV, mg/kg)	Maintenance Dosage (IV)*	Plasma Concentration (mg/L)	Toxicity
Theophylline	5.5-6.0	1 mg/kg every 8 hr, or 2 mg/kg every 12 hr	7-20† (~10 ideal)	Cardiovascular: tachycardia CNS stimulation: seizures, jitteriness Gastrointestinal: vomiting, distension
Caffeine	10	2.5-5 mg/kg every 24 hr	7-20†	Unlikely with plasma levels <50 mg/L
Caffeine citrate	20	5-10 mg/kg every 24 hr		As for caffeine

*Oral dosage = IV dosage × 1.25.
†Monitor levels and screen for signs of toxicity.

caffeine appears to prevent postoperative apnea/bradycardia and episodes of oxygen desaturation.[251]

The methylxanthines theophylline and caffeine are the most frequently used respiratory stimulants. These agents are respirogenic, primarily because they increase the respiratory center output.[246,252] In addition, they increase chemoreceptor sensitivity to carbon dioxide and strengthen diaphragmatic contractions.[188] The two agents may not have exactly the same mechanism of action. The tidal volume appears to be increased by theophylline, but the drug has minimal effect on respiratory frequency. In contrast, it is the respiratory frequency, not the tidal volume, that is increased by caffeine. Usual dosages for the methylxanthines are listed in Table 21-8. The biochemical and physiologic effects of xanthines are listed in Box 21-1.

Box 21-1 EFFECTS OF XANTHINES

Biochemical
Inhibition of phosphodiesterase

Central Adenosine Antagonism
Enhancement of calcium flux across sarcolemma (?)

Physiologic
Increased minute ventilation
Shift of CO_2 response curve to left, with or without increase in slope
Greater efficiency of diaphragmatic contraction
Improved pulmonary mechanics
Decreased hypoxic ventilatory depression

Theophylline

Theophylline (1,3-dimethylxanthine) has a half-life of approximately 30 hours. In the adult, theophylline is eliminated by hepatic biotransformation and urinary excretion. In the newborn, however, the hepatic biotransformation with *N*-demethylation is absent; instead, the occurrence of *N*-7-methylation produces caffeine.[246] The therapeutic plasma concentration is about 7 to 20 mg/L. In one study, levels greater than 6.6 mg/L controlled apneic spells, whereas cardiovascular toxicity with tachycardia was noted only at levels greater than 13.0 mg/L.[253] Some newborns manifested toxicity at levels of 9.0 mg/L of transplacentally acquired theophylline. Because of the problems at these lower levels and because of the potential additive effects of the caffeine produced from theophylline, 10 mg/L may be a desirable level. Signs of toxicity may include irritability, diaphoresis, diarrhea, seizures, gastroesophageal reflux, and tachycardia.[187] The usual intravenous loading dose of theophylline is 4.0 to 6.0 mg/kg, with a maintenance dose of 1 mg/kg every 8 hours or 2 mg/kg every 12 hours. Serum trough levels should be evaluated 48 to 72 hours after maintenance therapy has been started and periodically thereafter.

Caffeine

Caffeine (1,3,7-trimethylxanthine) has a plasma half-life of about 100 hours in the newborn. The extremely long half-life is due primarily to a slow elimination rate. In the adult, most of the caffeine is converted to demethylated xanthines and methyluric acids by the liver. In the neonate, however, most of the caffeine is excreted unchanged in the urine. This may be due to deficiency of the hepatic cytochrome P-450 enzyme system, which may be responsible for methylxanthine metabolism. The therapeutic plasma concentration is about 8 to 20 mg/L. Concentrations as low as 3 to 4 mg/L have controlled apneic spells, and no cardiovascular, CNS, or gastrointestinal toxicity was noted at levels up to 50 mg/L.[246] The usual loading dose of caffeine is 10 mg/kg, with a daily maintenance dose of 2.5 to 5 mg/kg. (The usual form of caffeine, the citrate in a 20-mg/mL solution, is equivalent to a 10-mg/mL solution of the base and may be administered intravenously [IV] or orally.)

The toxic manifestations of these agents are related to the relative activity each has on different sites. Theophylline has more cardiovascular than CNS activity. Consequently, early signs of toxicity are cardiovascular in origin, followed by seizure activity. Caffeine has more marked CNS than cardiovascular activity, but toxicity is rarely seen (except in drug dosing errors) because the levels required for toxic manifestations are extremely high. Although theophylline may have a slight advantage over caffeine in decreasing mean number of apnea events during the first 1 to 3 days of treatment, this advantage disappears later.[254] Because of the similar therapeutic profile combined with fewer toxicities,[254] we prefer to use caffeine as a first-line respiratory stimulant.

Recent studies have shown other benefits of caffeine in preterm babies. In a randomized trial in 2006, neonates between 500 and 1250 g birth weight, caffeine instituted in the first 10 days of life led to a lower incidence of chronic lung disease,[255] as well as improved the rate of survival without developmental disability.[256] These infants had slightly less weight gain in the NICU, but it appears that the benefits of caffeine outweigh the risks, with a number needed to treat of 16.

Doxapram

When methylxanthine therapy fails to prevent apneic spells, other respiratory stimulants, including doxapram, have occasionally been used successfully.[257] Studies of its use have been hampered by small sample sizes, and its long-term benefits are unclear.[258] Doxapram is formulated in sodium benzoate, which is the suspected cause of the "gasping syndrome" in neonates, and thus it is not currently recommended for neonatal use.[259]

Aerosol Delivery to Neonates

The fetus has a fully defined conducting airway early in its development, but the size of the airways changes dramatically in the first years of life. Because infants have low tidal volume, low vital capacity, low functional residual capacity, and short respiratory cycle, aerosol particles have a short residence time in the airways, which hampers pulmonary deposition. In addition, narrow airways tend to trap or impact larger particles. Because of these factors, aerosol delivery to neonates presents a relatively simple concept: smaller patients receive less aerosol than larger children or adults, with a lower percent of the initial dose reaching the infants' lungs.

The upper respiratory tract is designed to trap particles before they enter the lung. The filtering capacity of the neonate may actually be weight appropriate in that the lower deposition efficiency may result in infants receiving weight appropriate doses of medical aerosols. For example, deposition efficiency of 0.5% in a 4-kg infant of a standard dose of albuterol sulfate (2500 mcg) would result in a lung dose of 3.12 mcg/kg, whereas a 70 kg adult with 10% deposition would receive a comparable lung dose of 3.6 mcg/kg. Consequently, rationales to reduce standard adult doses for infants and small children have not been well substantiated in the literature.[260]

We have only limited data regarding inhaled particle mass, lung deposition, and regional distribution of aerosols in neonates and infants. Pulmonary deposition of medical aerosol to neonates may be less than 1% of the nominal dose with standard jet (JN) and ultrasonic (UN) nebulizers and pressurized metered-dose inhalers (pMDI), compared to 6% to 22% in larger children and adults.[261,262] Recent research suggests that local delivery of aerosol to the lung may be as efficient via mechanical ventilation as spontaneous breathing with face mask, and different technologies may increase available lung dose.[262]

Delivery Devices and Drug Dose Delivery

The only study of drug delivery efficiency in neonates and infants of 1 to 4 kg found only 0.2% to 0.9% of the nebulizer or pMDI dose deposited in the lung whether the infant was breathing spontaneously or intubated and mechanically ventilated.[263] Animal studies support these observations, showing similar lung delivery with jet and

TABLE 21-9 Advantages and Disadvantages of Aerosol Generators in Neonates

Aerosol Generator	Advantages	Disadvantages
Pressurized metered-dose inhaler (pMDI)	More consistent aerosol particle size and output Less time consuming to administer Less preparation time Less contamination Less expensive than single-use nebulizers	Technique problems Lack of pure medications Not all medications available in pMDI New HFA formulations needed for clinical study
Jet nebulizer	Tidal breathing Passive cooperation May be used for long periods to deliver high doses Wide range of medications output	Expensive and inconvenient Inefficient and highly variable aerosol output Numerous environmental factors affect aerosol particle size and Poor aerosolization of suspensions and viscous solutions Preparation time Time consuming to administer Contamination potential Requires compressed gas
Ultrasonic nebulizer	More efficient than jet nebulizer and pMDI Tidal breathing Passive cooperation Use for long periods to deliver high doses	Expensive and inconvenient Requires power source Contamination potential Limited medications available for use Preparation time Time consuming to administer

From Cole C: Neonat Respir Dis 10:1-12, 2000.

ultrasonic nebulizers as well as pMDI.[264] A recent study in 2-kg macaques confirmed 0.7% deposition with a jet nebulizer, but 13.9% using a vibrating mesh nebulizer.[265] This suggests that selection of aerosol generator type may have a substantial impact on lung delivery in the neonate. Table 21-9 lists some principles that impact aerosol delivery efficiency to the neonate.

Outcome Studies in Ventilated Infants

The relatively low efficiency of aerosol deposition during infant ventilation may be misleading, in that a small absolute lung dose provides a larger dose/kg of body weight than in adults, and has been shown to have pharamacokinetic actions. Administration of bronchodilators to ventilated low-birth-weight infants leads to improvements in static compliance and respiratory resistance with standard dose ranges with nebulizers (1.25-2.5 mg) and pMDIs (1-2 puffs).[193,266,267] Inhaled steroids have been reported to have some therapeutic effects.[268-270] However, a recent meta-analysis[271] concluded that inhaled steroids had very small effects on the occurrence of chronic lung disease in ventilator-dependent infants, probably because of inefficient aerosol delivery methods. Indeed, the use of a pMDI with spacer may be more efficient than a conventional jet nebulizer for delivering both salbutamol or budesonide to neonates.[272] Others have reported effective aerosol delivery of prostacyclins to treat pulmonary hypertension in the infant.[176]

New Directions and Devices

New technologies have been applied to increase aerosol delivery with nasal CPAP in early studies to demonstrate safety in the delivery of exogenous surfactant to prevent RDS.[273] Interesting in vitro work with high-frequency oscillation suggests double digit deposition.[274]

As the aerosol technology evolves, particle size, residual drug, mechanical dead space, and precise patterns of aerosol generation have been highlighted as the keys to improved efficiency. As we learn to exceed single digit deposition to neonates, on and off the ventilator, we will find expanded opportunity to develop a broad variety of inhaled drugs for treatment of this patient population. This will also demand pharmacodynamic and pharmacokinetic studies for determination of safe and effective dosing.

Summary

All of the drugs discussed should be dispensed by personnel who are competent in their administration, know their effects, and are aware of the attention required for patient monitoring. Techniques for the monitoring of many serum drug levels now are available in many centers. The information that such monitoring provides may allow the clinician to use these agents with greater accuracy and safety. A list of some drugs commonly used for ventilated infants and their recommended dosages is found in Appendix 33.

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22 Pharmacologic Adjuncts II: Exogenous Surfactants

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The development of exogenous surfactant therapy in the early 1990s was an historic advance in neonatology that led to significant reductions in neonatal mortality.[1-3] Exogenous surfactant therapy is now routinely used in the management of respiratory distress syndrome (RDS) in preterm infants and increasingly in other neonatal respiratory disorders such as meconium aspiration syndrome (MAS). This chapter provides an evidence-based overview of the current use of exogenous surfactant therapy in neonatal respiratory disorders.

History

The development of effective surfactant preparations was the culmination of a series of investigations by pioneers of surfactant research, who described the existence and composition of surfactant, the role of surfactant in lowering surface tension, and the role of surfactant in maintaining alveolar stability.[4-6] A landmark in our current understanding of RDS was the demonstration of surfactant deficiency in the lungs of infants dying of extreme prematurity or hyaline membrane disease.[7] Although the introduction of surface active substances into the lung was suggested as early as 1947,[8] the initial attempts to provide exogenous surfactant therapy for immature lungs were unsuccessful.[9,10] These were followed several years later by successful attempts in animals[11] and then in human neonates.[12] After these initial efforts, numerous animal experiments and human clinical trials were conducted to study the efficacy of surfactant therapy, the relative efficacy of different surfactant preparations, the optimal timing of administration, the optimal dosage, and other aspects of exogenous surfactant therapy. The history and evolution of surfactant therapy have been reviewed in detail by several authors.[13-17]

Surfactant Function, Composition, and Metabolism

The function, composition, secretion, and metabolism of mammalian surfactant have been reviewed by several authors[18-20] and are summarized below.

Function

Pulmonary alveoli, where gas exchange occurs, are bubble shaped and have a high degree of curvature. The surface tension of the moist inner surface is due to the attraction between the molecules in the alveolar fluid and tends to make the alveoli contract. Unchecked, this tendency would result in lung collapse. Surfactant greatly reduces the surface tension on the inner surface of the alveoli, thus preventing the alveoli from collapsing during expiration.

Composition

Accurate determination of the composition of pulmonary surfactant is difficult. To obtain surfactant for analysis, one must either wash out lungs (with the possible limitation of leaving important components behind) or extract surfactant from minced lungs (with the possible problem of adding cellular contaminants). Mammalian surfactant obtained by lung lavage consists of 80% phospholipids, 8% neutral lipids and 12% protein. The predominant class of phospholipid (nearly 60%) is dipalmitoyl phosphatidylcholine (DPPC), with lesser amounts of unsaturated phosphatidylcholine compounds (25%), phosphatidylglycerol (15%) and phosphatidylinositol. Of all the constituents of surfactant, DPPC alone has the appropriate properties to reduce alveolar surface tension. However, DPPC alone is a poor surfactant because it adsorbs very slowly to air-liquid interfaces. Surfactant proteins or other lipids facilitate its adsorption.

Approximately half the protein in surfactant consists of contaminating protein from the plasma or lung tissue.[21] The remaining proteins include four unique surfactant-associated apoproteins—SP-A, SP-B, SP-C, and SP-D.[22,23] SP-A and SP-D are hydrophilic proteins and belong to a subgroup of mammalian lectins called *collectins.* They may play important roles in the defense against inhaled pathogens, and SP-A may have a regulatory function in the formation of the monolayer that lowers the surface tension.[18] SP-B and SP-C are hydrophobic proteins and are required to enhance spreading of phospholipid in the airspaces. SP-B promotes phospholipid adsorption and induces the insertion of phospholipids into the monolayer, thus enhancing the formation of a stable surface film.[18] SP-C enhances phospholipid adsorption, stimulates the insertion of phospholipids out of the subphase into the air-liquid interface, and may increase the resistance of surfactant to inhibition by serum proteins or by edema fluid.[18,19]

Secretion and Metabolism

Surfactant is produced in the type II cells of the alveoli (Fig. 22-1). It is assembled and stored in the lamellar bodies, which consist of concentric or parallel lamellae,

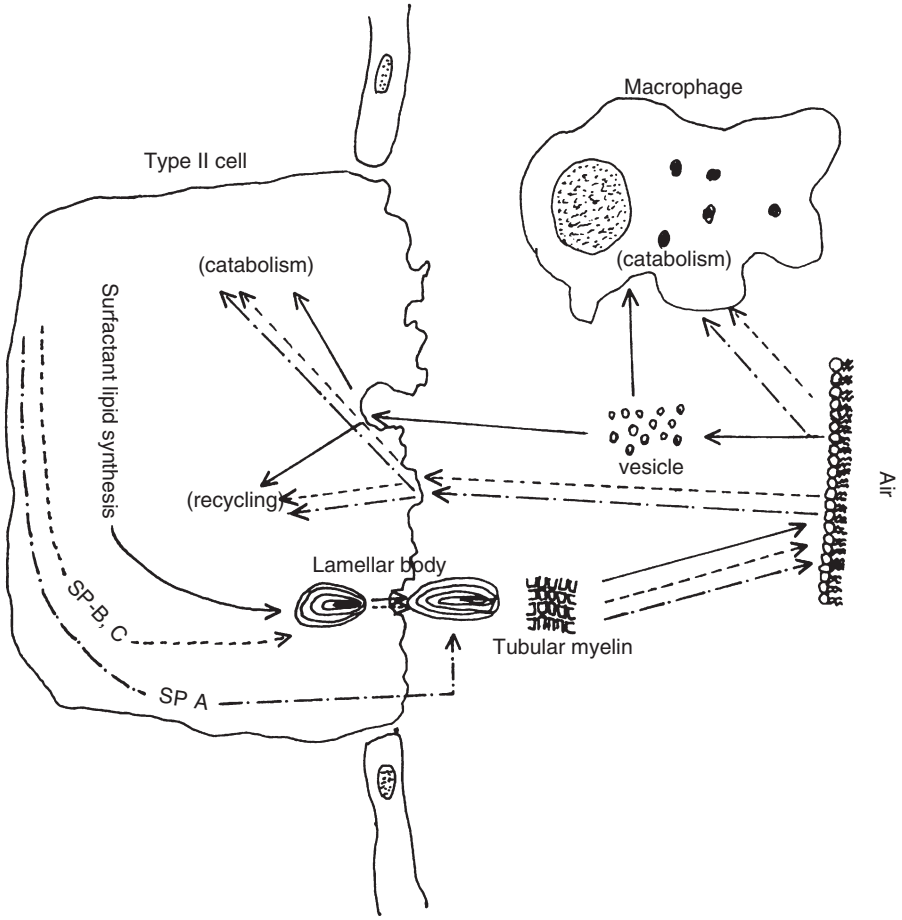

Figure 22-1 ■ Metabolism of surfactant. *Solid line,* Surfactant + liquid; *dashed and dotted line,* SP-A; *dashed line,* SP-B, SP-C. (From Jobe AH, Ikegami M: Clin Perinatol 28:655, 2001.)

predominantly composed of phospholipid bilayers. Lamellar bodies are extruded into the fluid layer lining the alveoli by exocytosis and form structures known as *tubular myelin*. Tubular myelin consists of long stacked tubes composed mainly of phospholipid bilayers, the corners of which appear fused, resulting in a lattice-like appearance on cross section. Tubular myelin is thought to be the major source of the monolayer surface film lining the air-liquid interface in the alveoli, in which the hydrophobic fatty acyl groups of the phospholipids extend into the air whereas the hydrophilic polar head groups bind water.[24] This surfactant monolayer lowers the surface tension at the air-liquid interface by replacing water at the surface.[24] The phospholipid from the monolayer eventually re-enters the type II cells through endocytosis and forms multivesicular bodies. These multivesicular bodies are either "recycled" by rapid incorporation into the lamellar bodies or degraded in lysosomes. Of note, all critical components of surfactant (DPPC, phosphatidylglycerol [PG], SP-A, SP-B, and SP-C) are recycled.[20]

Types of Surfactant

Three types of exogenous surfactant are available: (1) surfactant derived from animal sources, (2) synthetic surfactant without protein components, and (3) synthetic surfactant containing protein components.

Animal-derived Surfactants

Current commercially made animal-derived surfactants are obtained from either bovine or porcine lungs. Beractant (Survanta) and Surfactant TA (Surfacten) are lipid extracts of bovine lung mince with added DPPC, tripalmitoylglycerol, and palmitic acid. Calf lung surfactant extract (CLSE, calfactant, Infasurf), SF-RI 1 (Alveofact), and bovine lipid extract surfactant (BLES) are bovine lung washes subjected to chloroform-methanol extraction. Poractant (Curosurf) is a porcine lung mince that has been subjected to chloroform-methanol extraction and further purified by liquid-gel chromatography. It consists of approximately 99% polar lipids (mainly phospholipids) and 1% hydrophobic, low-molecular-weight proteins (SP-B and SP-C).[25] All the animal-derived surfactants contain SP-B and SP-C, but the lung mince extracts (Survanta and Curosurf) contain less than 10% of the SP-B that is found in the lung-wash extracts (Infasurf, Alveofact, and BLES).[26] The purification procedure including extraction with organic solvents removes the hydrophilic proteins SP-A and SP-D, leaving a material containing only lipids and small amounts of hydrophobic proteins. Poractant, which is further purified by liquid gel chromatography, contains only polar lipids and about 1% hydrophobic proteins (SP-B and SP-C in an approximate molar ratio of 1:2).[27] None of the commercial preparations contain SP-A.[26] A surfactant obtained from human amniotic fluid was originally tested in clinical trials[28,29] but is currently not used.

Synthetic Surfactants without Protein Components

The original exogenous products tested in the 1960s were synthetic surfactants composed solely of DPPC, which by itself cannot perform all the functions required of pulmonary surfactant. Current synthetic surfactants without protein are mixtures of a variety of surface active phospholipids (principally DPPC) and spreading agents to facilitate surface adsorption. These products include Exosurf and ALEC (artificial lung expanding compound). Colfosceril palmitate, hexadecanol, tyloxapol (Exosurf) consists of 85% DPPC, 9% hexadecanol, and 6% tyloxapol (a spreading agent). ALEC (Pumactant), which is no longer manufactured,[30] was a 7:3 mixture of DPPC and phosphatidylglycerol. These synthetic surfactants lack many of the components of animal-derived surfactant, particularly the hydrophobic surfactant proteins B and C.

Protein-containing Synthetic Surfactants

The protein-containing synthetic surfactants contain synthetic phospholipids and proteins produced through peptide synthesis and recombinant technology that function similarly to the hydrophobic proteins (SP-B and SP-C) of native human surfactant. Research is in progress to develop component protein analogs of the hydrophilic proteins SP-A and SP-D as well.

Of the surfactants containing SP-B analogs, the best studied is lucinactant (Surfaxin), which contains a mimic of SP-B called *sinapultide* or *KL4 peptide*. KL4 is a 21-residue peptide consisting of repeated units of four hydrophobic leucine (L) residues, bound by basic polar lysine (K) residues arranged in the following order—KLLLLKLLLLKLLLLKLLLK. This structure mimics the repeating pattern of hydrophobic and hydrophilic residues in the C-terminal part of SP-B and stabilizes the phospholipid layer by interactions with the lipid heads and the acyl chains.[31] In lucinactant, sinapultide is combined with dipalmitoyl phosphatidylcholine, palmitoyl-oleoyl-phosphatidylglycerol and palmitic acid.[32,33] Another synthetic SP-B analog currently under testing is called *dSP-$B_{1\text{-}25}$*, which resembles the N-terminal segment of SP-B, and when combined with synthetic phospholipids, has shown some efficacy in animal studies.

Of the surfactants containing SP-C analogs, rSP-C surfactant or lusupultide (Venticute) has been studied in vitro and in animals and has shown efficacy. It contains recombinant SP-C (rSP-C) combined with DPPC, palmitoyl-oleoyl-phosphatidylglycerol, palmitic acid, and calcium chloride.[34,35] rSP-C is similar to the 34-amino acid human SP-C sequence, except that it contains cysteine (in place of phenylalanine) in positions 4 and 5 and contains isoleucine (instead of methionine) in position 32.

Acute Pulmonary and Cardiac Effects of Surfactant Therapy

Immediate Pulmonary Effects of Surfactant Therapy

In animal models of RDS, administration of exogenous surfactant results in improved lung function (Fig. 22-2)[36]

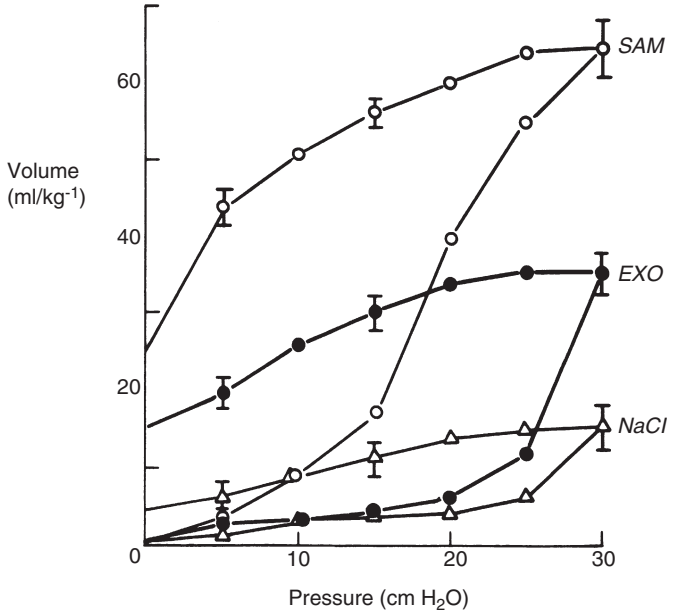

Figure 22-2 ■ Pressure-volume characteristics of lungs from 10 matched prematurely delivered rabbits after treatment with saline (NaCl), Exosurf (EXO), or surface active material obtained by lavaging lungs of young adult rabbits with saline (SAM), plus ventilation for 30 minutes. Measurements were made 10 minutes after the animals died and their lungs were allowed to degas spontaneously. (From Tooley WH, Clements JA, Muramatsu K, et al: Am Rev Respir Dis 136:651, 1987.)

and improved alveolar expansion (Fig. 22-3).[37] Several studies in human neonates have shown that the administration of exogenous surfactant therapy leads to rapid improvement in oxygenation and a decrease in the degree of support provided by mechanical ventilation (Fig. 22-4).[38] These rapid changes are accompanied by an increase in the functional residual capacity and are followed by a slower and variable increase in lung compliance.[39-41] A decrease in pulmonary ventilation-perfusion mismatch has also been reported.[42-44]

Immediate Effects on Pulmonary Circulation

The effect of surfactant treatment on the pulmonary circulation is unclear. In three studies pulmonary blood flow was unchanged with surfactant therapy.[45-47] In contrast, others have reported a decrease in pulmonary artery pressure or an increase in pulmonary artery flow with surfactant therapy,[48-51] as well as an increase in the ductal flow velocity from the systemic to the pulmonary circuit.[50] It is uncertain whether these changes in pulmonary circulation are related to ventilation practices, blood gas status, or to surfactant treatment itself.[52]

Radiographic Changes

In addition to these physiologic changes, treatment with exogenous surfactant also results in radiologic improvement, with chest radiographs after treatment often (but not always) showing a decrease in the signs of RDS. This clearing of the lungs can be uniform, patchy, or asymmetric, sometimes with disproportionate improvement of radiologic changes in the right lung.[53-57]

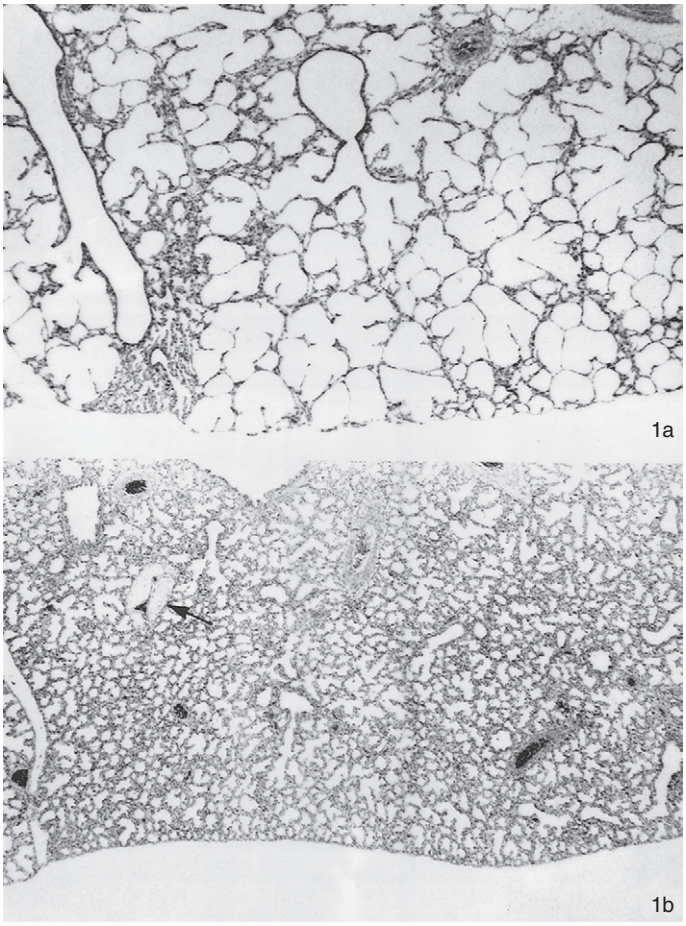

Figure 22-3 ■ Expansion patterns in lung sections from premature rabbits.**1a,** Well-expanded area in surfactant-treated fetus. The rounded appearance of the aerated alveoli contrasts with the pattern in **1b** and with the wedge of unexpanded parenchyma *(lower left).* **1b,** "Unexpanded" lung in control fetus that did not receive surfactant. The configuration of the alveoli reflects the fluid-filled state. Note abundant interstitial fluid around a pulmonary vein *(arrow)* (hematoxylin and eosin, magnification ×27). (From Robertson B, Enhorning G: Lab Invest 31:54, 1974.)

Clinical Trials of Surfactant Therapy

Surfactant therapy is one of the best-studied interventions in neonatology and has been subjected to numerous randomized controlled trials comparing various treatment strategies. The findings from these trials, many of which are included in multiple systematic reviews in the Cochrane Database of Systematic Reviews,[58] are summarized in the following sections. The results of meta-analyses are presented as the "typical" or "pooled" estimates of relative risk (RR) and absolute risk difference (ARD), with 95% confidence intervals (CI).

Surfactant Therapy Compared to Placebo or No Therapy

Many of the early trials in the late 1980s and early 1990s studied the effects of surfactant therapy compared to placebo or no therapy. Some of these trials studied the effects of prophylactic administration of surfactant to preterm infants at risk for developing RDS (prophylactic or prevention trials). Others studied the effects of treatment with surfactant in preterm infants with clinical and/or radiologic features of RDS (rescue or treatment trials). Some of these studies used animal-derived surfactant and others used synthetic surfactant. Systematic reviews of these trials[59-62] show that, compared to placebo or no therapy, surfactant treatment or prophylaxis (with either animal-derived or synthetic surfactant) decreases the risk

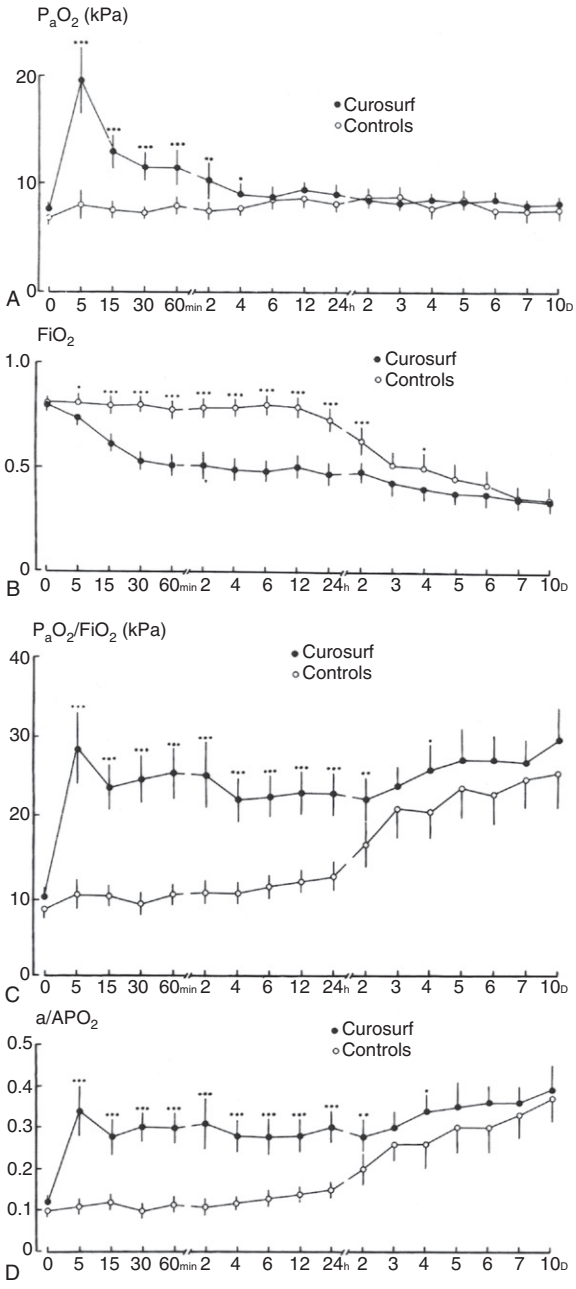

Figure 22-4 ■ Oxygenation measurements in Curosurf-treated and control infants at various intervals after randomization. Results are mean values and 95% confidence intervals. If confidence intervals are overlapping, bars are shown on only one side of data point. Note that the time scale is not linear. Conversion factor: 1 kPa = 7.52 mm Hg. **P* less than 0.05; ***P* less than 0.01; ****P* less than .001. (From Collaborative European Multicenter Study Group: Pediatrics 82:683, 1988.)

of pneumothorax and of mortality. Estimates from the meta-analyses indicate that there is a 30% to 65% relative reduction in the risk of pneumothorax and up to a 40% relative reduction in the risk of mortality. There were no consistent effects on other clinical outcomes such as chronic lung disease, patent ductus arteriosus, and intraventricular hemorrhage.

Further evidence of the benefits of surfactant therapy is derived from studies demonstrating decreased mortality and morbidity in very-low-birth-weight infants after the introduction of surfactant therapy into practice.[1,3,63-67]

Prophylactic Surfactant Administration Compared to "Rescue" Administration

The rationale for prophylactic administration of surfactant is provided by the observation that in animal studies a more uniform and homogenous distribution of surfactant is achieved when it is administered into a fluid-filled lung[68,69] and by the belief that administration of surfactant into a previously unventilated or minimally ventilated lung will diminish acute lung injury. Even brief (15-30 min) periods of mechanical ventilation prior to surfactant administration have been shown, in animal models, to cause acute lung injury resulting in alveolar-capillary damage, leakage of proteinaceous fluid into the alveolar space, and release of inflammatory mediators[70-72] and to decrease the subsequent response to surfactant replacement.[73,74] Surfactant deficient animals who receive assisted ventilation develop necrosis and desquamation of the bronchiolar epithelium as early as 5 minutes after onset of ventilation.[75]

Eight randomized controlled trials compared the effects of prophylactic surfactant administration to surfactant treatment of established RDS.[28,76-82] All these trials used animal-derived surfactant preparations. Trials varied according to whether surfactant was given before or after the onset of air breathing (preventilatory or postventilatory administration), but all administered surfactant before 15 minutes of age. The average time of administration of surfactant in the selective treatment groups ranged from 1.5 to 7.4 hours. The results of the meta-analysis of these trials from a systematic review[83] are summarized in Figure 22-5.

Compared to surfactant treatment of established RDS, prophylactic administration of surfactant resulted in a decrease in the risk of pneumothorax (typical RR 0.62, 95% CI 0.42, 0.89; typical ARD −0.02, 95% CI −0.04, −0.01), a decrease in the risk of pulmonary interstitial emphysema (typical RR 0.54, 95% CI 0.36, 0.82; typical ARD −0.03, 95% CI −0.04 −0.01), a reduction in the risk of neonatal mortality (typical RR 0.61, 95% CI 0.48, 0.77; typical ARD −0.05, 95% CI −0.07, −0.02) and a trend towards a decrease in the risk of intraventricular hemorrhage (typical RR 0.92, 95% CI 0.82, 1.03; typical ARD −0.03, 95% CI −0.06, 0.01). Because of the greater risk of RDS and mortality with decreasing gestational age, the benefits of prophylactic administration compared to selective administration were of greater magnitude. The meta-analysis demonstrates that compared to selective administration, prophylactic administration of animal-derived surfactant to infants less than 30 weeks' gestation resulted in a greater reduction in neonatal mortality (typical RR 0.62, 95% CI 0.49, 0.78; typical ARD −0.06, 95% CI −0.09, −0.03) and a reduction in the combined outcome of bronchopulmonary dysplasia or death (typical RR 0.87, 95% CI 0.77, 0.97; typical ARD −0.05, 95% CI −0.09, −0.01).

Although a strategy of surfactant prophylaxis is beneficial in infants with RDS, it does result in some infants without RDS being intubated and given surfactant unnecessarily. Based on data from the trials, almost twice as many infants less than 30 weeks' gestation will require intubation using this approach. Based on current practice in the Vermont Oxford Network, over 75% of infants less than 1000 g are already intubated in the delivery room, and over 80% receive surfactant at some point during their hospitalization. Therefore, approximately 20% to 25% more extremely low-birth-weight (ELBW) infants would require intubation and surfactant treatment using this approach.[84] At what threshold do the potential benefits of decreased mortality, decreased pneumothorax, and decreased lung injury from prophylactic surfactant exceed the potential risks of endotracheal intubation and the costs of surfactant dosing to infants who would not have required it? Based on the available evidence, this threshold is likely to be at 28 to 30 weeks' gestation,[26,30,85] although some institutions have managed babies at this and smaller gestational ages with nasal continuous positive airway pressure (nCPAP) alone.

Preventilatory Versus Postventilatory Prophylactic Surfactant Administration

The initial studies using prophylactic surfactant administered the drug as an immediate bolus after intubating the infants rapidly after birth (i.e., "before the first breath").

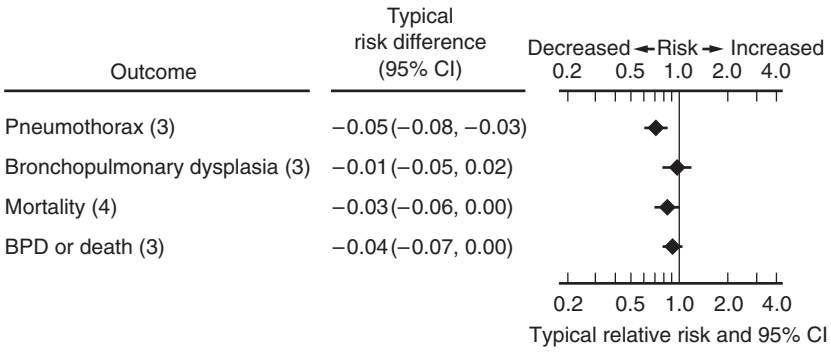

Figure 22-5 ■ Meta-analysis of eight randomized trials comparing prophylactic and rescue treatment with surfactant. Numbers in parentheses following the outcomes are the numbers of trials in which that outcome was reported. *BPD,* Bronchopulmonary dysplasia; *CI,* confidence interval; ◆, point estimate; *horizontal bars,* 95% confidence interval of the relative risk. (From Soll RF, Morley CJ: Cochrane Database Syst Rev (2):CD000510, 2001.)

This approach delays the initiation of neonatal resuscitation, including positive pressure ventilation, and is associated with a risk for surfactant delivery into the right mainstem bronchus or esophagus. A randomized trial demonstrated that prophylaxis may be administered in small aliquots soon after resuscitation and confirmation of endotracheal tube position, with equivalent or greater efficacy.[86] Based on this trial, prophylactic surfactant is recommended to be administered after initial resuscitation of the infant at birth and administration prior to the "first breath" is unnecessary.

Early Versus Late Treatment of Established RDS

In preterm infants who do not receive prophylaxis, early surfactant treatment of infants with signs and symptoms of respiratory distress syndrome (RDS) is supported by many of the same arguments that support prophylactic surfactant administration. Four randomized controlled trials,[87-90] including the largest randomized trial conducted in neonatology (the OSIRIS trial) have evaluated early versus delayed selective surfactant administration. The results of these trials are summarized in a systematic review.[91] In these trials, early administration of surfactant consisted of administration of the first dose within the first 30 minutes to the first 2 hours of life. Two of these studies used animal-derived surfactants and two used synthetic surfactant. The results of the meta-analysis of these studies are summarized in Figure 22-6.

Early selective treatment resulted in a decrease in the risk of pneumothorax (typical RR 0.70, 95% CI 0.59, 0.82; typical ARD −0.05, 95% CI −0.08, −0.03), a decrease in the risk of pulmonary interstitial emphysema (typical RR 0.63, 95% CI 0.43, 0.93; typical ARD −0.06, 95% CI −0.10, −0.01), a decrease in the risk of chronic lung disease (requirement for supplemental oxygen at 36 weeks' gestation, typical RR 0.70, 95% CI 0.55, 0.88; typical ARD −0.03, 95% CI −0.05, −0.01) and a decrease in the risk of neonatal mortality (typical RR 0.87, 95% CI 0.77, 0.99; typical ARD −0.03, 95% CI −0.06, 0.00). Therefore preterm infants who do not receive prophylactic surfactant and exhibit the signs and symptoms of RDS should receive the first dose of surfactant as early as possible. Outborn infants are at highest risk of delayed administration. Tertiary referral units accepting outborn infants should attempt to develop systems to ensure that surfactant is administered as early as possible to these infants, either by the transporting team or, if appropriate, by the referring hospital. In inborn infants, delays in administration of surfactant occur if other admission procedures such as line placement, radiographs, and nursing procedures are allowed to take precedence over surfactant dosing soon after birth. Surfactant administration should be given priority over other admission procedures.

There are no trials comparing the effects of prophylactic intubation and surfactant administration shortly after birth to infants at high risk of RDS (with intubation primarily performed to administer surfactant) to very early selective administration (e.g., at 30 to 60 min of life) in intubated infants with early RDS or respiratory insufficiency.

Early Surfactant Administration Followed Immediately by Extubation to Nasal Continuous Positive Airway Pressure

When surfactant therapy was first used, infants were maintained on mechanical ventilation after surfactant administration, ventilator support was gradually weaned as the pulmonary status improved, and the infant was extubated from low ventilator settings. This approach has been compared to a strategy of surfactant administration followed immediately (within 1 hour) by extubation to nasal continuous positive airway pressure (nCPAP) to prevent ventilator-induced lung injury (VILI) that can result from even brief periods of mechanical ventilation.[92,93] This newer approach has been called the *INSURE technique* (**IN**tubate, **SUR**factant, **E**xtubate to CPAP). Six randomized trials, all of which are trials of rescue surfactant administration, have compared the INSURE approach in spontaneously breathing infants with signs of RDS to later, selective administration of surfactant in infants with respiratory insufficiency related to RDS, followed by continued mechanical ventilation and extubation from low respiratory support. These trials are summarized in a systematic review.[94] Most of these studies included infants with a gestation of 35 weeks or less, and a birth weight of 2500 g or less. The meta-analysis in this review showed that compared to the traditional management strategy of gradual weaning, the INSURE approach reduced the need for mechanical ventilation (typical RR 0.67, 95% CI 0.57, 0.79), air leak syndromes (typical RR 0.52, 95% CI 0.28, 0.96), and BPD (oxygen at 28 days, typical RR 0.51, 95% CI 0.26, 0.99). A lower threshold for treatment at study entry (FIO_2 less than 0.45) resulted in a lower incidence of air leak (typical RR 0.46, 95% CI 0.23,

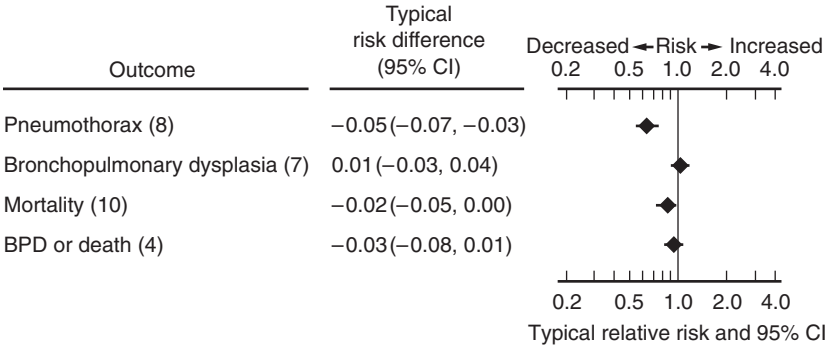

Figure 22-6 ■ Meta-analysis of four randomized trials comparing early and delayed administration of surfactant. Numbers in parentheses following the outcomes are the numbers of trials in which that outcome was reported. *BPD,* Bronchopulmonary dysplasia; *CI,* confidence interval; ◆, point estimate; *horizontal bars,* 95% confidence interval of the relative risk. (From Yost CC, Soll RF: Cochrane Database Syst Rev (2):CD001456, 2000.)

0.93) and BPD (typical RR 0.43, 95% CI 0.20, 0.92). A higher treatment threshold (FIO_2 greater than 0.45) at study entry was associated with a higher incidence of patent ductus arteriosus requiring treatment (typical RR 2.15, 95% CI 1.09, 4.13). In another recent randomized trial,[95] infants 27 to 31 weeks' gestation with RDS who were randomly assigned within the first hour of life either to intubation, very early surfactant, extubation, and nCPAP required less ventilation and had a lower incidence of mortality and air leaks (pneumothorax and pulmonary interstitial emphysema) than infants assigned to nasal continuous airway pressure alone.

These data suggest that spontaneously breathing preterm infants who show early signs of RDS should be given surfactant at a low threshold, after which they can be quickly extubated and placed on nCPAP to reduce VILI. Whether the same approach should be followed when prophylactic surfactant therapy is used is not clear due to lack of evidence.

Single Versus Multiple Surfactant Doses

Many of the initial trials of surfactant therapy tested a single dose of surfactant. However, surfactant may become rapidly metabolized, and functional inactivation of surfactant can result from the action of soluble proteins and other factors in the small airways and alveoli.[20] The ability to administer repeat or subsequent doses of surfactant is thought to be useful in overcoming such inactivation. The results of two randomized controlled trials that compared multiple dosing regimens to single-dose regimens of animal-derived surfactant extract for treatment of established respiratory distress syndrome[96,97] have been evaluated in a systematic review.[98] In one study,[96] after the initial dose of bovine lipid extract surfactant, infants assigned to the multiple-dose group could receive up to three additional doses of surfactant during the first 72 hours of life if they had a respiratory deterioration, provided they had shown a positive response to the first dose and a pneumothorax had been eliminated as the cause of the respiratory deterioration. In the other study,[97] infants in the multiple-dose group received additional doses of poractant at 12 and 24 hours after the initial dose if they still needed supplemental oxygen and mechanical ventilation. Approximately 70% of the infants randomized to the multiple-dose regimen received multiple doses.

The meta-analysis supports a decreased risk of pneumothorax associated with multiple-dose surfactant therapy (typical RR 0.51, 95% CI 0.30, 0.88; typical ARD 0.09, 95% CI 0.15, 0.02). There was also a trend toward decreased mortality (typical RR 0.63, 95% CI 0.39, 1.02; typical ARD 0.07, 95% CI 0.14, 0.00). No differences were detected in other clinical outcomes. No complications associated with multiple-dose treatment were reported in these trials. In a third study, in which synthetic surfactant was used in a prophylactic manner, the use of two doses of surfactant in addition to the prophylactic dose led to a decrease in mortality, respiratory support, necrotizing enterocolitis, and other outcomes when compared to a single prophylactic dose.[99] In the OSIRIS trial, which used synthetic surfactant, a two-dose treatment schedule was found to be equivalent to a treatment schedule permitting up to four doses of surfactant.

Criteria for Repeat Doses of Surfactant

The use of a higher threshold for retreatment with surfactant appears to be as effective as a low threshold and can result in significant savings in costs of the drug. The criteria for administration of repeat doses of surfactant have been investigated in two studies, both of which used animal-derived surfactant. In one study[78] the retreatment criteria compared were an increase in the fraction of inspired oxygen by 0.1 over the lowest baseline value (standard retreatment) versus a sustained increase of just 0.01 (liberal retreatment). There were no differences in complications of prematurity or duration of respiratory support. However, short-term benefits in oxygen requirement and degree of ventilator support were noted in the liberal retreatment group.

In another study,[100] retreatment at a low threshold (FIO_2 greater than 30%, still requiring endotracheal intubation) was compared to retreatment at a high threshold (FIO_2 greater than 40%, mean airway pressure greater than 7 cm H_2O). Again, there were minor short-term benefits to using a low threshold with no differences in major clinical outcomes. However, in a subgroup of infants with RDS complicated by perinatal compromise or infection, infants in the high threshold group had a trend toward higher mortality than the low-threshold group. Based on current evidence, it appears appropriate to use persistent or worsening signs of RDS as criteria for retreatment with surfactant. A low threshold for repeat dosing should be used for infants with RDS who have perinatal depression or infection.

Methods of Administration of Surfactant

A theoretical model for the transport of exogenous surfactant through the airways has been proposed,[101] consisting of four distinct mechanisms: (1) the instilled bolus may create a liquid plug that occludes the large airways but is forced peripherally during mechanical ventilation; (2) the bolus creates a deposited film on the airway walls, either from the liquid plug transport or from direct coating, that drains under the influence of gravity through the first few airway generations; (3) in smaller airways, surfactant species form a surface layer that spreads because of surface-tension gradients, that is, Marangoni flows; and (4) the surfactant finally reaches the alveolar compartment where it is cleared according to first-order kinetics.

Administration Through Catheter, Side-Port, or Suction Valve

According to the manufacturers' recommendations, beractant and poractant should be administered through a catheter inserted into the endotracheal tube; colfosceril should be administered through a side-port adapter attached to the endotracheal tube, and calf lung surfactant extract can be administered either through a feeding catheter or through a side-port adapter. Other methods of administration of surfactant have been tested in randomized trials. In one randomized trial, the administration of beractant through a catheter inserted through a neonatal suction valve without detachment of the neonate from the ventilator was compared to the administration of the dose (with detachment from the ventilator) in two aliquots through a catheter and to the standard technique of administration

of the dose in four aliquots through a catheter.[102] Administration through the suction valve led to less dosing-related oxygen desaturation but more reflux of beractant than the two-aliquot catheter technique. In another study,[103] the administration of poractant as a bolus was compared in a randomized trial to administration via a catheter introduced through a side-hole in the tracheal tube adaptor without changing the infants' position or interrupting ventilation. The numbers of episodes of hypoxia and/or bradycardia, as well as other outcomes, were similar in both groups. A slight and transient increase in $PaCO_2$ was observed in the side-hole group.

Administration Through Dual-Lumen Endotracheal Tube

The administration of poractant through a dual-lumen endotracheal tube without a change in position or interruption of mechanical ventilation was compared to bolus instillation in a randomized trial.[104] The dual-lumen group had fewer episodes of dosing-related hypoxia, a smaller decrease in heart rate and SaO_2, and a shorter total time in increased supplemental oxygen than the bolus group. The dual-lumen method has also been compared to the side-port method of administration of colfosceril in a randomized trial.[105] No difference was found between the two methods in dosing-related hypoxemia.

Administration Through a Laryngeal Mask Airway

Surfactant administration through a laryngeal mask airway (LMA) is noninvasive, avoids endotracheal intubation, and has been reported in a series of eight preterm infants (mean birth weight 1700 g) with RDS managed with nasal CPAP.[106] The mean arterial-to-alveolar oxygen tension ratio improved significantly after the treatment and no complications were reported. This method of administration is promising because it potentially avoids the complications associated with intubation, but requires testing in a large randomized trial before it can be recommended. Moreover, although the smallest infant in this study was 880 g, the use of the currently available LMA is only recommended for babies above 1500 g.

Nasopharyngeal Administration of Surfactant

Another noninvasive method of surfactant administration is instillation of surfactant into the nasopharynx during or immediately after delivery and before the first breath. Such instillation is thought to cause the surfactant to be aspirated into the fluid-filled airway as an air-fluid interface is established. A case series[107] of 23 preterm infants of 27 to 30 weeks' gestation receiving such intrapartum nasopharyngeal instillation of surfactant followed by placement on CPAP immediately after birth (mask CPAP initially followed by nasal CPAP) demonstrated the feasibility of such administration. However, more evidence is required to prove the efficacy of this approach before it can be used or recommended.

Other Methods

In one randomized clinical trial,[108] the slow infusion of colfosceril using a microinfusion syringe pump over 10 to 20 min was compared to manual instillation over 2 min. Pump administration resulted in fewer infants with loss of chest wall movement during dosing as well as a lesser increase in peak inspiratory pressure than with hand administration. However, in animals, slow infusion of surfactant into the endotracheal tube results in nonhomogeneous distribution of surfactant in the lung.[109,110] Therefore, currently, bolus administration of surfactant is preferred. Other methods of administration, such as nebulization or aerosolization[111-114] and in-utero administration to the human fetus[115,116] have also been reported. These methods require further clinical testing, may require specialized nebulization equipment, and are not currently recommended.

Chest Position During Administration of Surfactant

In a study in rabbits, pulmonary distribution of intratracheally instilled surfactant was largely determined by gravity, and changing the chest position after instillation did not result in any redistribution of the surfactant. Therefore, for neonates receiving surfactant, keeping the chest in the horizontal position may result in the most even distribution of the surfactant in the two lungs.[117]

Summary of Administration Methods

In summary, based on available evidence, surfactant should be administered in the standard method of aliquots instilled into an endotracheal tube. There is evidence to suggest that the administration of surfactant using a dual-lumen endotracheal tube or through a catheter passed through a suction valve is effective and may cause less dosing-related adverse events than standard methods. The side-port method of administration and the catheter method of administration appear to be equivalent. More studies are required before firm conclusions can be drawn about the optimal method of administration of surfactant and whether the optimal method is different for different types of surfactant.

Choice of Surfactant Product

Comparison of Animal-Derived and Synthetic Surfactants Without Protein

Although both synthetic and animal-derived surfactants are effective, their composition differs. Animal-derived surfactant extracts contain surfactant-specific proteins that aid in surfactant adsorption and resist surfactant inactivation.[22,118] Eleven randomized trials have compared the effects of animal-derived and synthetic surfactants in the treatment or prevention of RDS.[119-129] A total of over 4500 infants were studied in these trials. A systematic review of these trials is available.[130] The results of the meta-analysis are summarized in Figure 22-7.

Compared to synthetic surfactant, treatment with animal-derived surfactant extracts resulted in a significant reduction in the risk of pneumothorax (typical RR 0.63, 95% CI 0.53, 0.75; typical ARD −0.04, 95% CI −0.06, −0.03) and the risk of mortality (typical RR 0.87, 95% CI 0.76, 0.98; typical ARD −0.02, 95% CI −0.05, 0.00). Natural surfactant extract is associated with a marginal increase in the risk of intraventricular hemorrhage (typical RR 1.09, 95% CI 1.00, 1.19; typical ARD 0.03, 95% CI 0.00, 0.06), but no increase in grades 3 to 4 intraventricular hemorrhage (typical RR 1.08, 95% CI 0.92, 1.28; typical ARD 0.01, 95% CI −0.01, 0.03). The meta-analysis

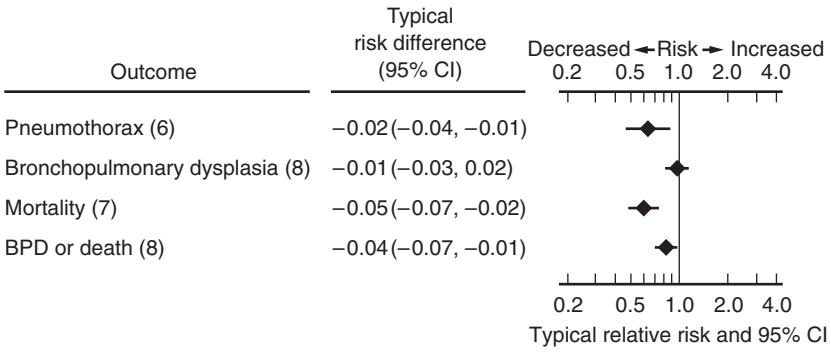

Figure 22-7 ■ Meta-analysis of 10 randomized trials comparing animal-derived surfactant. Numbers in parentheses following the outcomes are the numbers of trials in which that outcome was reported. *BPD,* Bronchopulmonary dysplasia; *CI,* confidence interval; ◆, point estimate; *horizontal bars,* 95% confidence interval of the relative risk. (From Soll RF, Blanco F: Cochrane Database Syst Rev (2):CD000144, 2001.)

also supports a marginal decrease in the risk of bronchopulmonary dysplasia or mortality associated with the use of natural surfactant preparations (typical RR 0.95, 95% CI 0.90, 1.01; typical ARD −0.03, 95% CI −0.06, 0.00).

In addition to these benefits, animal-derived surfactants have a more rapid onset of action, allowing ventilator settings and inspired oxygen concentrations to be lowered more quickly than with synthetic surfactant.[122,123,126,131,132] A comparison of physical properties and the results of animal studies also suggest that animal-derived surfactants have advantages over synthetic surfactants.[133] These properties are attributed to the presence of the surfactant proteins SP-B and SP-C in animal-derived surfactants.[134]

The use of animal-derived surfactant preparations should be favored in most clinical situations, because their use results in greater clinical benefits than synthetic surfactants. However, all animal-derived surfactants have to be refrigerated for storage. The synthetic surfactant colfosceril is available as a lyophilized powder that is to be stored at below 30° C in a dry place (not to be frozen) and reconstituted with sterile water before use. Therefore in situations where refrigeration is a problem (as in developing countries), it may be more practical to use colfosceril than animal-derived surfactants.

Comparison of Animal-Derived and Synthetic Surfactants with Protein

Clinical trials have compared the effects of synthetic surfactants containing peptides to animal-derived surfactant preparations. These synthetic surfactants do not have the theoretical concerns associated with animal-derived surfactants, namely, transmission of microorganisms, exposure to animal proteins and inflammatory mediators, susceptibility to inactivation, and inconsistent content.[135] Lucinactant, the synthetic surfactant containing an analog of SP-B, sinapultide, has been compared with beractant in the safety and effectiveness of Lucinactant versus Exosurf in a clinical trial of RDS in premature infants (SELECT), a multicenter, masked randomized trial of surfactant prophylaxis in infants of 24 to 32 weeks' gestation.[136] Lucinactant was also compared with poractant in surfaxin therapy against Respiratory Distress Syndrome (STAR), a multicenter randomized trial of surfactant prophylaxis in infants 24 to 28 weeks' gestation that was structured as a noninferiority trial.[137] A meta-analysis of these two studies[138] found no significant differences in outcomes between lucinactant and the comparison animal-derived surfactant in mortality at 36 weeks' postmenstrual age (typical RR 0.81, 95% CI 0.64, 1.03), chronic lung disease at 36 weeks' postmenstrual age (typical RR 0.99, 95% CI 0.84, 1.18), the composite outcome of mortality or chronic lung disease at 36 weeks' postmenstrual age (typical RR 0.96, 95% CI 0.82, 1.12), or in other respiratory outcomes. A decreased risk of necrotizing enterocolitis, a secondary outcome, was noted in infants receiving lucinactant (typical RR 0.60, 95% CI 0.42, 0.86; typical RD −0.06, 95% CI −0.10, −0.01).

However, both trials of lucinactant described above had multiple methodologic problems[139] that undermined their validity, and at present there is no clear evidence of the equivalence or superiority of lucinactant over any animal-derived surfactant product.[30] At the time of this writing, lucinactant has not been approved for use by the Food and Drug Administration. Although these newer surfactants show promise, further research is required to elucidate their role in the prevention or treatment of RDS.

Comparison of Different Types of Synthetic Surfactants

In the SELECT trial,[136] the randomized trial of lucinactant mentioned above, in which lucinactant was compared with beractant, lucinactant was also compared to colfosceril. Compared to infants receiving colfosceril, infants receiving lucinactant had less RDS (39% versus 47%) and less RDS-related mortality (4.7% versus 9.4%, RR 0.50, 95% CI 0.32, 0.80). All-cause mortality at 36 weeks' postmenstrual age was not significantly different (21% for lucinactant versus 24% for colfosceril). A trend toward a reduction in BPD or death at 36 weeks' postmenstrual age was associated with lucinactant treatment when compared to colfosceril (RR 0.88, 95% CI 0.77, 1.01).

Comparison of Different Types of Bovine Surfactants

Two randomized trials, both from the same group of investigators, have compared the efficacy and adverse effects of different bovine surfactant products. In a comparison of beractant (Survanta) and calf lung surfactant extract (CLSE) (Infasurf),[140] there were no differences detected between the two groups in the frequency of air leaks, complications associated with dosing, complications of prematurity, mortality, or survival without chronic lung disease. However, some differences were noted among subgroups of infants. Among infants treated for established RDS, those who received CLSE had a significantly longer interval between

doses, a lower inspired oxygen concentration, and a lower mean airway pressure in the first 48 hours of life than infants treated with beractant. Among infants in whom these surfactants were administered in a preventive manner, mortality in infants with a birth weight less than 600 g was significantly higher with calf lung surfactant extract than with beractant. In a second report,[141] that included two separate trials—a prophylaxis trial and a treatment trial—the trials were halted prematurely because of recruitment problems, and hence had inconclusive results with no demonstrated differences in outcomes between the two products. Thus there is no evidence of the superiority of one bovine preparation over the other.

Comparison of Porcine and Bovine Surfactants

Five studies comparing surfactant treatment of established moderate to severe RDS with poractant versus beractant have been published.[142-146]

A meta-analysis of these studies[17] found that compared to beractant, poractant treatment led to a significant reduction in neonatal mortality (typical RR 0.57, 95% CI 0.34, 0.96). The dose of beractant was uniformly 100 mg/kg across all five studies. When only studies that used a 100-mg/kg dose of poractant were considered, the reduction in mortality was not statistically significant (typical RR 0.82, 95% CI 0.44, 1.58), emphasizing the fact that the most significant effect on mortality was seen with a 200-mg/kg dose of poractant (typical RR 0.29, 95% CI 0.10, 0.79). Two of these five studies[143,146] also reported more rapid improvement in oxygenation with poractant compared to beractant. The difference in outcomes described above between poractant and beractant may well be related to the dose of phospholipids and not to other characteristics of the products. There are no studies to determine whether poractant, especially in a 100-mg/kg dose, is superior to beractant when surfactant is dosed for prophylaxis.

Adverse Effects of Surfactant Therapy

Transient hypoxia and bradycardia can occur as a result of acute airway obstruction immediately after surfactant instillation.[102,147] Other acute adverse effects of surfactant administration include reflux of surfactant into the pharynx from the endotracheal tube, increase in transcutaneous carbon dioxide tension, tachycardia, gagging, and mucous plugging of the endotracheal tube. These complications of surfactant administration generally respond to a slower rate of surfactant administration or to an increase in the airway pressure or F_{IO_2} during administration. Rapid improvement in oxygenation after surfactant administration necessitates close monitoring and appropriate reduction of ventilatory parameters.

Several authors have reported a transient decrease in blood pressure,[148-150] a transient decrease in cerebral blood flow velocity,[151-153] a transient decrease in cerebral oxyhemoglobin concentration,[153] and a transient decrease in cerebral activity on amplitude-integrated electroencephalography[148] immediately after surfactant administration. The electroencephalogram (EEG) depression observed after surfactant instillation is not caused by cerebral ischemia,[154] and the EEG suppression is not directly related to alterations in blood gases or systemic circulation.[155] The clinical significance of these findings is uncertain. One study[156] reported an increase in the incidence of intraventricular hemorrhage, and a case report documents a temporal association between the development of intraventricular hemorrhage and the administration of Surfactant TA to improve respiratory failure caused by pulmonary hemorrhage.[157] However, the meta-analyses of multiple trials do not show an increase in the risk of intraventricular hemorrhage with surfactant therapy compared to placebo.[59-61]

There is a well described increase in the risk of pulmonary hemorrhage with surfactant therapy.[158,159] Although trials in which animal-derived surfactants were used reported a higher incidence (5%-6%) of pulmonary hemorrhage than trials of synthetic surfactant (1%-3%), direct comparison of the two types of surfactants demonstrates no difference in the risk of pulmonary hemorrhage. The overall incidence of pulmonary hemorrhage was low, and the absolute magnitude of the increased risk is small.[158] However, moderate and severe pulmonary hemorrhage is associated with an increased risk of death and short-term morbidity. It is not associated with increased long-term morbidity.[160] The occurrence of pulmonary hemorrhage may be related to the presence of a hemodynamically significant patent ductus arteriosus.[161] Seppanen et al.[162] studied the association of neonatal complications with the Doppler-derived aortopulmonary pressure gradient (APPG) across the ductus arteriosus, which reflects pulmonary artery pressure during the first day of life. Infants in whom the APPG decreased after birth had a lower frequency of patent ductus arteriosus and pulmonary hemorrhage than those whose APPG remained low. Another mechanism for the pulmonary hemorrhage may be a direct cytotoxicity, which has been demonstrated in in vitro studies and appears to be different for different surfactants and different dosages.[163]

When surfactant initially became available for clinical testing, there was concern that the introduction of foreign proteins from animal-based lung surfactants into the lungs of preterm infants could lead to immunologic responses. Two studies did not find antibodies specific to surfactant protein in the sera of preterm infants treated with bovine surfactant.[164,165] In other studies, immune complexes or antibodies to the protein in exogenous porcine, bovine, or human surfactant have been identified in the sera of neonates with RDS. However, similar immune complexes or antibodies were also noted in control infants who did not receive surfactant, and no significant differences were noted between surfactant-treated and control infants.[166-168] The presence of antibodies in control infants may be the result of leakage of endogenous surfactant proteins into the circulation.[166]

With animal-derived surfactants, there is a theoretical risk of the transmission of infectious agents, including bovine spongiform encephalitis with surfactants derived from bovine sources and other viral infections in swine. Organic solvent processing of phospholipids, terminal sterilization techniques, and screening of animal sources have been used to minimize this risk.

Economic Aspects of Surfactant Therapy

With the introduction of surfactant therapy, there was concern that the increased number of survivors and a possible increase in the length of hospital stay would lead to an increase in the overall cost of neonatal care.[169] These increased costs can be offset to a variable extent by the fact that surfactant therapy can lead to lower hospital charges,[170] reduce the costs or charges per survivor of neonatal intensive care,[3,171-173] as well as reduce the charges for infants who ultimately die.[3] In an economic analysis for a hypothetic cohort of infants weighing 700 to 1350 g and treated with synthetic surfactant, based on the results of a randomized controlled trial,[174] the total hospital charges through 1 year adjusted age were similar to those for a comparable cohort of infants receiving air placebo, despite the fact that more babies in the synthetic surfactant cohort survived and thus required prolonged hospital care during their first year of life. The incremental cost per survivor estimated in this study was $1585 (1995 dollars).

In 1990, the cost per quality-adjusted life year (QALY) with surfactant therapy was estimated in one study to be $1500[175] and in another study to be 710 pounds.[176] From a societal perspective, the cost-effectiveness of surfactant therapy is more favorable than that of health-care interventions such as renal transplantation, coronary bypass surgery, and dialysis.[176] In a geographically defined, population-based study from Australia, cost-effectiveness and cost-utility ratios in pre-surfactant and post-surfactant periods were compared for 500-to-999-g birth weight infants. When costs incurred during the primary hospitalization were considered, both of these ratios were lower (i.e., economically better) in the post-surfactant era than in the pre-surfactant era (pre-surfactant versus post-surfactant, $7040 versus $4040 per life year gained; $6700 versus $5360 per QALY). Both ratios fell with increasing birth weight. With costs for long-term care of severely disabled children added, both cost ratios were higher in the post-surfactant era.

Factors Affecting the Response to Surfactant Therapy

Several factors have been reported by various authors to be associated with a poor response to surfactant therapy, either in terms of immediate pulmonary response or in terms of later morbidity and mortality. These factors include high total fluid and colloid intake in the first days of life,[177] a low mean airway pressure relative to the FIO_2,[177] the presence of an additional pulmonary disorder such as infection,[178] perinatal asphyxia, infection, other complications of prematurity[89] high fraction of inspired oxygen requirement at entry (had a negative impact on a-APO_2 6 hours and 24 hours after treatment), lower birth weight, male sex, outborn status, perinatal asphyxia, and high airway pressure requirement at entry.[179] Low birth weight, low Apgar scores, and initial disease severity were associated with an increased mortality.[180]

A high pulmonary resistance prior to therapy was associated with a poor response to therapy at 24 and 48 hours.[181] In addition, the immediate response to surfactant therapy itself has been reported to be a significant prognostic indicator for mortality and morbidity.[182] In animal studies poor response to surfactant has been associated with delayed administration[69] and the leakage of proteinaceous fluid into the alveolar spaces. Within some multicenter trials, significant differences in outcomes of surfactant-treated infants have been noted between participating hospitals,[179,180] suggesting that variations in patient care practices have an important influence on the outcomes of surfactant-treated infants.

As noted earlier, observational studies have demonstrated a decrease in mortality and morbidity for such infants after the introduction of surfactant therapy. However, racial differences in this decline in mortality have been reported. In one study, the overall neonatal mortality for black very-low-birth-weight (VLBW) infants did not change after the introduction of surfactant therapy,[65] and in another study, declines in neonatal mortality risks caused by RDS and all respiratory causes were greater for non-Hispanic white VLBW infants than for black VLBW infants.[183] Although such racial differences have been noted at a population level, the role of racial factors in the response pattern of individual infants with RDS to exogenous surfactant therapy is unknown.

Long-Term Outcomes After Surfactant Therapy

Long-term outcomes after surfactant therapy have been well studied for synthetic surfactant. Follow-up studies of long-term outcomes after animal-derived surfactant therapy have consisted of small numbers of patients, with a variable proportion of survivors being tested. For both synthetic and animal-derived surfactant, the *long-term* outcomes reported consist of outcomes predominantly in the first 3 years of life, with very few reports of outcomes at school age or higher. Given these limitations, the evidence suggests that not only do more infants survive from surfactant therapy, but they also are at no selective disadvantage for neurodevelopmental sequelae due to the surfactant therapy. Most comparisons of long-term outcomes have been between infants treated with surfactant and placebo. There are few or no comparisons of long-term outcomes between infants treated with different types of surfactant or different regimens of the same surfactant. The following sections mainly address comparisons between infants treated with surfactant and placebo.

Neurodevelopmental Outcomes

No significant differences have been reported in the long-term neurodevelopmental outcomes of infants treated with surfactant compared to those treated with placebo, either with synthetic surfactant[99,184,185] or animal-derived surfactant.[6,68,71,186-190]

Long-Term Respiratory Outcomes

Compared to infants treated with placebo, infants treated with surfactant in the neonatal period have been reported either to have improved[191-193] or to have equivalent[194-196] results on pulmonary function testing. Some studies have

reported a lower frequency of subsequent clinical respiratory disorders in surfactant-treated infants compared to placebo,[188,197] whereas others have reported no difference[168,184,186,191] or a trend towards an increase in allergic manifestations.[190]

Physical Growth

No significant differences have been reported in weight or height outcomes between surfactant-treated and placebo-treated infants on follow-up.*

Outcomes of Prophylactic Versus Rescue Treatment Strategies

Two studies compared the long-term outcomes of infants treated with prophylactic surfactant to those treated with a "rescue" strategy. In one, there were no differences at school age in neurodevelopmental outcome or in the results of pulmonary function testing between the two groups, although infants who had received prophylactic surfactant showed fewer clinical pulmonary problems than those that received rescue treatment.[199] In another study in which there was significant loss of infants to follow-up (and therefore a high likelihood of attrition bias), the mean scores on the Bayley scales of infant development at 12 months adjusted age were higher in the rescue group than in the prophylactic group.[200]

Exogenous Surfactant Therapy for Conditions Other Than RDS

Meconium Aspiration Syndrome

In vitro studies[201,202] and animal studies[203,204] have demonstrated that meconium inhibits surfactant function and is likely to be partially responsible for alveolar collapse in meconium aspiration syndrome (MAS). Components of meconium that may contribute to altered surfactant function include cholesterol, free fatty acids, bile salts, bilirubin, and proteolytic enzymes.[201-203,205]

In noncontrolled studies of human infants with MAS, improved oxygenation has been reported with exogenous surfactant therapy.[206-208] A randomized trial in infants greater than 34 weeks' gestation with severe respiratory failure on extracorporeal membrane oxygenation (ECMO) (including infants with MAS) showed that infants treated with beractant had improved lung function, a shorter duration of ECMO, and fewer complications after ECMO.[209]

Four randomized trials[210-213] have studied the effect of animal-derived surfactant in term infants with MAS and are included in a systematic review. In these trials, surfactant therapy was administered as a continuous infusion over 20 minutes[211] or as a bolus. The meta-analysis of these four trials[214] showed a decreased need for ECMO with surfactant therapy (typical RR 0.64, 95% CI 0.46, 0.91; typical ARD −0.17; 95% CI −0.30, −0.04). One trial reported a reduction in the length of hospital stay (mean difference = 8 days [95% CI, −14 days, −3 days]). There were no statistically significant effects on mortality (typical relative risk 0.98; [95% CI 0.41, 2.39]; typical risk difference 0.00; [95% CI −0.05, 0.05]) or other outcomes (duration of assisted ventilation, duration of supplemental oxygen, pneumothorax, pulmonary interstitial emphysema, air leaks, chronic lung disease, need for oxygen at discharge, or intraventricular hemorrhage).

In summary, infants with severe meconium aspiration syndrome are likely to benefit from treatment with animal-derived surfactants. Multiple doses are usually required in such infants. Only animal-derived surfactants have been tested in human clinical trials in this setting, and the efficacy of synthetic surfactants is unknown. Each dose should be administered cautiously, with close cardiac, respiratory, and oxygen saturation monitoring, because surfactant can aggravate preexisting airway obstruction from meconium, and transient oxygen desaturation and endotracheal tube obstruction have been reported with bolus administration in nearly one third of infants.[210]

Investigators have also attempted to treat MAS by lavaging the airways with diluted surfactant solutions to wash out residual meconium.[215-219] This approach to surfactant treatment remains experimental.

Acute Respiratory Distress Syndrome

Surfactant dysfunction is well described in acute lung injury.[220] Therefore, surfactant replacement has been proposed as a treatment for patients with acute lung injury and the acute respiratory distress syndrome (ARDS), which, although more common in adults and older children, can occur in term neonates.[221,222] Exogenous surfactant therapy has been attempted in ARDS in adults, but the results of clinical trials have not been promising.[223,224] There are no randomized trials of exogenous surfactant therapy specifically for ARDS in neonates, but in older children with acute respiratory failure, surfactant use decreased mortality and duration of ventilation.[225,226] Because of this, and based on the pathophysiologic, clinical, and radiologic similarities between RDS and ARDS, it is reasonable to provide exogenous surfactant therapy to term infants with clinical and radiologic features of ARDS (severe respiratory failure with pulmonary opacification and air bronchograms on chest radiographs).

Other Conditions

There are reports (anecdotal or case series) of the use of exogenous surfactant therapy in human infants for the management of pulmonary hemorrhage[227,228] and neonatal pneumonia.[206,229-231] However, the efficacy of surfactant in these conditions is uncertain, and its routine use in these conditions cannot be recommended. Surfactant therapy for infants with congenital diaphragmatic hernia has also been attempted[232-236] but actually resulted in worse outcomes, and therefore is not recommended.

Conclusions

Exogenous surfactant therapy has been a significant advance in the management of preterm infants with respiratory distress syndrome and has become established as a standard part of the management of such infants. Both animal-derived and synthetic surfactants lead to clinical improvement and decreased mortality, with animal-derived

*References 168, 185, 190-192, 197, and 198.

surfactants having advantages over synthetic surfactants. The use of prophylactic surfactant, administered after initial stabilization at birth, to infants at risk for respiratory distress syndrome has benefits over rescue surfactant given to treat infants with established RDS. In infants who do not receive prophylaxis, earlier treatment (before 2 hours) has benefits over later treatment. The use of multiple doses of surfactant as needed is a superior strategy to the use of a single dose, and the use of a higher threshold for retreatment appears to be as effective as a low threshold. Adverse effects of surfactant therapy are infrequent and usually not serious; long-term follow-up of infants treated with surfactant in the neonatal period is reassuring. New protein-containing synthetic surfactants are becoming available and show promise. Further research is required on the optimal use of surfactant in conjunction with other respiratory interventions.

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23 Complications

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The complications of assisted ventilation are major causes of neonatal mortality and morbidity (Box 23-1). This chapter addresses three entities: bronchopulmonary dysplasia (BPD), extraneous air syndromes (air leaks), and retinopathy of prematurity (ROP). The first two are direct lung injuries whereas the last is a destructive response of the immature retina to several noxious stimuli, of which oxygen is but one.[1]

Bronchopulmonary Dysplasia

History and Incidence

In 1967 Northway et al.[2] reported the clinical, pathologic, and radiologic features of BPD. The term *bronchopulmonary dysplasia* was chosen "to emphasize the involvement of all the tissues of the lung." Four stages of disease in graduated severity were described in terms of their times of occurrence, tissue changes, radiologic abnormalities, and clinical features (Table 23-1). Although the disease has changed remarkably in its clinical and radiologic progression, the four stages described in 1967 remain as valuable historic points of reference for the understanding of BPD in its altered contemporary form.

In the early 1960s prior to the use of mechanical ventilation for treatment of respiratory distress syndrome (RDS), affected infants often died within 5 to 7 days of birth. Among survivors, abnormal clinical signs and radiographic findings usually improved by day 5 to 7 postnatally; recovery was apparent by 7 to 10 days. Sequelae suggestive of chronic lung disease were not recognized until premature infants survived periods of mechanical ventilator support. Although mortality from RDS declined after introduction of ventilator therapy, the price paid was the emergence of BPD as a major cause of severe morbidity and significant mortality. Fundamentally, BPD occurred in immature lungs exposed to high ventilator pressure and continuously high oxygen concentrations while an endotracheal tube was in place.[3,4] Mature lungs were infrequently affected and BPD was rarely identified in babies who had not received ventilator support.

Wilson and Mikity in 1960[5] described their experience between 1956 and 1958, with five premature infants whose onset of abnormal respiratory signs was first identified at 1 to 5 weeks of age. None of the infants had mechanical respiratory support. Three of them died. Grossly abnormal x-rays were characterized by diffusely distributed nodular or reticular densities, with interspersed cyst-like translucencies representing focal hyperexpansion. In 1964, a report by Shepard et al.[6] described the radiologic appearance of "pulmonary fibrosis" in approximately half the 48 survivors of RDS, some of whom had received mechanical ventilator support. An example of progression from hyaline membrane disease to blatant emphysematous changes on x-ray was described, in which the disease had proceeded to overexpansion of both lungs by 12 and 18 months of age. The Wilson-Mikity report[5] may well have been the "new BPD" of most recent description,[7] which is characterized by mild or absent respiratory difficulty at birth or soon thereafter, and by progression to severe disease over subsequent weeks. The description by Shepard et al.[6] suggests radiologic progression to chronic lung disease similar to that reported in detail by Northway et al.[2] 4 years later.

The original definition by Northway et al.[2] included clinical signs, duration of oxygen therapy, radiologic appearance, and pathology. The most severe form of disease was stage 4 in which there was a need for oxygen and mechanical respiratory support beyond 28 postnatal days. Bancalari et al.[8] later modified this approach by including (1) ventilator support for at least the first 3 days; (2) respiratory signs at 28 postnatal days; (3) oxygen supplementation to maintain PaO_2 over 50 torr during the first 28 postnatal days; and (4) compatible x-rays. Later, administration of oxygen supplement at 28 or 30 postnatal days became in itself the mainstay for the diagnosis of BPD, the resultant level of PaO_2 notwithstanding.[9] In 1988, Shennan et al.[10] found that a need for oxygen in very-low-birth-weight (VLBW) infants at 28 postnatal days identified only 37% of infants who would have abnormal lung function at 2 years of age, but when prediction was made at 36 weeks' postmenstrual age (PMA), the positive predictive value for poor respiratory outcome was 63%. Furthermore, normal outcome occurred in 90% of infants who did not need oxygen at 36 weeks' PMA. Currently, supplemental oxygen at 36 weeks' PMA is the most frequently cited single basis for the diagnosis of BPD.[11-13]

The incidence of BPD was noted to be increasing as early as 1983, possibly as a result of increased survival rates of VLBW babies.[14] In 2007, the Neonatal Research Network (part of the National Institute of Child Health and Human Development [NICHD]) reported an incidence of BPD that was essentially unchanged (22.0%) from a previous report.[15] Incidence in each 250-g birth-weight group was

TABLE 23-1 Bronchopulmonary Dysplasia (Classic)

Stage	Time	Pathologic Findings	Radiologic Findings	Clinical Features
I (mild)	2-3 days	Patchy loss of cilia; bronchial epithelium intact; profuse hyaline membranes	Air bronchograms; diffuse reticulogranularity (identical to RDS)	Identical to RDS
II (moderate)	4-10 days	Loss of cilia; fewer hyaline membranes; necrosis of alveolar epithelium; regeneration of bronchial epithelium; ulceration in bronchioles	Opacification; coarse, irregularly shaped densities containing small vacuolar radiolucencies	Increased O_2 requirements and increasing ventilatory support when recovery is expected; rales, retractions
III (severe)	10-20 days	Advanced alveolar epithelial regeneration; extensive alveolar collapse; bronchiolar metaplasia and interstitial fibrosis; bronchial muscle hypertrophy	Small radiolucent cysts in generalized pattern	Prolonged O_2 dependency; $PaCO_2$ retention; retractions; early barrel chest; severe acute episodes of bronchospasm
IV (advanced-chronic)	1 mo	Obliterative bronchiolitis; active epithelial proliferation; peribronchial and some interstitial fibrosis; severe bronchiolar metaplasia	Dense fibrotic strands; generalized cystic areas; large or small heart; hyperinflated lungs; hyperlucency at bases	Increased chest anteroposterior diameter; cor pulmonale; frequent respiratory infection; prolonged O_2 dependency; failure to thrive

RDS, Respiratory distress syndrome.

also unchanged. Improved survival of VLBW babies was thought to explain at least partially, the unchanging rate of BPD.

In another study, which involved 5115 infants in six California centers,[16] the incidence of BPD was also unchanged overall, but severe disease (oxygen plus ventilator or CPAP at 36 weeks' PMA) diminished significantly from 9.7% in 1994 to 3.7% in 2002, representing an annual rate of decline at 11% during the 9 years of that study. Apparently, the incidence of BPD changed little since the inception of surfactant therapy, but there was a distinct lessening of severity among survivors.[17]

Estimates of the incidence of BPD have varied considerably since the relatively clear diagnostic delineations by Northway et al.[2] This was the "old BPD" (better called *classic BPD*), and it focused on changes that were characterized by injury to all types of lung tissue "involving mucosal, alveolar and vascular tissues," followed by a disorderly repair process that chronically disrupted respiratory function. However, a clinical course of persistent respiratory dysfunction, distinctly different from Northway's description, now pervades. It has been named the "new BPD."[18]

Calculating the incidence of BPD obviously requires a definition of the disease, but so far a universally applicable definition has been elusive. For the most part, definitions have relied heavily on duration of oxygen supplementation and the need for mechanical ventilatory support (or nasal CPAP) as indicators of the diagnosis and severity of the disease.

Use of oxygen supplementation as a major indicator of the disease has been a source of confusion largely because the practice has varied so widely from one center to another.[19-22] Oxygen therapy is affected substantially by administration of postnatal steroids and diuretics, and by various modalities and methods of respiratory support. Duration of oxygen administration is also significantly influenced by gestational age. Continuous supplementation over the first 28 days is not frequent now, even for the youngest and smallest infants.[19] The impact of incongruous policies of oxygen administration on estimates of BPD incidence was demonstrated in the study by Walsh et al.,[22] which sought a physiologic definition of oxygen use at 36 weeks' PMA. A room air challenge was presented to infants in 30% oxygen, and also to infants in greater than 30% oxygen if saturations exceeded 96%. If saturations remained at 90% or more for at least 30 minutes in room air, the infants were classified as "no BPD." If saturations fell below 90% in room air, they were classified as "BPD." The room air challenge is thus the patient's need rather

Box 23-1 COMPLICATIONS OF ASSISTED VENTILATION

Upper Airway
- Nasal septum necrosis (nCPAP)
- Palatal groove, abnormal dental development
- Nasofacial cellulitis (nasotracheal tube)
- Subglottic edema
- Subglottic tracheal stenosis
- Necrotizing tracheobronchitis

Lower Airway
- Bronchopulmonary dysplasia
- Extraneous air syndromes (air leaks)
- Pulmonary hemorrhage
- Atelectasis
- Pneumonia

Extrapulmonary
- Retinopathy of prematurity
- Sepsis
- Periventricular/intraventricular hemorrhage

than the physician's policy. The room air challenge diminished the incidence of unnecessary supplemental oxygen; and therefore it eliminated a substantial number of spurious diagnoses. The mean incidence of BPD among the 17 participating centers declined by 10% (center range: 0% to 44%). The authors noted that the magnitude of this reduction has varied little with the outcomes of some clinical trials. Ellsbury et al.[20] also described the impact of differences in oxygen administration on the incidence of BPD. Their study of data from the Vermont Oxford Network indicated considerable variation among centers in regard to the threshold saturations at which supplemental oxygen was initiated. They varied from less than 84% to less than 96% among surveyed institutions, while only 41% of all responders used the same saturation criterion (less than 90%) for starting oxygen supplementation.[20]

Davis and colleagues[21] evaluated the accuracy of different BPD definitions based upon the age at which O_2 was discontinued (32, 34, 36, 38, and 40 weeks' PMA). The accuracy of these definitions was limited overall, but it was highest at 36 weeks' PMA, at which time poor pulmonary outcome was predicted at 63%.

Reliable determinations of the incidence of BPD are pivotal for the evaluation of management, assessment of pharmacologic therapy, immediate and long-term effectiveness of respiratory support, and for predictions of disabling pulmonary and neurodevelopmental outcomes. The incidence of BPD is most consistently related to gestational age and/or birth weight. BPD is a disease of incompletely developed lungs that have been injured in utero or after birth. Incidence will therefore differ sharply among infants of the smallest birth weights compared to those who are larger. Today BPD is infrequent in babies whose birth weights are above 1200 g. The association of disease and immaturity is further illustrated by the births in 1995 and 1996 at a large NICU. The incidence of BPD in mechanically ventilated babies was 33% at birth weights below 1000 g and, in contrast, close to 2% at birth weights between 1000 and 1500 g.[23]

The most recent attempt to define BPD and its severity came from a National Institutes of Health (NIH)-sponsored workshop that was also concerned with proposals for future research.[12] The three fundamental points of differentiation in this proposed definition[19] were the intensity of O_2 therapy (FIO_2) with or without ventilatory support,[2] gestational age, and the age of measurement.[3] Severity of disease varied according to FIO_2 or positive pressure as measured at specified times. For gestational ages greater than 32 weeks, the time of measurement was 36 weeks' PMA. For gestational ages of 32 weeks or more, times of measurement were different, varying between more than 28 days' and less than 56 days' postnatal age (Box 23-2). The validity of this proposal remains to be documented, but its predictive accuracy was analyzed by Ehrenkranz et al.[24] using the NICHD Neonatal Research Network database. They concluded that the NIH workshop "consensus definition" identifies a range of risks for abnormal pulmonary and developmental outcomes in early infancy that will be clinically valuable in the management of neonates in the neonatal intensive care unit (NICU). The new definition will also accommodate useful comparisons of clinical practices.

Box 23-2 BRONCHOPULMONARY DYSPLASIA: DIAGNOSTIC CRITERIA

	Gestational Age	
	Less than 32 wk	**32 wk or more**
Time of Assessment	36 wk PMA or discharge to home, whichever comes first	Greater than 28 days' but less than 56 days' postnatal age or discharge to home, whichever comes first
Mild BPD	Oxygen greater than 21% for at least 28 days plus: Breathing room air at 36 wk PMA or discharge, whichever comes first	Breathing room air by 56 days' postnatal age or discharge, whichever comes first
Moderate BPD	Need for less than 30% oxygen at 36 wk PMA or discharge, whichever comes first	Need for less than 30% oxygen at 56 days' postnatal age or discharge, whichever comes first
Severe BPD	Need for ≥ 30% or higher oxygen and/or positive pressure (PPV or nCPAP) at 36 wk PMA or discharge, whichever comes first	Need for 30% or higher oxygen and/or positive pressure (PPV or nCPAP) at 56 days' postnatal age or discharge, whichever comes first

BPD, Bronchopulmonary dysplasia; *nCPAP,* nasal continuous positive airway pressure; *PMA,* postmenstrual age; *PPV,* positive-pressure ventilation.

The workshop report also alluded to a physiologic test for confirming the need for oxygen supplementation at the designated time of assessment. Documentation of a given supplement of FIO_2 is essential, but confirmation of the patient's need for it is more pertinent. These data and this procedure reported by Walsh et al.,[22] and discussed previously in this chapter, require further documentation. The procedure is potentially useful for standardizing oxygen therapy by realistic determination of its physiologic need.

Etiologic Considerations

A "new BPD" has been described, and with it, an expanded perspective on its etiology has evolved. The new version is notably milder in its clinical presentation than the advanced stages of the traditional disease first reported by Northway et al.[2] BPD is less likely to develop in larger preterm infants (weighing more than 1200 g)[25]; rather, it occurs preponderantly in smaller premature infants whose birth weights are 1000 g or less. BPD is still one of the most troublesome chronic diseases of prematurity, contemporary changes notwithstanding. Advances in management have probably contributed significantly to improved outcome and diminished severity of the clinical course. Surfactant, less vigorous respiratory support, and antenatal steroids seem to be largely responsible for the diminished incidence in larger prematures and for less severe lung injury in the smaller ones.

BPD begins in utero. Chorioamnionitis releases proinflammatory cytokines that result in pulmonary inflammation. Birth before 28 to 30 weeks limits lung development that has progressed only to the saccular stage with the beginnings of alveolarization. Development is impeded in utero and postnatally in response to a series of events that includes resuscitation with high pressures and FIO_2, hypoxia, acidosis, overhydration, patency of the ductus arteriosus, vertically transmitted or nosocomial infection, and suboptimal nutrition. Inflammation inhibits angiogenesis, which is intrinsic to the formation of alveoli. The result of these intrauterine and postnatal events is the *new BPD*—lungs with fewer alveoli and reduced gas exchange surface because of impaired alveologenesis.

BPD appears to involve an arrest of lung maturation with or without the superimposition of injury by hyperoxia, barotrauma (volutrauma), and other injurious factors. The halt in alveolarization that is now seen to characterize BPD[26] is associated with other maturational impediments such as abnormal capillary bed development, diminished antioxidants, and lack of surfactant. Whereas the primary trigger of progressive chronic inflammation was considered to be the barotrauma imposed by mechanical ventilation, as well as the damage of high oxygen concentrations, it now seems likely that in many instances, chronic change is initiated in utero by cytokines released from inflammatory processes of chorioamnionitis.[26,27] The role of intrauterine cytokines and its possible impact on the fetal lung and brain has received considerable attention in recent years.[28]

Mechanical ventilation, which entails delivery of high oxygen concentrations under high pressure to vulnerable lungs, is a pivotal postnatal etiologic factor. Van Marter et al.[29] clearly demonstrated in a comparison of three NICUs that an increased risk for BPD in two of them was "explained simply" by their more frequent use of mechanical ventilation. The appearance of BPD in some of the smallest infants who never received mechanical ventilator support is noteworthy, but these were events that occurred in a distinct minority of affected infants compared to the numbers of babies with BPD who required mechanical ventilator support at birth.[30] The vulnerability to BPD in premature lungs is in contrast to the reduced likelihood of BPD in term and near-term infants who need high inspiratory pressures and oxygen concentrations for the management of persistent pulmonary hypertension.[31] Some infants born weighing less than 1000 to 1250 g have been shown to have BPD in the absence of ventilator support.[30,32] Reports of these apparently spontaneous clinical onsets of BPD have been published for decades.[5,30,33-37] In most instances, these infants are asymptomatic until 6 to 9 days of age, when supplemental oxygen is first required or reinstituted.[30] The diminished use of damaging vigorous mechanical support has removed the mask of classic BPD to reveal a milder disease that is often initiated in utero. Maternal steroids and surfactant apparently have reduced the need for high pressures and oxygen concentrations, and now the significance of intrauterine events has become more apparent. The role of intrauterine factors, such as amniotic infection, cytokines, and the "fetal inflammatory response syndrome," are in better perspective. There is significant evidence supporting associations between intrauterine inflammatory responses, release of cytokines, impairment of lung development with subsequent progression to BPD, and the occurrence of periventricular leukomalacia and cerebral palsy.[28]

In essence new clinical manifestations of BPD have appeared, and they indicate a more diffuse etiology than had existed previously. These changes are probably the result of improved management. Intrauterine factors sensitize the lungs to injury postnatally, and as long as severe respiratory inadequacy occurs, there is little alternative to the intense respiratory support that injures immature lungs.

Oxygen Toxicity

In their original description, Northway et al.[2] considered the inspiration of high concentrations of O_2 the most likely cause of BPD. In their experience, affected infants had been given O_2 in concentrations of 80% or higher for at least 6 days. They stated that BPD was probably "the result of oxygen-induced lesions in the respiratory mucosa, with subsequent defective drainage, combined with lesions in the alveoli and capillaries induced by oxygen and respiratory distress." They speculated that intermittent positive-pressure ventilation (IPPV) and endotracheal intubation also may have played a role. Now more than 40 years after their original description, speculation lingers. The individual impacts of O_2, IPPV, and endotracheal intubation have yet to be delineated precisely. Contemporary consensus holds that all of these factors are significant.[38]

In the years since BPD was first described by Northway et al.,[2] successive investigators reported toxicity at lower O_2 concentrations and with shorter durations of therapy. As early as 1969, Pusey et al.[39] questioned the contention of Northway et al.[2] that 6 days of therapy at O_2 concentrations of 80% or higher were the essential antecedents of BPD. They cited three affected infants who did not receive "high oxygen concentrations" and two others who did, but for less than 24 hours. There followed a number of published studies that proposed direct links between various oxygen concentrations (FIO_2), duration of oxygen therapy, and the consequence of BPD.[40-43] A pervading concept evolved that the risk for BPD is high when oxygen supplementation is protracted, regardless of FIO_2. Edwards et al.[42] described BPD in babies whose FIO_2, though only 0.22 to 0.30, was administered for as long as 53 days.

There is no definite FIO_2 at which one can predict the appearance of BPD. Immaturity of the lungs is the common denominator. Increased vulnerability of lung tissue in smaller premature infants is well known: the more premature the lungs, the more likely it is that BPD will occur. In rabbits and other animals, antioxidant enzyme activity seems to develop within a timeframe that coincides with the maturation of surfactant synthesis.[44,45] The level of antioxidant enzymes (as well as that of surfactant) in newborn rats is significantly increased when maternal dexamethasone is given 24 and 48 hours before delivery.[46] The capacity to resist damage from oxygen radicals is in the development of antioxidant systems. Thus preterm rabbits are considerably more susceptible to airway hyperoxia than term pups. Antioxidant enzyme responses are almost nonexistent in prematures compared to term pups.[47]

Oxidant and protease activities are destructive, and they may operate synergistically. White[48] reviewed the subject of

pulmonary O_2 toxicity. The levels of O_2 metabolites (superoxide, hydrogen peroxide, hydroxyl radicals, and others) are augmented during periods of hyperoxia; their production in the lung is destructive. Hyperoxia generally incites a profuse inflammatory response; but it may injure epithelial cells even in the absence of inflammation. Infants with RDS who are destined to progress to BPD have been identified in the first postnatal week by demonstration of increased concentrations of oxyradical markers. Infants with RDS who did not develop BPD show no such increase.[49,50] Defense mechanisms against toxic O_2 metabolites (radicals) are critical to the prevention or attenuation of oxidant lung damage. Superoxide dismutase is probably the primary substance of this defense; glutathione peroxidase and catalase are also significant.

Superoxide dismutase promotes elimination of the superoxide radical; an effective pulmonary response to hyperoxia requires its enhancement. In human premature infants given supplemental O_2, however, superoxide dismutase does not increase in either the lungs or the blood.[51] This lack of response is compatible with the immature lung's susceptibility to oxidant injury.

Clinical studies of the effects of superoxide dismutase are not conclusive. Davis et al.[52] reported their multicenter trial of intratracheally administered CuZn superoxide dismutase, which was given for 1 month to extremely premature infants receiving ventilator support. There was neither a difference in mortality nor in the need for oxygen at 36 weeks' PMA, but in the treated group at 1 year of age, there was less hospitalization, fewer emergency room visits, and less frequent medication for asthma. In another study pertinent to the role of hyperoxia in BPD, an attempt was made to determine whether higher oxygen saturations might diminish the severity of prethreshold ROP (STOP-ROP Study). Increased incidence of BPD and lung infection were unanticipated outcomes among infants who received the higher oxygen concentrations.[53]

Other attempts to minimize oxidant damage to the lung have been reported in studies that evaluated the antioxidant activity of vitamin E. Vitamin E is a major antioxidant known to diminish peroxidation of polyunsaturated lipids by virtue of its scavenger activity. Vitamin E deficiency is pervasive among premature infants; supplementation would be logical. However, a summary of the several trials that evaluated vitamin E supplementation has indicated its ineffectiveness in diminishing the incidence of BPD.[54]

Hyperoxia inhibits lung growth and maturation, resulting in the development of smaller lungs with fewer alveoli and an inhibition of vascular development. It also causes interstitial edema by increasing capillary permeability. Hyperoxia incites profuse inflammation, setting the stage for subsequent fibrosis. Some investigators have been convinced that O_2 toxicity is the principal cause of BPD,[40,42,43,55,56] but the evidence is largely derived from animal experiments. In human infants, there is considerable evidence that oxygen radicals cause significant injury early in the course of BPD. Saugstad[50,55] and Frank and Sosenko[57] have published excellent reviews of the topic. Davis et al.[58] demonstrated in piglets that a minimal acute injury followed positive-pressure ventilation in room air; but when an F_{IO_2} of 1.0 was added, the severity of lesions increased significantly. Providing for enhanced antioxidant capacity could reduce vulnerability to lung damage. Suggested investigations include antenatal stimulation of antioxidant enzyme production, genetic manipulation to enhance production of enzymes, and perhaps a pharmacologic substitute for the enzymes.[57]

Barotrauma-Volutrauma

The association of high ventilator pressures, alveolar rupture (extraneous air syndromes), and subsequent BPD have long been recognized.[59] Moylan et al.[60] reported a close association between alveolar rupture and BPD. In the early 1980s Rhodes et al.[61] and Boynton et al.[62] were convinced of the advisability of using low peak inspiratory pressures and short inspiratory times to minimize barotrauma. Kraybill et al.[63] found in their multicenter retrospective study that lower arterial carbon dioxide (Pa_{CO_2}) levels were associated with a higher incidence of BPD, suggesting a role for higher ventilator pressures in the development of BPD. However, results from three other studies[64-66] are not in total agreement with these conclusions. If low Pa_{CO_2} does indeed indicate the use of high peak pressures, and presumably greater volumes, then the conclusion of Kraybill et al. is compatible with experimental and clinical evidence.[29,37,67-70] Wung et al.[37] reported a decrease in the incidence of BPD over a 12-month period, which they attributed to early continuous positive airway pressure (CPAP) and low inspiratory pressures. Taghizadeh and Reynolds[68] emphasized the importance of peak inspiratory pressure. In their series of autopsied infants, they calculated a statistically significant correlation between pressures of over 35 cm H_2O and the presence of "the most serious lesions" of BPD. In animals, exaggerated permeability of epithelial and endothelial tissues quickly follows overdistension of lungs for even short periods of time (volutrauma).[29,37,68-70] Because ventilator management of surfactant-deficient infants entails overdistension of small airways, a similar phenomenon may be involved in the early appearance of lung edema among mechanically ventilated infants.[71]

The most immediate and frequent cause of BPD is the lung injury imposed by mechanical ventilatory support.[72] Lower incidence of BPD has been associated with less frequent use of mechanical ventilation.[29,37,70,73] Inspiratory pressure (and F_{IO_2}) enhances both the likelihood and the severity of BPD.[29,68,69,73] High inspiratory pressure has long been identified as a major cause of BPD and extraneous air syndromes (air leak), but tissue damage is now more realistically attributed to excessive tidal volume (volutrauma) rather than pressure itself.[74,75] In clinical settings, however, high pressure usually delivers high volume, which in turn stretches (strains) alveolar walls and capillaries[76,77] Damage is in the stretch (strain). Strain produced by volume at any given pressure is modified by compliance of the strained structure and by transpulmonary pressure.

Dreyfuss et al.[78] demonstrated in an experiment on rat lungs that high volume rather than high pressure was the source of tissue damage characterized by pulmonary edema and microvascular permeability. They compared effects of low tidal volume delivered with high pressure to high tidal volume delivered with high or with low pressure. They also evaluated the effect of positive end-expiratory pressure

(PEEP) on resultant tissue injury. The low volume was delivered with high pressure to animals strapped with thoracoabdominal rubber bands. High volume was delivered with low pressure by use of negative pressure ventilators. The most severe injury was seen with high tidal volume, high or low pressure notwithstanding. There were no abnormalities with low volume at high pressures (strapped animals). They also observed that PEEP significantly diminished damage in the high-volume animals. Lung damage has thus been shown to be caused by high tidal volumes that produce hyperinflation, rather than by pressure itself.

In a subsequent publication, Dreyfuss and Saumon[79] suggested the term *volutrauma* to describe the stretch that results from high tidal volumes. They maintained that their experiments with rat lungs indicated increased airway pressure alone (without increased lung volume) did not produce tissue damage, whereas increased tidal volumes were injurious, whether airway pressure was high or low. A report by Hernandez et al.[80] soon followed, and it came to the same conclusions. That study clearly demonstrated the effect of pressure (barotrauma) compared to the stretch of overinflation (volutrauma). Tissue damage in three different rabbit preparations was compared using three different peak pressures in each preparation. In one preparation, expansion of the chest wall was virtually eliminated by a full body cast, thereby restricting lung expansion and alveolar distention in spite of high pressure. In another preparation, distension was somewhat restricted only by the chest wall of intact animals. In a third preparation, the lungs were excised and isolated, thereby allowing for the most unrestricted lung expansion in response to inflation. Airflow was adjusted to yield peak pressures of 15, 30, and 45 cm H_2O for each of the three rabbit preparations. Microvascular permeability was compared in the three groups and was found to be maximal in the completely exposed lung preparation, and in the intact chest wall preparation. Minimal changes were noted in the body cast preparation where lung inflation was virtually eliminated despite high airway pressure. These data indicate that injury is a function of the distension caused by high volume alone.

Alveolar distension is generated by tidal volume. In one study of lambs at birth, high tidal volume in lambs was observed to cause low compliance, less ventilator efficiency, and high protein leakage.[81] In another study of lambs at birth, application of only six manual inflations of 35 to 40 mL/kg caused blunted responses to surfactant administered immediately after the six inflations.[82] The lungs of the bagged lambs who received surfactant were poorly expanded compared to controls that were not bagged prior to surfactant insufflation. Inspiratory capacity and deflation compliance in control lambs were much higher, whereas lambs with prior bagging were more difficult to ventilate. In addition, tissue injury was more extensive in the lungs of bagged lambs. These experimental observations are compatible with clinical studies that have demonstrated or suggested that BPD was more frequent and severe with use of mechanical ventilation, particularly with high inspiratory pressures.[29,37,68-70,73]

Injury imposed by ventilators produces alveolar capillary leak as well as seepage of fluid, plasma, and blood into airways, alveoli, and interstitial tissue. Preexisting (intrauterine) inflammation and premature birth enhance vulnerability to ensuing ventilator injury. The seepage from capillary leak inactivates surfactant, leading to a need for higher ventilator pressures to overcome unopposed surface tension forces. Ventilator pressure also increases the accumulation of inflammatory cells. In ventilated animals, lung lavage has been shown to contain increased quantities of inflammatory mediators such as platelet activating factor, thromboxane-β_2, and tumor necrosis factor (TNF)-α.[80,83] This has been demonstrated with clarity in a multicenter study of mechanically ventilated adults with RDS.[84] Two different tidal volumes (12 versus 6 mL/kg) were applied and the cytokine content of bronchoalveolar lavage fluid was analyzed. Concentrations of inflammatory mediators in lungs and in plasma were significantly lower in the group that received lower tidal volumes. The study was stopped early because significant survival benefits were demonstrated in the low tidal volume patients.[85]

Inflammation/Infection

There is general agreement that inflammation plays a pivotal role in the development of BPD.[86,87] Proinflammatory cytokines, including interleukin (IL)-1β, TNF-α, IL-8, and IL-6 are elaborated during the inflammatory process, and they are regularly identified with intrauterine lung injury.[88-90] Chorioamnionitis occurs with entry of microorganisms from the cervix and below into decidual membrane and then through fetal membranes into the amniotic fluid, an ascending route of bacterial invasion that was described by Bernirschke et al.[91,92] in 1960 and by Blanc[93] in 1961. Although the primary and most frequent trigger of inflammation in utero is infection (in the form of chorioamnionitis or colonization by low pathogenic bacteria), several other factors are known to initiate and/or prolong the inflammatory process postnatally as well. These include modalities of treatment and resuscitation such as volutrauma, oxygen-free radicals, and pulmonary edema caused by a patent ductus arteriosus, and excessive fluid loads. Postnatal sepsis also enhances pulmonary inflammation and therefore exacerbates BPD.[94,95]

The inflammation that characterizes BPD is often initiated in utero, in the presence of chorioamnionitis. Most babies born at 30 weeks' gestation or less have been exposed to chorioamnionitis. This is the usual time of onset of the pulmonary inflammatory process, which may persist throughout pregnancy and may also be extended postnatally by resuscitative and therapeutic measures necessary for survival. It has become increasingly apparent that this inflammatory process impedes normal distal development of the saccular and alveolar lung. Septation and microvascular development are blunted, and as a consequence, hypoalveolarization minimizes the surface available for gas exchange.

The diagnosis of chorioamnionitis is at best nebulous. It has been aptly pointed out that chorioamnionitis is a maternal and/or fetal inflammatory response that is associated with most VLBW deliveries, yet we know little about its duration, severity, or its specific etiologic organisms.[89,96]

Intrauterine bacterial infection or colonization may affect one or more sites. The process may transpire in the

areas between maternal tissue and fetal membranes (choriodecidual space), or within fetal membranes (amnion and chorion), or in the placenta (rare), amniotic fluid, and ultimately in the fetus and umbilical cord (funisitis). At the time of preterm labor, intrauterine bacteria have ascended from the vaginal tract. The ascending organisms first enter the choriodecidual space, thence through intact chorioamniotic membranes, into the amniotic fluid, and infrequently into the fetus where a systemic inflammatory response may be stimulated. Although this intrauterine process is common, congenital and early onset bacterial infections (onset within 72 hours after birth) are comparatively infrequent, having been reported in as few as 2.0% of a large VLBW cohort.[97]

Chorioamnionitis is often chronic. It may persist and progress, yet remain asymptomatic till labor is initiated or membranes are ruptured. In its chronic, asymptomatic state the diagnosis of chorioamnionitis is a major challenge.[98] Diagnostic difficulty notwithstanding, the intensity of inflammation in chorioamnionitis has been shown to relate to severity and incidence of BPD[99] in one report; and to neonatal morbidity, mortality, and incidence of BPD in another.[100] In lungs already primed by exposure to chorioamnionitis, postnatal factors may add to the injury and severity of BPD. Watterberg[101] reported a higher incidence of BPD in ventilated neonates, but only those who were exposed to chorioamnionitis. Early tracheal aspirates contained proinflammatory mediators (IL-1, IL-6, IL-8) indicating the intrauterine origin of inflammation. Van Marter et al.[102] reported increased BPD in infants exposed to chorioamnionitis, but only if they were ventilated for at least 7 days or if they developed postnatal sepsis. Infants who were neither ventilated nor infected did not develop BPD.

Fetal lung inflammation is apparently related to an imbalance between proinflammatory and anti-inflammatory cytokines in which the former are predominant.[103] The intrauterine process is most often precipitated by bacterial invasion early in pregnancy. Early, the fetal inflammatory response is characterized by accumulation of neutrophils (and later macrophages) in pulmonary tissue and airways. An array of proinflammatory mediators is released, followed by alveolar and capillary injury, which results in edema and seepage of plasma.[103,104]

Pulmonary inflammation is detectable in the tracheal aspirates of affected infants. The most frequently cited cytokine markers are IL-1β, IL-6, IL-8, IL-16 and TNF-α.[103] The process is initiated by strong chemotactic recruitment of neutrophils to the injured tissue. Almost simultaneously, as neutrophils migrate to lung, the number of systemic circulating neutrophils declines. This decline has been observed in ventilated preterm lambs;[105] it was considered to be a marker of the activation of a systemic inflammatory reaction. The response (lowered circulating neutrophils) was noted within 5 minutes after the onset of mechanical ventilation. Another study of premature lambs demonstrated the same phenomenon and, in addition, correlated the intensity of the cellular response to the severity of capillary permeability and pulmonary edema.[106] Similar observations of pulmonary neutrophil influx and depleted circulating neutrophils have been made in human premature infants.[107]

Elevated plasma IL-6 is identified in fetal inflammatory response syndrome.[28,108] Neonatal complications occur more frequently in affected fetuses; their mothers often have asymptomatic bacterial invasion of the amniotic cavity.[108] In 1961 Blanc[93] reported a series of infants with congenital pneumonia in whom chorioamnionitis was identified in virtually all cases. More than 4 decades later, Watterberg et al.[101] reported a series in which chorioamnionitis was associated with a diminished incidence of RDS but with a later increased incidence of BPD. Tracheal lavage showed higher concentrations of IL-1β on the first postnatal day in infants who later developed BPD; thromboxane β_2 was higher on days 2 and 4. Chorioamnionitis was thought by the authors to be a significant initiating factor in the development of BPD.

Funisitis is evidence of chorioamnionitis. It is present in all fetuses in whom the inflammatory response syndrome has appeared.[109] Neonates with funisitis are more likely to develop neonatal sepsis,[110] cerebral palsy,[111] and BPD.[28] Elevated cytokines in amniotic fluid and in tracheal lavage have been detected in babies who either have BPD or are destined to have it.[28,112-115] Fetal aspiration of amniotic fluid that contains microorganisms or high concentrations of proinflammatory cytokines may lead to arrested development and an inflamed lung that is substantially more vulnerable to postnatal barotrauma-volutrauma and oxidant injury.[25,28] Additionally, capillary damage leads to plasma leakage and alveolar destruction.[28] Groneck et al.[116] performed a series of extensive assessments of tracheobronchial aspirates on postnatal days 10 and 15. They concluded that BPD involved inflammation and microvascular permeability in the presence of a high content of proinflammatory mediators. Lung lavage has demonstrated increased IL-6 activity repeatedly. Several reports have also described a high content of IL-1β, IL-6, and TNF-α in amniotic fluid and in lung lavage prior to clinical recognition of BPD.[115-118] In summary, BPD is associated with accumulations of inflammatory cells and the elaboration of cytokines and other inflammatory mediators intrinsic to the lung.[119] The release of these substances may be stimulated by a variety of factors that include prenatal and postnatal infection, ventilator injury, and oxygen toxicity. The immature lung is particularly vulnerable to these insults. Prenatal and postnatal alveolar development is markedly impeded when any of these injuries occur. Alveoli are larger but fewer, whether fetal or neonatal, with or without surfactant treatment.[25,120] There are no data to indicate a difference in the inflammatory response elicited by microbes, hyperoxic injury, or ventilator barotrauma-volutrauma.[86]

Attention has been directed to the possible significance of *Ureaplasma urealyticum* infection (or colonization) in the lung. This organism colonizes the female (and occasionally the male) genital tract. Cervical colonization was observed in 44% of pregnant women who were followed longitudinally during gestation.[121] In another study, at the time of cesarean section 20% of endometrial cultures were positive for the organism, even though membranes had not yet ruptured.[122] Cassell et al.[123] documented *U. urealyticum* as the most common organism associated with chorioamnionitis. Review articles by Holtzman et al.[124] and Wang et al.[125] summarized several investigations that

demonstrated a strong relationship between *U. urealyticum* from tracheal cultures and the subsequent development of BPD. Infants with positive cultures are at least twice as likely to develop BPD as infants whose cultures are negative, but this association has been demonstrated only for smaller premature infants whose birth weights were 1250 g or less.

If *U. urealyticum* is a cause of BPD, it may involve a subset of infants. Infection with *U. urealyticum* may trigger an inflammatory cascade that produces tissue destruction and hypoalveolarization. A number of studies indicate association between the organism's colonization of the airway and a later appearance of BPD, but there is no clear evidence that these findings are independent of prematurity.[126] If the organism is a cause of BPD, then masked, randomized trials with effective antibiotics may demonstrate a reduced incidence of the infection and of BPD.

There are no data to suggest a direct etiologic role for infections caused by other organisms. Several reports describe associations between bacterial, viral, or fungal organisms with BPD. The data are equivocal; a distinct and direct causal relationship between specific organisms and BPD has not been shown.[126]

The risk of BPD is enhanced in the presence of postnatal sepsis, and even more so if a patent ductus is active at about the same time.[95,127] In the presence of infection, the ductus may persist in patency or may reopen after closure. Increased prostaglandin levels persisted after indomethacin treatment in infected infants; but decreased in uninfected infants. TNF-α levels were increased in the infected babies with a significant correlation between TNF-α and prostaglandin levels.[127]

Nutrition, Vitamin A, and Vitamin E

A number of speculations have been made regarding the roles of specific nutritional deficiencies in the pathogenesis of BPD. Undernutrition of the premature infant is often cited as a major factor; but in most instances, these speculations have not been documented in human infants.[128-131] The relatively high caloric needs of premature infants and their meager nutritional stores at birth have been pointed out repeatedly. Furthermore, the aggregate of requirements for growth, overall metabolism, and work of respiration impose unmet nutritional needs. The combination of high need and meager stores is speculated to contribute to BPD. Inadequate nutrition may well amplify the damage of barotrauma-volutrauma and O_2 toxicity. Theoretically, the deficiency of antioxidant enzymes and, therefore, the extent of hyperoxic lung injury could be prevented or minimized through supplementation with the trace elements that are integral parts of antioxidants (copper, zinc, selenium). These are reasonable speculations, but they do not seem to be clinically significant in the management of infants with BPD. No attempts have been made to prevent BPD in human infants by means of specific supplementation of these and other trace elements. However, the preventive roles of vitamin E and vitamin A have been studied. Meta-analysis of eight randomized trials demonstrated that supplemental vitamin E did not diminish the incidence of BPD.[54] Vitamin A supplementation may be more hopeful.

Similar to so many other nutritional components, vitamin A stores in premature infants are lower at birth than they are in adults or in older infants.[128,129] Furthermore, vitamin A deficiency apparently causes changes in the lower respiratory tract that are similar in appearance to those of BPD.[132] Hustead et al.[133] demonstrated that infants who developed BPD had low levels of vitamin A at birth and 28 days after birth compared to babies who did not have BPD. Shenai et al.[134] confirmed these findings and, in a subsequent controlled study,[135] demonstrated diminished incidence and severity of BPD in infants who were given vitamin A supplements for 28 days, beginning with the fourth day after birth. The study of Papagaroufalis et al.[136] demonstrated similar beneficial effects. Two other studies[137,138] did not, perhaps because their populations differed somewhat from those of the earlier successful studies. In a large trial from the NICHD Neonatal Network, Tyson et al.[139] studied 807 infants whose mean birth weight was 769 g. The primary outcome was death or BPD at 36 weeks' PMA. BPD occurred with significantly reduced frequency in the vitamin A group (55%) compared to controls (62%). The authors calculated that one additional infant survived without BPD for every 14 to 15 infants who received vitamin A prophylactically for 4 weeks beginning 24 to 96 hours after birth. In a meta-analysis from the Cochrane Neonatal Review Group, which involved six eligible trials,[140] the authors suggest that vitamin A administration reduced the need for oxygen at 36 postmenstrual weeks. There was also a trend toward reduction of death or need for oxygen at 36 postmenstrual weeks. The evidence for vitamin A usefulness is apparently sound. The positive outcome, however, is modest. A survey of 207 level III units indicated that a minority of neonatal units were routinely administering vitamin A. Sound evidence notwithstanding, clinicians seem reluctant to commit to three intramuscular injections weekly for 4 weeks because the benefit seems modest.[141]

Role of Patent Ductus Arteriosus

Left-to-right shunting across the ductus arteriosus increases pulmonary blood flow, which may result in pulmonary edema. Lung compliance is reduced and airway resistance is increased, creating a need for more vigorous and protracted ventilatory support. With this in mind, the impact of early closure of the ductus arteriosus in reducing the incidence or severity of BPD has been investigated in several studies. A meta-analysis by Ehrenkranz and Mecurio[54] reviewed 12 studies that sought closure of the ductus arteriosus, either prophylactically or therapeutically. Their data did not support the hypothesis that early closure of a patent ductus arteriosus diminishes the incidence of BPD. The impact of patent ductus arteriosus and temporally related infection has been described in the preceding subsection on inflammation/infection.

In a large international study of 1202 infants with birth weights of 500 to 999 g, 574 received prophylactic indomethacin within 24 hours after birth. The incidence of PDA was reduced, but the incidence of BPD was unaffected.[142] Later analysis of 999 infants examined the incidence of BPD in two subgroups, one with PDA and the other without PDA.[143] In the subgroup of infants with PDA, there was no significant difference between treated and nontreated cohorts. However, in the subgroup of infants without PDA, the incidence of BPD was 43% with

indomethacin treatment versus 30% with placebo. The authors considered the possibility of harmful side effects on oxygenation and lung edema formation when indomethacin is given prophylactically in the absence of a patent ductus.

The risks of PDA ligation were calculated in a later report on another subgroup of infants who were participants in the same aforementioned international study.[144] Ligation was performed in 110 infants and medical therapy in 316. The authors concluded that PDA ligation may increase risks for BPD, severe ROP, and neurosensory impairment. The role of surgery in these negative outcomes is not clear. In another report, surgical ligation was significantly associated with BPD independent of gestational age. The authors state that these findings enhance the uncertainty about benefits and risks of PDA ligation during the neonatal period.[145]

Fluid Balance

Several studies indicate an increased risk of BPD with high volumes of fluid intake.[146-149] They suggest that excessive fluid intake during the first few days of life causes pulmonary edema and an increased incidence of BPD because of the resulting need for more vigorous ventilatory support. Lower fluid volumes seem to be associated with a diminished risk of BPD.[146-151] Other investigators could not demonstrate a higher incidence of BPD with larger volumes of fluid intake.[152,153] The report of Lorenz et al.[154] analyzed outcomes according to varying weight loss. They assigned infants to two different weight loss groups (8%-10% versus 13%-15%). The daily volume of fluid administration was governed by daily weight losses. They concluded that when fluid intake achieves weight loss within 5% to 10% during the first week of life, there are no significant differences in the incidence of BPD and several other major negative outcomes (PDA, intracranial hemorrhage, necrotizing enterocolitis [NEC], dehydration, acute renal failure, or metabolic disturbances). The emphasis of that study was on fluid balance (weight loss), rather than fluid input itself.

In a Cochrane meta-analysis of five studies, by Bell and Acarregui,[153] the principal results indicated that restricted fluid intake increases weight loss and significantly decreases the risk of PDA and NEC. The risk of BPD was not significantly associated with greater fluid volumes, but "the direction of effect" was toward a reduced incidence of BPD when intake was restricted. Although the aggregate of data is equivocal in regard to fluid intake and incidence of BPD, there is unquestioned general agreement that maintenance of a physiologic fluid balance is more likely to minimize the incidence of BPD, and it may be that volumes administered can be quite varied, so long as weight loss is maintained at 5% to 15% over the first postnatal week.[153,154]

Angiogenesis and Alveolarization

The term *bronchopulmonary dysplasia* was designated by Northway et al. in 1967 "to emphasize the involvement of all the tissues of the lung in the pathologic process." This somewhat prophetic remark was subsumed in the voluminous literature that accumulated during the following decades. BPD was generally considered to be an air space disease. Pulmonary vasculature was thought to evolve alongside the developing airways primarily for delivery of nutrients and oxygen. This concept has changed significantly in recent years. Vascular and alveolar development are mutually indispensable for normal development of the lung. Ongoing reactivity between airways and vasculature is driven by expression of specific growth factors in the epithelium of airways and the endothelium of vasculature. Among these growth factors, vascular endothelial growth factor (VEGF) is pivotal. VEGF is a specific mitogen, and later a survival factor, for alveolar epithelium and vascular endothelium in the lung. With its receptors it plays a critical role in normal vascular and alveolar development.[155] In a study that blocked VEGF receptors (VEGFR-2), resultant inhibition of angiogenesis decreased alveolarization in rat lungs. The authors speculated that angiogenesis was necessary for alveolarization.[156]

In another study of rat lungs, administration of multiple doses of VEGFR inhibitor disrupted normal postnatal alveolarization and vascular growth.[157] Thebaud et al.[158] reported that in rats VEGF blockade diminished VEGF and VEGFR-2 expression, thus impairing alveolar development, which ultimately caused alveolar simplification and diminution in capillary density. Hyperoxia-induced BPD in rats was associated with diminished VEGF and VEGFR-2 expression, increased air space and capillary loss. Intratracheal VEGF gene therapy subsequently improved survival and promoted lung capillary formation and alveolar development. These findings indicate the fundamental importance of blood vessel development in formation of the airway, and the possibility that restoration of vascular growth may improve overall lung growth, and perhaps pulmonary function.[159] Kunig et al.[160] showed that recombinant human VEGF enhances alveolarization of oxygen-injured rat lungs. They speculate that the disruption of lung structure that follows hyperoxia may be partially attributable to diminished VEGF signaling. These recently reported data introduce the possibility that therapeutic reversal of lung injury may restore vascular growth and alveolarization.[159]

Pathology: Classic BPD

Table 23-1 lists the most frequently observed structural changes in the "classic" BPD, according to severity and anatomic component involved. Although the description first proposed distinctly categorized four stages of the disease and the duration of each, changes in the clinical course described in recent years have blurred the sharp distinctions. Early, the morphologic changes of classic BPD consist of cellular necrosis, edema, and inflammation. These changes represent an acute stage that is followed by fibroproliferation, the intensity of which determines the ultimate extent of structural disruption. In the airways, widespread fibroproliferative activity, squamous metaplasia of epithelial linings, loss of ciliary function with accumulation of debris, and hypertrophy of smooth muscle result in maldistribution, obstruction, and trapping of air (atelectasis and emphysema). In the pulmonary vasculature, late reparative responses narrow the lumens of blood vessels, causing maldistribution of blood flow (hypoperfusion and pulmonary hypertension). The cardiac consequences of these late vascular abnormalities include right-sided ventricular hypertrophy and cor pulmonale. In general, these are the morphologic characteristics of classic BPD.

Mild classic BPD is said to be indistinguishable from RDS. It is characterized by slight septal edema at the alveolar level, patchy loss of cilia with focal loss of epithelium in the bronchi and bronchioles, and slight edema in the interstitial tissue. Hyaline membranes abound.

Moderate classic BPD is characterized by necrosis of scattered individual alveolar cells, progressive septal edema, small foci of collapsed alveoli, and fewer hyaline membranes than are seen in mild BPD. The lumens of bronchi and bronchioles now contain small quantities of eosinophilic material, inflammatory cells, and mucus. Obstruction of smaller bronchioles probably leads to the appearance of isolated foci of alveolar collapse. Peribronchial, peribronchiolar, and perivascular edema appear, interstitial edema becomes widespread, and interstitial fibrosis is prominent. The interstitial edema is a consequence of leakage through damaged capillary endothelium. With disease of this moderate severity, F_{IO_2} requirements and inspiratory pressure must be increased at a time when recovery from RDS is anticipated.

Severe classic BPD is characterized by continuation of the acute responses to injury and by a widespread appearance of reparative processes. Necrosis of alveolar cells is generalized, and previously clear alveolar spaces are now filled with fibrinous exudate, connective tissue overgrowth, macrophages, and debris. Alveolar collapse is more extensive, with the collapsed areas often surrounding spherical foci of trapped air (focal emphysema). Airway obstruction is more pervasive because bronchial and bronchiolar lumina contain larger quantities of debris, denuded necrotic epithelial cells, inflammatory cells, and mucus. The airway mucosa is frankly necrotic. Active chronic inflammation within the walls of the bronchi and bronchioles sometimes extends externally to adjacent tissue. Whereas in earlier stages only patchy areas of squamous metaplasia are present in larger bronchi, in severe disease the metaplastic process becomes widespread to involve the lower airways, causing luminal encroachment and consequent obstruction of airflow caused by newly generated cells. Hypertrophy of smooth muscle progresses to cause recurrent episodes of bronchospasm. Edema of the peribronchial and peribronchiolar areas becomes widespread, but fibrosis in these particular areas is negligible, if it occurs at all. Edema is prominent in the interstitium and perivascular spaces, where fibrosis becomes conspicuous. Alteration of blood vessel structure is rather extensive, giving the appearance of early hypertensive changes (medial hypertrophy, degenerated intima, and thrombi). The ductus arteriosus is often patent, and some degree of right-sided ventricular hypertrophy is almost the rule at this stage of the disease. In the presence of extensive airway obstruction, alveolar collapse, focal emphysema, widespread edema, and vascular damage, oxygenation is increasingly troublesome and CO_2 retention is a significant problem.

Advanced classic BPD is largely a manifestation of the extensive structural disruption brought on by ongoing reparative processes. Alveoli are alternately emphysematous and atelectatic; multilobular involvement pervades. Destruction of alveolar septae results in bullous emphysema. Edema of alveolar structures has disappeared. Lower airways are everywhere plugged by dense eosinophilic debris and extensive squamous metaplasia; lumina are often obliterated. Terminal bronchioles are either distended by trapped air or are constricted. Bronchial and bronchiolar smooth muscles are severely hypertrophic. The interstitium, peribronchial, peribronchiolar, and perivascular tissues are fibrotic. Lymphatics are distended and tortuous. Vascular changes are substantially more severe. Adventitial fibrosis is conspicuous, and continued endothelial proliferation further narrows lumina and sometimes completely obliterates them. Overall, the lungs are severely overexpanded; diaphragms are depressed. In the heart, right-sided ventricular hypertrophy is advanced, and in the sickest babies, cor pulmonale supervenes. Advanced involvement progresses inexorably to pulmonary and cardiac failure.

Pathology: New BPD

The severely distorted structure described above serves as an instructive comparison to the milder changes that characterize the new disease. The extensive destruction of "classic BPD" is not as frequent nowadays. It was largely attributable to the high pressures and high oxygen concentrations that were used for mechanical ventilatory support.[161-163] The lesions that we now label as "new BPD" first became evident just prior to the widespread use of antenatal maternal steroids and exogenous surfactant, which in turn further reduced the use of vigorous support that was pervasive at that time. The early improvements are thought to be the result of upgraded clinical management and respiratory support strategies.[163,164] Coalson summarized several studies from the existing literature (and from her own contributions as well) that convincingly indicate that the advent of milder disease occurred prior to the era of antenatal steroids and surfactant. This early appearance of favorable changes in microscopic findings has evolved into today's *new BPD*.

The pathology of new BPD, like its clinical course, bespeaks a milder disease process. Classic disease is characterized by neighboring areas of atelectasis and emphysema. In new disease the lungs are more evenly expanded, although some overdistension may occur. In classic BPD, the airway is severely affected by obstructive lesions (squamous metaplasia with epithelial and goblet cell hyperplasia). With the exception of severe disease, new BPD rarely involves lesions of airway obstruction. In the fibroproliferation of severe classic BPD, architecture is distorted, alveolar walls are destroyed, and the alveoli are fewer in number. In new disease fibrotic changes are infrequent or perhaps minimal, even in more advanced versions. In classic BPD, airway smooth muscle is extremely hypertrophied whereas in the new disease hypertrophy is usually minimal. The arteries of classic disease are remodeled by thickened hyperplastic walls and slit-like lumens. They appear hypertensive. In the new disease arteries are fewer but dysmorphic. The most visible and significant difference between the two BPDs is hypoalveolarization. Although hypoalveolarization has been noted in classic BPD, it is considerably more extensive and prominent in the new disease in which there is a paucity of alveolar crests, air spaces are larger and fewer, and capillaries are dysmorphic. In essence, new BPD is a disorder of immature lungs that have been struck prenatally by inflammation or postnatally by the measures required for treatment,

that is, barotrauma-volutrauma and oxygen and by postnatal infection.

Clinical Course: The Early Weeks

In considering BPD today, we are preoccupied with a population that differs from the one that was described originally by Northway.[2] Increasing severity through the four delineated stages of disease was based on experience with infants whose average gestational age was 34 weeks' for those who survived, and 31 weeks for those who died; average birth weight of survivors was 2200 g, and for those who died, 1600 g. Now 75% of infants with BPD weigh less than 1000 g at birth. At birth weights of 500 to 599 g, 85% have BPD, and in contrast, at birth weights of more than 1500 g, 5% have BPD. Other estimates may vary somewhat but the pattern persists: BPD is a disease of VLBW premature infants; the smaller the baby, the greater the likelihood of frequent and severe disease.

Babies who are destined to develop BPD usually have some degree of respiratory distress at birth, but this varies from normal breathing to the gasping of life-threatening pulmonary insufficiency. There is usually a need for oxygen supplementation, which may disappear in a few days, only to reappear soon thereafter. In one report,[19] approximately half of the infants who needed supplemental oxygen on day 28 also needed it at 36 weeks' PMA (postmenstrual age). Ninety percent of babies born at 30 weeks' or less gestation did not require continuous oxygen during the first 28 days, yet 20% of them developed BPD.[19] A significant number of VLBW babies experience the mild new BPD, but severe disease is frequent nevertheless. Among the babies with mild disease whose abnormal clinical signs are at first minimal or absent, some will ultimately deteriorate and require months of supplemented oxygen and/or ventilatory support. These severe forms of the disease occur in about 25% of affected babies.[165] In a few infants, respiratory insufficiency, pulmonary hypertension, and cor pulmonale progress to death later on.

Radiologic appearance of mild BPD is often uncertain, even though O_2 supplementation is needed and retractions, diminished breath sounds, and crepitant rales are prominent. The early phases of moderate and severe disease are associated with a radiographic appearance that indicates BPD, but lacks specificity. Inflation may be normal or homogeneously distended. During the ensuing days or weeks, if O_2 concentrations and ventilatory pressures require progressive increase, the x-ray reflects overdistension and a classic barrel chest becomes obvious. Carbon dioxide retention then worsens and the resultant respiratory acidosis is eventually compensated by renal conservation of bicarbonate and a positive base excess.

Generally, if the need for respiratory support diminishes steadily during the first postnatal month, the subsequent course of BPD may be mild or at worst, moderate. On the other hand, an ongoing need for increased support at about this time may indicate a troublesome complication or it may portend severe protracted disease. Chest film abnormalities progress with enhancement of generalized hyperinflation, focal emphysema, focal atelectasis, and sometimes cardiac enlargement.

Acute episodes of respiratory deterioration often punctuate the course of the disease for weeks, and in themselves, may be life-threatening. These acute threatening events may be caused by (1) infection; (2) pulmonary edema associated with patent ductus arteriosus, overhydration, or progression of chronic disease; (3) congestive heart failure; or (4) severe airway obstruction caused by bronchospasm or tracheobronchomalacia.[166-168]

Bronchospasm may occur early (first week) or later, while infants are mechanically supported or when they are simply receiving O_2 by nasal cannula or in a hood. Cyanosis appears abruptly, and when breath sounds are virtually inaudible, wheezing cannot be heard with the stethoscope. The absence of breath sounds is particularly dramatic in infants who had previously breathed with little difficulty, but who now exert maximum effort to no avail. The absence or marked diminution of breath sounds is generalized; it is not restricted to one area. Even if the infant is on mechanical support, insufflations may be inaudible, simulating total obstruction of the endotracheal tube. A temporary increase in peak inspiratory pressure by 2 or 3 cm H_2O with an increase of FIO_2 to 1.0 may end the episode without the need for pharmacologic management (bronchodilatation). If, however, the upgraded respiratory settings are ineffective after a few minutes, treatment with bronchodilating agents is indicated. The mechanism of severe bronchospasm is unknown, but a significant role for airway muscle hypertrophy is presumed. Hypoxia is considered to be important in the stimulation of airway constriction.[169,170] In BPD infants, sensitive bronchial reactivity has been demonstrated during hypoxic intervals.[170]

In the infant older than age 1 month, progressive BPD may involve right-sided heart failure (cor pulmonale) as a result of increased pulmonary vascular resistance (pulmonary hypertension). In the autopsy series of Bonikos et al.[171] right-sided heart failure was considered the immediate cause of death in 30% of infants. Changes seen postmortem in arteriolar intima and media reflect pulmonary hypertension. In a careful study of only one infant, the cross-sectional area of pulmonary vasculature was shown to be significantly contracted.[172] To some extent, increased pulmonary vascular resistance may also be caused by distorting parenchymal fibrotic changes; right-sided heart failure develops as vasculature changes progress and resistance increases. Even in the absence of cardiac failure, right-sided ventricular hypertrophy resulting from increased pulmonary vascular resistance is virtually universal during progressive BPD. Pulmonary blood vessels are responsive (diminished resistance) to O_2 supplementation; pulmonary artery pressures are significantly lower when continuous O_2 is given via nasal cannula.[173] On the other hand, small decrements of FIO_2 may result in diminished PaO_2 and prolongation of right-sided systolic time intervals.[174-176] Catheterization data indicate the need for an appropriate FIO_2. In the presence of hypoxia an increased FIO_2 diminishes pulmonary artery pressure significantly.[177-179] These data suggest the need for individualized strategies for O_2 supplementation, bearing in mind the prescribed oxygen restrictions that are currently used in efforts to reduce the incidence of retinopathy of prematurity.[180-183] Maintaining prescribed ranges of oxygen saturation may be quite frustrating in BPD infants in whom constriction of pulmonary vasculature and airways are so sensitive to small decrements in FIO_2.

Growth failure is prominent in the early weeks of BPD. It is not uncommon for affected infants to require up to 25% more calories for satisfactory growth compared to unaffected infants.[184] Exaggerated work of respiration, chronic hypoxia, increased metabolic rate, and O_2 consumption have all been described as bases for increased caloric needs.[184,185]

Osteopenia is common in smaller premature infants, who may develop it even in the absence of BPD. In infants with BPD, vulnerability to osteopenia is greater, presumably because of low calcium and vitamin D intake, but more often because diuretic therapy causes significant urinary calcium loss. Fractures of the long bones and ribs may occur, often identified unexpectedly on x-ray or during routine assessments by nurses.

Extubation frequently is followed by a capricious respiratory course. Inspiratory stridor from tracheal edema, scarring, or both may be evident immediately upon extubation. Tracheal stenosis may become apparent only after several days, when severe stridor appears while laryngeal scarring progresses. Even if complications of intubation are absent, the course is often undulating. Severe episodes of wheezing related to bronchospasm are frequent. Oxygen requirements wax and wane for no discernible reason. Overproduction of airway secretions requires frequent chest physiotherapy, and many infants tolerate the procedure poorly. Whether these infants are managed at home or in the hospital, O_2 supplementation may be required for weeks or months. Among infants who recover from BPD, decrements of inspired O_2 are feasible only at a slow rate; room air ultimately may be tolerated after a course of weeks or months.

Systemic hypertension occurs in a significant number of infants with BPD, aside from pulmonary hypertension. Anderson et al.[186] described 11 of 87 BPD patients whose systemic hypertension was identified in the nursery or after discharge. In another report, 5 (12%) of 41 infants with BPD were affected.[187] Mean age of onset was 105 days. Clinical risk factors for hypertension included a high incidence of bronchodilator therapy and use of diuretics, as well as the need for a longer course of O_2 therapy at home. The presence of these risk factors may simply indicate that severe disease is more likely to be associated with systemic hypertension. Abman et al.[188] observed systemic hypertension in 13 (43%) of 30 patients who were managed at home. Three of these patients had left-sided ventricular hypertrophy, and another had a cerebrovascular accident. In the aggregate, experience seems to indicate that among survivors, systemic hypertension is benign and amenable to appropriate therapy.[189]

Clinical Course: The Later Months and Beyond

Risks to surviving infants continue through the first year or two of life, depending on disease severity. Thereafter, in most instances, the difficulties created by chronic disease diminish gradually. Reports on outcomes vary considerably because of diversity in patient characteristics, inability of investigators to account for and control all significant variables, and the inevitable differences in study design. Added to these confounding factors are lag time between the year that intensive care methodology is being studied and the outcomes reported years later.

Growth is retarded and does not assume a normal rate until after the child is 2 to 5 years old.[190] As many as 67% of infants with BPD may continue in growth failure after discharge.[191] The child with BPD often resists feeding, is difficult to nourish, and is recurrently beset with acute illness. The BPD infant is often difficult to feed, and this is largely related to abnormalities in the coordination of respiration-swallow sequences. Integration of breathing and swallowing is compromised in BPD infants. Irregular breathing patterns and recurrent apnea impair establishment of longer suck and swallow runs. Increased apneic swallow sequences and the peculiarities of feeding behavior thus require more than the usual insight into differences between babies with and without BPD.[192-196]

Closer scrutiny and more than the usual number of rest intervals are required for BPD babies. Maturation of suck, swallow, and respiration is largely related to postmenstrual age rather than postnatal age.[192] The severity of BPD must also be considered when evaluating feeding performance. Mizuno et al.[196] demonstrated significant diminution in sucking pressure and frequency in infants with severe disease compared to those with mild or moderate BPD. The authors appropriately called attention to the protracted time required for feeding of BPD infants, including an increase in the frequency and length of rest periods.

Feeding problems are particularly frustrating for anxious parents who have been sensitized to the importance of caloric intake. Sound parental counseling is necessary to improve feeding behavior and increase intake. However, the growth of some BPD children is impaired even when caloric intake is apparently adequate. With improved respiratory status beyond 2 years of age, growth in height and head circumference is accelerated, as is weight gain, but to a lesser degree.[197] With more normal respiratory function, growth pattern differs little from infants without BPD.

It has been hypothesized that lung growth in these children consumes an inordinately large fraction of energy intake and, as pulmonary difficulties subside, catch-up of body growth ensues. Recurrent illness and readmissions to the hospital surely contribute to growth impairment. Abnormal growth has been shown to be related to severity of respiratory dysfunction and recurrence of lung infection.[198] On the other hand, Sell and Vaucher[199] noted persistent growth delay throughout early childhood, and they concluded that, more than any other factor, delay in growth was significantly related to earlier growth parameters (prior weight, length, and head circumference). The presence or absence of BPD was not important.[199] Results of another study that compared prematures with and without BPD also indicated that growth retardation may be more directly related to birth weight and gestational age than to BPD itself.[200]

Infants with BPD have increased energy expenditure. Up to 25% more than usual caloric allocations may be indicated.[191] This has been attributed to the extra energy requirement for increased work of breathing; increased resting metabolic requirement;[191] and increased pulmonary oxygen consumption. The need for enhanced nutrition combined with impaired feeding performance together may contribute to the growth failure that characterizes BPD. In a Cochrane review of studies on the impact of increased energy intake, the authors concluded that there were no randomized controlled trials that compared

augmented versus standard energy intake.[194] There are thus no data to indicate that increased energy intake above standard level would be of benefit.

Recurrent hospitalizations are particularly frequent through the second year of life, with decline in frequency thereafter. Recurrent illness is an ongoing source of stress to parents.[201] Wheezing illness is common[202] Respiratory infection is by far the most frequent cause of readmission. Recurrent illness is reported in 50% to 85% of patients[203] and rehospitalization in 50%.[204-207] Exacerbations of respiratory distress, often life threatening, are primarily due to lower tract infections.[208] The most frequent infection is probably due to respiratory syncytial virus, which is particularly prevalent in the wintertime.[209,210] Extended lung damage is often a result of severe acute infections, especially when ventilator support is necessary. Acute pulmonary edema may follow abrupt, indiscrete increments in formula intake, which elevate fluid load beyond pulmonary tolerance. Other causes of readmission are bronchospasm, cor pulmonale, upper airway obstruction, surgery, systemic hypertension, and family social crises.[211]

Complications of prematurity, prenatal and postnatal, have confounded the clear conclusion that BPD is an independent factor in poor neurodevelopmental outcome. Some studies have indicated no difference in the outcomes of extremely premature infants with or without BPD.[190,212] Other studies have indicated a persistent independent effect by BPD after control of other factors.[213,214] BPD children are apparently unaffected by a characteristic cluster of impediments. Rather the outcomes are more global, including lower IQ (intelligence quotient), delayed speech and language development, and behavioral problems. Cerebral palsy is more frequent in BPD children.[213,214]

Abnormal pulmonary sequelae include diminished compliance and increased resistance to airflow, expiratory airflow difficulties caused by bronchospasm, bronchomalacia (or both), air trapping, increased work of breathing, and reactive airway disease.[215] The most frequent clinical signs of illness as reported in the data of the High Frequency Ventilation in Premature Infants (HIFI) Study Group include crepitant rales, retractions, palatal groove, wheezing, and prolonged exhalation at rest. Stridor, subglottic stenosis, cyanosis, and tracheostomy were considerably less frequent in this study.[215] Children and teenagers who have had BPD in their infancy usually have residual abnormal pulmonary functions. Generally, the more severe the neonatal illness, the greater are the later abnormalities of pulmonary function.[216] Most of the available follow-up data on older children and adults concern classic BPD. Details of long-term outcomes of the new disease are largely unknown.[217]

In a study of 8- to 9-year-old children by Doyle et al.,[218] airflow was significantly diminished in ELBW infants (less than 1000 g) compared to normal birth weight infants; (greater than 2499 g). Differences between the study and control groups were unchanged from those described earlier in the pre-surfactant era.[218] In another study, Doyle et al.[219] followed 147 late adolescent VLBW survivors, among whom 22% had BPD. Patients who had BPD had worse lung function than those who did not have BPD. Reduced airflow was more frequent in BPD survivors.

Greenough et al.[220] compared lung volumes of 17 infants whose BPD was "mild-moderate" to an equal number who did not have BPD. All were born at less than 33 gestational weeks. Regression analysis demonstrated that reduced lung volume was significantly related to BPD. Blayney and colleagues[221] evaluated pulmonary function in 32 BPD patients at 7 years of age and again at 10 years of age. All were born between 1977 and 1980, and they had grown normally. These investigators demonstrated continued improvement in lung function, and they therefore speculated that among the more recent patients with BPD, only a small number would experience respiratory dysfunction in adulthood.

Northway et al.[222] reported the abnormal pulmonary residua in 26 adults who were born between 1964 and 1973. Some of these patients were described in the author's original description of BPD,[2] and most of them had some degree of pulmonary dysfunction including airway obstruction, airway hyperreactivity, and hyperexpansion. Furthermore, they had more respiratory infections and wheezing episodes than the controls. More than half had evidence of airway obstruction. A number of studies of children in school had also demonstrated persistent pulmonary dysfunction.[223,224] Again a reminder that most of these studies involve patients who had classic BPD.

Halvorsen et al.[225] analyzed pulmonary function in a population-controlled cohort of patients who were 28 or fewer weeks' gestational age, or 1000 or fewer g birth weight. One group was born in 1982 to 1985, a second group was born in 1991 to 1992, and a third cohort was a control group of infants who were born at term. The overall incidence of BPD was similar in the two time periods. Airway obstruction, hyperresponsiveness and hyperinflation were increased to the same extent in both groups of preterm infants compared to the matched controls born at term. Abnormalities were related to neonatal respiratory disorders. Lack of maternal antepartum steroids and a protracted need for supplemental oxygen best predicted the airway obstruction in both preterm groups. The authors' principal conclusion was that late abnormal lung function was of similar incidence in both of the analyzed eras, and as long as prolonged oxygen supplementation is required for neonatal rescue, airway obstruction may continue to be a long-term abnormality.

Radiologic Characteristics

The radiologic and morphologic abnormalities of BPD are fairly well correlated in several reports, particularly BPD in the advanced stages.[2,226-228] The radiologic appearance of mild BPD is similar to RDS: diffuse reticulogranularity and air bronchograms. The severity of these features is not related to the severity of subsequent changes of BPD.

Moderate BPD is sometimes characterized by diffuse, virtually homogenous opacification of the lungs that obscures cardiac margins. The early radiographic changes seen in mild disease often are replaced by coarse, irregularly shaped densities that are confluent and occasionally contain very small vacuolar radiolucencies (Fig. 23-1). Areas of density apparently are caused by interstitial and septal edema and by atelectasis related to the obstruction of small bronchioles with luminal debris. Small vacuolar radiolucencies represent early foci of emphysema.

In the severe form of BPD, the lucent vacuoles have expanded and are identifiable as air cysts among dense

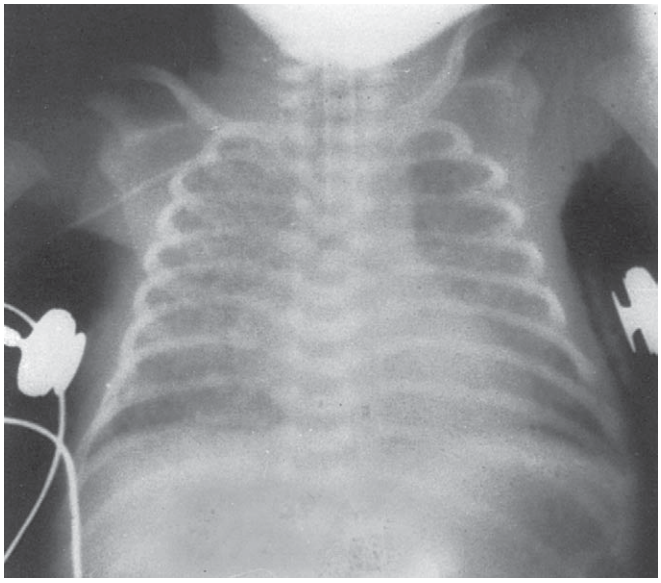


Figure 23-1 ■ Moderate (stage II) bronchopulmonary dysplasia. Note virtually homogeneous density of both lungs that is cast by interstitial edema and atelectasis. A few small round radiolucencies are dispersed through both lungs. (From Korones SB: High-Risk Newborn Infants: The Basis for Intensive Nursing Care, 4th ed. St. Louis, Mosby, 1986, p. 262.)

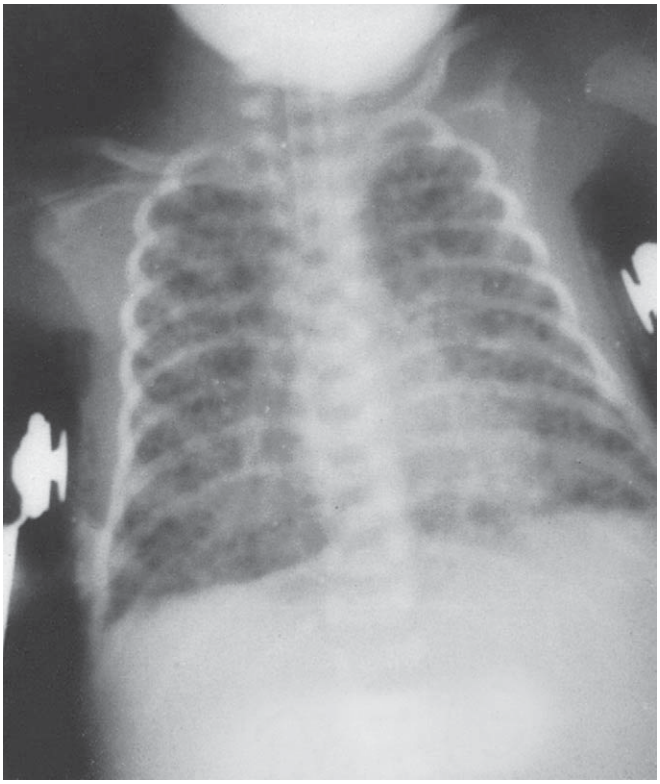


Figure 23-2 ■ Severe (stage III) bronchopulmonary dysplasia. The small radiolucent vacuoles have expanded. They are now cysts, representing multifocal emphysema. Dense patches are collapsed alveoli, interstitial edema, and fibrosis.

patches, which themselves have been smaller than previously described (Fig. 23-2). The dense patches, compressed by expanding air cysts are evidence of progressive multifocal emphysema. The dense patches, compressed by expanding air cysts, are largely indicative of alveolar collapse, edema and fibrosis of the interstitium, and distension of lymphatics.

In advanced disease, the lungs appear bubbly on radiography as air cysts continue to enlarge. Opacities are further reduced in size to strands, streaks, and small patches as cysts expand. Overall, the lungs are extensively hyperinflated and emphysema has progressed considerably (Fig. 23-3). The presence of cardiomegaly usually portends right-sided heart failure.

Several reports[226-229] have aptly indicated that this classic progression through the radiographic stages first described by Northway et al, has largely disappeared. Thus the dense opacification that was described for stage II is now uncommon; the bubbled pattern that characterized stage III is likewise infrequent. The appearance of advanced disease is less dramatic. Hyperexpansion is less severe and the typical streaky opacities between large areas or radiolucency are not so pronounced; rather, the streaks are somewhat delicate and their dispersion throughout hyperexpanded lungs is more uniform. These subtle radiologic abnormalities are nevertheless associated with a persistent need for O_2 therapy for several weeks, whether by hood, nasal cannula, or ventilator. The chest radiograph often is optimistic compared to the actual severity of pulmonary pathophysiology. In more than half of published cases, x-ray appearance "lagged behind" the actual stage of pathology.[229] Despite the clinical course, the radiographic changes may remain subtle for as long as 3 weeks. Hyperexpansion is marginal; streaky densities are discernible, but their significance is

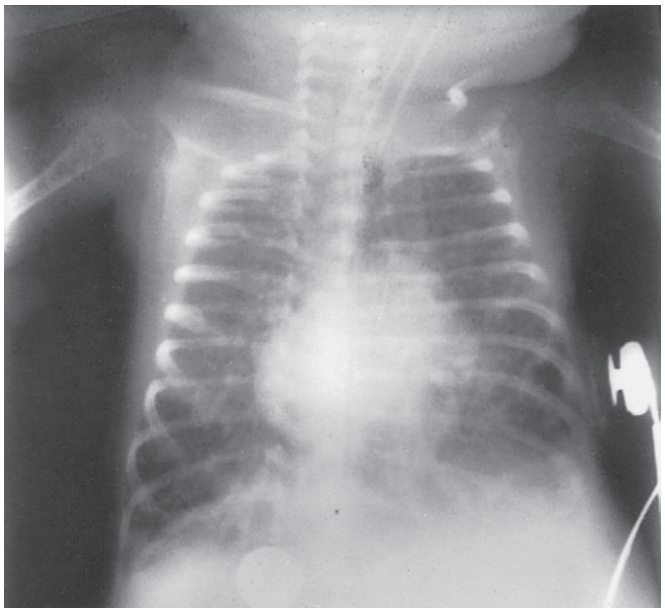


Figure 23-3 ■ Advanced (stage IV) bronchopulmonary dysplasia. The lungs are now bubbly because air cysts continue to expand. The lungs are extensively hyperinflated. (From Korones SB: High-Risk Newborn Infants: The Basis for Intensive Nursing Care, 4th ed. St. Louis, Mosby, 1986, p. 262.)

equivocal. At approximately 3 to 4 weeks, the radiographic changes are more clearly indicative of BPD.

Management

Respiratory Support

Mechanical ventilation both induces and treats BPD. The goals in maintaining mechanical support are brevity of duration and attenuation of vigor, each of which is ultimately influenced by the severity of disease and by care providers.

A number of techniques for the support of neonatal respiratory failure have been formulated and tried with primary goals of providing maximum benefit and minimal damage, using CPAP, permissive hypercapnia, conventional pressure-limited ventilation, high-frequency ventilation, synchronized ventilation, and volume-targeted ventilation. Reviews of these strategies consistently conclude that by rigid clinical trial, no technique has proven to lessen the incidence of BPD or death.[230-237] A variety of technologies have been tested and there is little agreement about the value of any of them—even the simple administration of oxygen by flow.[238]

Nasal continuous positive pressure (nCPAP) is now widely used to avoid intubation and mechanical ventilation. There are a number of studies that suggest a diminished incidence of BPD with more frequent use of nCPAP and sparing use of mechanical ventilators.[237] In 1987, Avery et al.[73] reported a survey of BPD incidence among eight centers; one of them (Columbia University) had the lowest rate. The authors recorded several differences in practices between Columbia and the other institutions that were observed: At the Columbia unit, nCPAP was used soon after birth for respiratory distress; elevated $PaCO_2$ was allowed to a level of 60 mmHg before intubation was initiated; muscle relaxants were not used; most infants were in incubators by 1.0 hour postnatally; and a single physician supervised ventilatory support. The more frequent use of nCPAP was thought to be most significantly associated with the diminished incidence of BPD.

More than a decade later, Van Marter et al.[29] compared practices at Columbia in New York to two hospitals in Boston. There was a significantly higher rate of BPD in Boston, which was attributed to more frequent use of mechanical ventilation than in New York. In another study, the role of early CPAP remained questionable in two compared hospitals, one in Boston and the other in Stockholm.[239] The author's main claim was that "less aggressive" respiratory management was associated with less oxygen dependency at 40 postmenstrual weeks. Boston had a significantly higher incidence of "moderate-severe BPD."

In recent years, mechanical ventilation has often been avoided by use of nasal CPAP, even from the first minutes after birth in the smallest babies.[240] Several investigators have observed a marked diminution in BPD rates as a consequence.[241-243] Duration of ventilatory support and length of hospital stay are also diminished with preferential use of nasal CPAP. When applied after extubation, nCPAP reduces the incidence of reintubation and respiratory difficulties such as apnea and respiratory acidosis.[240,241,244-246]

Most recently a multicenter, international, randomized trial (COIN Trial investigators) assessed the possibility that nCPAP applied shortly after birth instead of intubation and ventilation, would diminish the rate of BPD or death in very preterm infants.[235] They randomized 610 infants at 25 to 28 gestational weeks to nCPAP or to intubated mechanical ventilation within 5 minutes after birth. Early nCPAP did not significantly diminish the rate of BPD or death. Forty-six percent of the infants randomized to nCPAP were intubated later during the first 5 postnatal days. There were fewer days of ventilation in the CPAP group, and fewer CPAP infants received oxygen at 28 postnatal days, but not at 36 postmenstrual weeks. Outcomes of the CPAP and intubated groups were similar at 36 postmenstrual weeks. Pneumothorax occurred in 9% of the CPAP infants and in 3% of the intubated infants.

The value of early CPAP as a replacement of intubation and mechanical ventilation apparently remains to be established. This large randomized international study (COIN Trial) has not narrowed the gap between those investigators who are convinced that early nCPAP diminishes the incidence of BPD and those who do not. The controversy has even taken on an international, quasi-theatrical flavor with pro-CPAP "softly-softly Danes and Swedes and the Columbia neonatologists" on one side, and the "hard-line neonatologists mainly in North America and the UK" on the other.[233,234,247]

The difficulties become more apparent when one considers the outcome of a cluster-randomized study by the Neonatal Research Network (NICHD).[248] Carefully designed and meticulously executed, this group of institutions activated a number of prescribed better practices at seven intervention hospitals, whereas seven control institutions used unchanged practices. With benchmarked best practices, it was postulated that rates of survival without BPD would be augmented. The benchmarking and multimodal quality improvement successfully changed practices at the intervention hospitals, but the rates of BPD did not change.

A variety of nasal CPAP delivery modalities have additionally been evaluated (continuous flow, variable flow, bubble CPAP, nasal prongs, nasopharyngeal tubes, face mask), but the superiority of one over the other also has not been established. Although nasal CPAP seems to improve a number of measured outcomes (less oxygen, shorter duration of mechanical ventilation), the avoidance of mechanical ventilation is probably the pivotal benefit. Among infants for whom respiratory support was unavoidable, Van Marter et al.[29] found an elevated risk of BPD when, on the day of birth, peak inspiratory pressure (greater than 25 cm H_2O) and FIO_2 (1.0) were high.

If mechanical support is unavoidable, respiratory settings must minimize barotrauma-volutrauma and O_2 toxicity. PaO_2 should be maintained between 50 and 70 mm Hg; $PaCO_2$ may rise to 55 mm Hg provided pH does not fall below 7.20. A meta-analysis from the Cochrane Neonatal Review Group[249] involving only two studies found no evidence to support the use of "permissive hypercapnia" to prevent or reduce morbidity and mortality. In a recent report that reviewed the subject, Miller and Carlo[250] cautioned that more research and additional outcome data are required. They indicate, however, that maintaining $PaCO_2$ values over 40 mm Hg in preterm babies is safe and beneficial.

Inspiratory times should generally range between 0.3 and 0.4 second; flow rates of 5 to 7 L/min are desirable. PEEP is variable. It may be required at levels of 6 cm H_2O to minimize airway resistance and to enhance alveolar ventilation. Inappropriately high levels of PEEP impair alveolar ventilation, diminish lung perfusion and cardiac venous return, and increase the intensity of barotrauma-volutrauma. FIO_2 must be maintained at levels that provide optimal PaO_2. FIO_2 may vary extensively. Excessive concentrations may worsen hyperoxic lung damage and enhance the possibility of ROP. Inappropriately low FIO_2 may induce pulmonary vasospasm and/or bronchospasm with resultant increases in frequency of apneic episodes and hypoxia.

Weaning from mechanical support must be slow and gentle. When peak pressure is gradually reduced to 12 cm H_2O and FIO_2 is lowered slowly to 0.4, the respiratory rate can be reduced, generally in decrements of five breaths. Establishment of spontaneous breathing requires gradual diminution of dependence on mechanical support. Patient-triggered ventilation is an effective weaning device.

Evaluation of arterial blood gases by percutaneous arterial sampling is impractical because spurious results from the painful sampling procedure preclude accurate values. The same may be said for capillary sampling, which is equally painful and often inaccurate.[251] Transcutaneous PaO_2 determination is not reliable after a few days postnatally. Oxygen saturation by pulse oximetry is the most practical method currently in use. Arterial O_2 saturations between 90% and 95% usually indicate a PaO_2 of no less than 50 mm Hg and no more than 100 mm Hg.[252,253] Observational studies suggest that oxygen saturation maintained between 80%/85% and 92%/95% are effective in reducing the incidence of ROP.[180-183]

After the infant is weaned from the ventilator, O_2 supplementation may be essential for protracted periods of time, delivered through a hood, nasal cannula, or nasal CPAP. The flow rate delivered by nasal cannula cannot be directly correlated with specific FIO_2, but useful calculated estimations can be reliably applied.[254] Adequate arterial O_2 levels should be maintained as steadily as possible so that pulmonary vasoconstriction is minimized.[173,255] Pulmonary vessels are exquisitely sensitive to periods of hypoxemia. Resultant vasoconstriction can be relieved by an enhanced FIO_2. Frequent periods of hypoxemia or ongoing marginal oxygenation raise pulmonary artery pressure, further stressing right-sided heart function. Desaturation after oral feeding is common but is not generally appreciated.[256] Desaturation is accentuated by fast feeding and larger-volumes.

Diuretics

Pulmonary edema (interstitial and alveolar) is intrinsic to the changes of BPD, particularly in earlier stages of the disease process. The accumulation of fluid impairs (diminishes) compliance, thereby decreasing tidal volume; whereas narrowed terminal airways increase resistance to flow.[257-259] Positive lung fluid balance is a consequence of excess fluid delivery or diminished fluid egress, or both. The imbalanced accumulation of lung fluid may be a consequence of several factors including iatrogenic fluid overload, increased capillary permeability caused by the inflammatory responses to lung trauma (volutrauma-barotrauma), to hyperoxia or infection, and to pulmonary hyperperfusion resulting from large left-to-right shunts across a patent ductus arteriosus.[260,261]

Enhanced reabsorption of lung fluid appears to be the principal benefit of diuretic therapy. Two different mechanisms converge to augment lung fluid egress by reabsorption.[260] One of them is unrelated to diuresis. It involves almost immediate reabsorption of lung fluid by virtue of expanded venous capacitance, which reduces pulmonary blood flow and in turn increases absorption and/or decreases fluid filtration. Vasodilation has been attributed in animals to increased prostaglandins stimulated by furosamide.[262] The second mechanism of lung fluid evacuation is diuresis, somewhat delayed, that reduces extracellular fluid volume by increasing plasma oncotic pressure.[260] Removal of excessive lung fluid improves pulmonary mechanics. Furosemide is a loop diuretic. Its effect is largely attributable to inhibition of the 2 Cl^-, Na^+, K^+ cotransporter, which minimizes absorption of sodium, potassium, and chloride in the thick ascending limb of Henle. The result is diuresis with significant excretion of these electrolytes, as well as excretion of phosphorus, calcium, and magnesium.[260]

Half-life and bioavailability of furosemide have important clinical implications in determination of dose intervals and routes of administration. Half-life shortens progressively as gestational age lengthens. In the study by Mirochnick et al.,[263] at postconceptional age of less than 31 weeks, half-life frequently exceeded 24 hours. At a postconceptional age of 33 weeks, half-life shortened to less than 12 hours; and at term, it was as short as 4 hours. Thus patients of shorter postconceptional age, who frequently have furosemide half-lives of greater than 24 hours, should be given furosemide no more frequently than once daily. More frequent administration, especially to infants less than 29 weeks postconceptual age, often results in excessive plasma accumulations that are potentially ototoxic. At ages greater than 32 weeks, dosing every 12 hours is appropriate.

Bioavailability must be considered when determining dose according to route of administration. An enteral dose of 2 mg/kg of furosemide is generally accepted as equivalent to an intravenous dose of 1.0 mg/kg.[260,263]

Careful monitoring is mandatory in BPD infants who are treated with diuretics. Electrolyte and mineral imbalances are frequent, and supplements of potassium, sodium, and chloride often are necessary. Treatment-induced hypokalemia and alkalosis may occur if the dose of the diuretic is large or repeatedly given over time, if sodium and chloride intake are inadequate, or if KCl supplement is not administered. Infants with ongoing BPD usually have a compensated respiratory acidosis because of renal retention of bicarbonate. A pH of 7.30 to 7.40 is expected in the usual course of BPD, hypercapnia notwithstanding. However, a diuretic-induced primary metabolic alkalosis causes higher pH and hypoventilation. Thus, with an apparently elevated pCO_2, an increased dose of diuretic would seem appropriate at first thought, but in fact the dose should be reduced to alleviate the primary diuretic-induced metabolic alkalosis and hypercarbia.[258]

Furosemide may cause hypercalciuria that advances to nephrocalcinosis when calcium is deposited in renal interstitial tissue. The etiologic role of furosemide is not as clear as is generally believed. The first report of nephrocalcinosis in preterm babies in 1982 cited a major etiologic role for furosemide.[264] Since then, the reported incidence in all premature babies has varied from 20% to 64%.[265] Karlowicz et al.[266] emphasized family history of kidney stones and white race as the most important determinants of nephrocalcinosis. Jacinto et al.[267] reported overall incidence of 64%. Most, but not all, of the affected infants had received furosemide.

Multifactorial origin was emphasized in another study of nephrocalcinosis, which was identified in 16% of all babies less than 32 weeks' gestation. These authors cited extreme prematurity, severe respiratory disease requiring ventilation, male sex, frequency and duration of gentamicin administration, and high urinary oxalate and urate excretion as major causes. Approximately half of affected infants received furosemide.[265] In a follow-up study of nine patients, Ezzedeen et al.[268] found that at a mean age of 21.3 months, calcification improved in five patients and resolved completely in four. Pope et al.[269] reported resolution of calcification 5 to 6 months after cessation of furosemide therapy in 50% of treated infants. Jones et al.[270] studied 11 premature children with calcifications and 17 controls. Children in both groups were 4 to 5 years old. They concluded that renal calcification in the neonatal period does not seem to be a major predisposition to abnormal renal function at a later age. Ototoxicity has also been associated with long-term furosemide use.

These undesirable side effects notwithstanding, the benefit of improved pulmonary function that is achieved with long-term diuretic treatment is believed to outweigh the hazards.[54] The most recent Cochrane review of loop diuretic therapy for BPD concluded that (1) in infants less than 3 weeks' postnatal age, the effect of furosemide is either inconsistent or undetectable; (2) in infants greater than 3 weeks of age, chronic administration of furosemide improves oxygenation and pulmonary mechanics; and (3) there is little evidence for benefit of furosemide on ventilatory support, length of hospital stay, survival or long-term outcome.[260]

Thiazide diuretics (chlorothiazide and hydrochlorothiazide) are used in combination with spironolactone, which is potassium sparing. Studies on the short-term effectiveness of diuretic therapy with these preparations are inconclusive,[271] but a study by Kao et al.[272] indicated long-term effectiveness of spironolactone and chlorothiazide in improving pulmonary function. In extubated O_2-dependent infants, a lower FIO_2 was possible, but the duration of dependency was unaffected.[272] A Cochrane review indicates that only a few infants have been studied in randomized trials,[259] but in infants older than 3 weeks, thiazide and spironolactone improved lung compliance after 4 weeks of treatment. Only one study in that meta-analysis showed significantly reduced mortality among intubated infants.

Bronchodilators

The treatment of acute and sometimes life-threatening episodes of severe bronchospasm requires a rapid response to bronchodilator therapy. Increased airway resistance is characteristic of the moderate and advanced stages of BPD. Control of bronchial smooth muscle tone is probably the most prominent factor in acute bronchospastic episodes. Bronchial hyperreactivity is a characteristic component of BPD. Its early appearance sometimes heralds the onset of BPD, and occasionally the hyperreactivity persists even after the infant is relatively asymptomatic.

Bronchodilator therapy is used for acute bronchospastic episodes. For acute episodes, beta-adrenergic agonist therapy is generally used. Sometimes, anticholinergic therapy is given as an adjuvant. Albuterol is a specific $beta_2$-adrenergic agent that effectively reverses acute episodes of bronchospasm and causes few cardiovascular side effects. Lung compliance increases and airway resistance decreases within minutes of inhalation treatment. The effect lasts for approximately 4 hours. Cardiovascular side effects are less frequent with albuterol than with the other $beta_2$-agonists, such as isoproterenol and metaproterenol. The side effects from the latter two preparations include tachycardia, hypertension, hyperglycemia, and tremor. Albuterol is more specifically a $beta_2$-agonist than the other preparations and is currently the bronchodilator of choice. Atropine is less effective than the beta-agonists. Side effects include tachycardia, diminished intestinal motility, tremor, and inspissations of airway secretions. Ipratropium bromide is another anticholinergic preparation that dilates airways, principally the larger ones.[271]

Theophylline and caffeine are weak bronchodilators compared with the $beta_2$-agonists. Caffeine is the weaker of the two drugs. These preparations also have diuretic and respiratory stimulation effects. Their weak bronchodilating activity has led to their infrequent use in ongoing treatment.[271]

Corticosteroids

Prenatal use of glucocorticoids is known to diminish the incidence of RDS by 50%, and the recommendation of the Consensus Conference on Antenatal Steroids remains unchanged.[273] There is a strong suggestion, however, that maternal betamethasone in two doses given 12 hours apart is preferred to other preparations and other schedules.[274] If the benefit and safety of a single course of prenatal steroids are now accepted widely, the status of repeated antenatal courses of treatment is unsettled.[275] The incidence of BPD has not been shown to diminish after administration of antenatal steroids.

Postnatal use of glucocorticoids was widespread for a number of years[276] until poor neurodevelopmental outcomes were reported in an abstract by Yeh et al.[277] in 1997, fully published 1 year later.[278] Subsequently, other studies suggested similar adverse outcomes. In February 2002, a negative advisory jointly issued by the American Academy of Pediatrics and the Canadian Pediatric Society[279] reviewed the "short- and long-term effects of systemic and inhaled corticosteroids for prevention or treatment of evolving or established chronic lung disease." Short-term benefits were limited and long-term benefits were absent. Routine use of systemic dexamethasone for these purposes was "not recommended." Use of steroids postnatally should be limited to appropriate trials. Clinical use should be limited to serious situations in which maximal respiratory support is

already in place. Parents should be fully informed regarding short- and long-term effects and risks, and they should agree to the use of steroids.

Postnatal steroids have been widely used to ameliorate or prevent BPD. In 1983, Mammel et al.[280] reported more rapid ventilatory weaning with steroid therapy, and those observations were confirmed in 1985 by Avery et al.[281] Lung compliance was shown to increase. Steroid treatment suppressed inflammatory mediators, lung function improved demonstrably, and earlier extubation was achieved.

Postnatally administered steroids are effective by virtue of several mechanisms.[282,283] Steroids are powerful antiinflammatory agents, a probable fundamental reason for their effectiveness. They diminish the attraction and aggregation of polymorphonuclear leukocytes in the lung,[284] and they lessen the elaboration of prostaglandins, elastase, leukotrienes, interleukins, and tumor necrosis factor. Ultimately, they diminish the permeability of the pulmonary microvasculature and therefore minimize pulmonary edema. They increase diuresis and heighten beta-adrenergic activity. They dilate airways and may enhance the synthesis of surfactant and antioxidants. These responses alleviate pulmonary inflammation, edema, fibrosis, and bronchospasm. Lung compliance increases and airway resistance diminishes; allowing for diminished respirator pressures and FIO_2.

The acute adverse effects of dexamethasone are multiple; their frequency is low.[285] Earlier reports on the incidence of severe infections have not materialized in the trials of BPD. Among the acute side effects, hypertension is quite common.[281,286,287] Gastrointestinal complications include perforated gastric and duodenal ulcers and life-threatening upper gastrointestinal hemorrhage.[288,289] Hyperglycemia is common.[286,290-293] Occasionally, insulin may be required. Adrenal gland function is suppressed during the treatment period. The effect is apparently temporary,[294,295] adrenal responsiveness is fully restored within 4 to 5 weeks after discontinuation of steroid therapy.[296] Obstructive hypertrophic cardiomyopathy, which is reversible, has also been reported.[297,298] In one report, the cardiac effects were transient, reaching maximum intensity by week 3 of treatment and disappearing by week 6 of treatment.[298] Thickness was increased in the interventricular septum and in the right and left ventricular free walls.

Holliday and Ehrenkranz[299] published three Cochrane reviews on the use of postnatal steroids that they classified by age at onset of treatment.[299-301] In studies of treatment within the first 96 postnatal hours, steroids were given intravenously.[299] All studies except two used dexamethasone. Short-term effects were encouraging. Steroid treatment significantly diminished the combined outcome of BPD and death to the time of discharge, but there was no effect on mortality itself. The incidence of BPD was diminished, and weaning from the ventilator was easier. Acute side effects included hypertension, hyperglycemia, gastrointestinal bleeding or perforation, and hypertrophic obstructive cardiomyopathy. Pulmonary air leak and patent ductus were decreased, and there was no increase in infection, necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), or severe ROP. A relative risk of 1.41 for periventricular leukomalacia was calculated.

The studies of infants who were treated from 7 to 14 postnatal days[300] all used dexamethasone given intravenously for 2 to 42 days. BPD combined with death was decreased at 28 days' postnatal age (PNA) and at 36 weeks' PMA, but mortality itself was not diminished. BPD incidence was decreased at 28 days' PNA and 36 weeks' PMA. Extubation at 7 and 28 days after onset of treatment was more likely in dexamethasone-treated infants. Duration of hospitalization and need for supplemental oxygen were unchanged. Incidence of pneumothorax, severe ROP, intraventricular hemorrhage, and NEC were unaffected by dexamethasone.

In the studies of infants whose therapy was initiated beyond 3 postnatal weeks,[301] dexamethasone was given intravenously or enterally for 3 days to 3 weeks. Combined outcome of BPD and death was diminished in the treated group, but survival to discharge was unchanged. Dexamethasone increased lung compliance and decreased the need for supplemental oxygen; thus there was a marginally significant diminution of BPD at 36 weeks' PMA. Treated infants were at risk for hypertension but not for infection, NEC, or gastrointestinal bleeding.

Watterberg[302] and Finer et al.[303] point out three studies[278,304,305] that have shown a significantly higher incidence of neurodevelopmental dysfunction associated with pharmacologic doses of dexamethasone. Meta-analysis of the three studies revealed increased odds ratios for the occurrence of cerebral palsy or abnormal findings on neurologic evaluation. For every three to four treated survivors, one child would have an abnormal neurodevelopmental outcome.[303] Mertz et al.[306] reported an increased incidence of periventricular leukomalacia among steroid-treated infants (23% versus 9% in controls). In another extensive review, O'Shea and Doyle[307] expressed similar concerns about long-term outcomes. Barrington[308] commented that pharmacologic doses should be abandoned, estimating that for every 30 infants treated, there will be four extra infants with cerebral palsy and three extra infants with some form of neurodevelopmental dysfunction.

Forty controlled studies on use of dexamethasone were identified involving more than 4000 neonates in a meta-analysis by Banks.[309] Only 18 studies ($n = 2613$) were included in the meta-analysis. Treating 100 ventilated infants with dexamethasone in the first 48 postnatal hours would result in 11 fewer instances of death or BPD at 36 weeks' PMA. Among infants so treated, there would be approximately 4 with gastrointestinal hemorrhage and 18 children with cerebral palsy and abnormal neurodevelopmental outcomes. Yeh et al.[274] studied the school age outcomes of children who participated in their study of dexamethasone administration within 12 hours after birth and tapered over the following 28 days. The incidence of BPD was reduced, but more important, there were significantly more adverse effects on neuromotor and cognitive function, as well as somatic growth in the dexamethasone children.[274]

The accumulated evidence that adverse neurodevelopmental outcomes are the likely results of early high-dose dexamethasone has led to a substantial reduction in its routine use.[310,311] A report from Israel describes a temporal association between an increased need for prolonged oxygen therapy and a diminished use of dexamethasone.[310]

Despite the reductions in steroid therapy, steroid use by neonatologists persisted.[311,312]

The improved respiratory function that so often follows steroid therapy continues to stimulate the search for a substitute steroid, or an effective regimen using lower doses of dexamethasone. Watterberg et al.[313] described a multicenter trial of low-dose hydrocortisone in which there was a significant increase in survival, and survival without BPD, in treated babies, but only those who had been exposed to chorioamnionitis. A follow-up report of outcomes at 18 and 22 months corrected age indicated that early low-dose hydrocortisone did not increase the incidence of cerebral palsy and seemed to benefit neurodevelopment as observed at the time of follow-up.[314]

In the Netherlands, a cohort of 226 preterm babies was followed and evaluated at 8 years of age.[315] They represented a 2-year cohort of neonates who were treated in a single center between 1991 and 1993, where hydrocortisone was the drug of choice to prevent pulmonary injury. Treatment was initiated at a median age of 19 days and was tapered over a 22-day period. Treated children were compared at follow-up to controls that had not been treated with steroids soon after birth. There were no differences between the treated and control group at the 8-year follow-up evaluation. Motor and cognitive dysfunction and cerebral palsy were similarly frequent in both groups. Brain lesions on MRI were no different. The authors had previously reported no difference between the two groups in total intracranial volume, total gray or white matter, and cerebrospinal fluid and hippocampal volume. Survival rates were no different between the two groups. The authors concluded that their neonatal treatment of BPD with hydrocortisone did not adversely affect neurodevelopmental outcome or magnetic resonance imaging (MRI) findings at school age.

Value of hydrocortisone for the management of BPD must be fully determined before we find ourselves in the midst of another therapeutic episode of enthusiastic overuse. Watterberg has appropriately commented that the role of glucocorticoid therapy will be based upon "the drug, the dose, the timing and the length of therapy." Such data were not available during the years when dexamethasone was a standard of treatment for BPD.

Extraneous Air Syndromes (Air Leaks)

Extraneous air syndromes are a group of clinically recognizable disorders initially produced by alveolar rupture with subsequent escape of air into tissue in which air is not normally present. Table 23-2 lists the sites in which extraneous air has been reported. All the clinical variations of air leak syndromes originate in overdistended alveoli, which ultimately rupture. Overdistension may follow initial spontaneous vigorous respirations (usually larger term babies) at birth, high pressure with mechanical ventilation (either PEEP or peak inspiratory pressure), vigorous ventilatory resuscitation, and air trapping in the presence of a ball valve mechanism. Although most of the syndromes have long been known to occur spontaneously, their incidence increased as the use of ventilatory support became widespread, particularly since the advent of PEEP ventilation.[316] The occurrence of air leaks has diminished considerably since the advent of surfactant treatment, and the use of less intense pressure settings for ventilator support. Besides BPD, air leak syndromes are the most frequent life-threatening complications of ventilatory assistance. The capacity for instant recognition, evaluation, and relief of these disorders is a primary requisite for personnel who assume responsibility for sustained neonatal ventilatory support.

TABLE 23-2 Extraneous Air Syndromes

Site of Extraneous Air	Syndrome
Pulmonary interstitium (perivascular sheaths)	Interstitial emphysema
Alveoli-trabeculae-visceral pleura	Pseudocysts
Pleural space	Pneumothorax
Mediastinum	Pneumomediastinum
Pericardial space	Pneumopericardium
Perivascular sheaths (peripheral vessels)	Perivascular emphysema
Vascular lumina (blood)	Air embolus
Subcutaneous tissue	Subcutaneous emphysema
Retroperitoneal connective tissue	Retroperitoneal emphysema
Peritoneal space	Pneumoperitoneum
Intestinal wall	Pneumatosis intestinalis
Scrotum	Pneumoscrotum

Incidence

Few authors have reported the combined incidence of all of the air leak syndromes. Kirkpatrick et al.[317] were one of the few teams of investigators who did so, but their numbers were small. Fifteen of their 37 infants (41%) with RDS developed one or more of the syndromes. Their case reports included pulmonary interstitial emphysema (PIE), pneumomediastinum, pneumothorax, pneumoperitoneum, and air embolus. Yu et al.[318] also reported on air leaks as a group; 11% of infants with RDS (with or without ventilatory assistance) developed pneumothorax, pneumoperitoneum, or interstitial emphysema. Although Thibeault et al.[319] appropriately considered interstitial emphysema, pneumomediastinum, and pneumothorax as a single pathologic continuum, they did not cite incidence. Most reports describe selected clinical syndromes to the exclusion of others. A true estimate of the frequency of air leak should include all of its manifestations.

Incidence varies according to the type and severity of disease, gestational age, mode of therapy, and expertise of personnel. Complications are most frequent during treatment for RDS. Interstitial emphysema and pneumothorax, for example, were observed more often in babies with RDS than in infants with other disorders.[319,320] Frequency is also significantly influenced by the vigor of ventilatory assistance, which itself is usually a reflection of the severity of disease and "style" of ventilator support. Berg et al.[316] observed that interstitial emphysema, pneumothorax, and pneumomediastinum occurred twice as often with the use of PEEP (39.7%) than without it (20.7%). In babies with RDS, Ogata et al.[321] noted that the frequency of pneumothorax increased as therapy became more vigorous. Only 3.5% of infants were affected when assisted ventilation was not used; 11.0% when total management consisted of

CPAP, 24.0% when CPAP was used at first and IPPV with PEEP later; and 3.3% when only IPPV and PEEP were used throughout the course of treatment.

Pneumopericardium was described as a "very rare condition" in neonates by Matthieu et al.[322] in 1970. These authors could find descriptions of only seven cases. In 1974, Yeh et al.[323] found 13 cases in the English literature since 1942, yet they reported four infants they had observed within a 12-month period. In 1976, Brans et al.[324] described six babies with pneumopericardium in an interval of 6 months in their intensive care unit. They found 57 cases in their review of the literature. Pneumopericardium, a "very rare condition" in 1970, increased in frequency until the early 1990s. Most reports allude to a relationship between the increased frequency of pneumopericardium and the vigor of ventilatory therapy. A similar course of events has been noted for pneumoperitoneum. The association of pneumoperitoneum with extraneous air in thoracic structures probably indicates transdiaphragmatic passage of air into the peritoneal space, which strongly suggests the absence of gastrointestinal perforation. It was a rare event in 1972,[325,326] but it was not unusual just a few years later.[317,327,328]

Most clinical trials of surfactant have demonstrated a striking reduction in the incidence of pneumothorax among treated versus control babies.[329] Extraneous air syndromes will continue to occur; however; their incidence remains related to high ventilator pressures and severe disease.

Pathogenesis

The 1939 publication by Macklin[330] and the masterful 1944 review of Macklin and Macklin are the basis for our contemporary understanding of the extraneous air syndromes. Macklin postulated that all air leaks are caused by high intra-alveolar pressure that follows inhalation, insufflation, or retention of inordinately large volumes of air. The resultant pressure gradient from affected alveoli to adjacent tissue space may be of sufficient magnitude to rupture the bases of alveoli that overlie capillaries. Air escapes through the meshes of capillaries. It enters perivascular sheaths and migrates toward the hilum. More recent observations indicate that, in addition to the phenomena observed by Macklin, a somewhat different mechanism prevails in immature, surfactant-deficient lungs.[331-333] In the immature lung of baboons, rupture occurs in the small, compliant terminal airways rather than in the noncompliant, unexpanded, more distant saccules (premature alveoli).[334] The result is the more frequent occurrence of PIE that usually does not progress to pneumothorax. Often, extrusions of air occur in contiguous connective tissue, and at times, in trabeculae through which air migrates to pleura, forming blebs which apparently burst into the pleural space.

Macklin also speculated that atelectasis poses a considerable risk for rupture of the adjacent expanded alveoli because they become overdistended when, during inspiration, negative pressure is applied to a reduced number of distensible alveoli for a prolonged time interval. The result is overdistension and rupture. In a lucid discussion published in 1963, Chernick and Avery[335] applied Macklin's reasoning when they postulated the pathogenesis of spontaneous pneumothorax occurring during the first few breaths of the newborn infant. When aspirated mucus or meconium prevents expansion of a sufficient number of alveoli, overdistension of already expanded alveoli causes their spontaneous rupture soon after birth. During the first few breaths, normal infants create intrapleural pressures that are 40 to 100 cm H_2O below atmospheric.[336] When this negative pressure is transmitted to atelectatic areas, there is no gradient between unexpanded alveoli and the pleural space. However, a gradient does exist between pleural space and distended alveoli. When a significant portion of the neonate's lung remains unexpanded during peak inspiration, the gradient between intra-alveolar and intrapleural pressures in the expanded areas is higher and sustained for a longer period of time than is normal. Apparently, the resultant elevated and protracted tension on alveolar walls causes spontaneous ruptures.

Air in perivascular sheaths dissects toward the hilum and invades the mediastinum and thus causes pneumomediastinum. Air bubbles may accumulate at the hilum to form large blebs that sometimes compress hilar vessels. The blebs are situated where the visceral pleura reflects onto the parietal pleura. As pressure mounts, rupture of blebs at this location releases air into the pleural space to give rise to pneumothorax. Apparently, air also passes from other points in the mediastinal wall to the pleural cavity. The pathway and mechanism of extension to the pericardial space are still conjectural. The point of invasion by air may be where the pericardium reflects onto pulmonary vessels to join the pleura. Figure 23-4 depicts the migration of air from alveolar rupture through the lung interstitium (*A*) into the pleural (*B*) and the pericardial (*C*) cavities (the chest films in Fig. 23-4 correspond to the diagrams).

Far-flung dispersion of air was noted experimentally in cats by Macklin.[330] He described "freshlets breaking through downward" to enter the retroperitoneal space and upward into the neck, chest wall, arm, axilla, and face. Pneumoperitoneum is thought to result from the extension of mediastinal air along the great vessels and esophagus into the retroperitoneal space and from there to the peritoneal cavity after rupture through the posterior peritoneum.[325,326,330] Pneumoscrotum is sometimes associated with pneumoperitoneum. Presumably, migration of air occurred from the peritoneal cavity through the processus vaginalis into the scrotum. Air embolism occurs when extremely high pressures are used for ventilatory assistance. Air may be injected directly into the pulmonary capillaries at the time of alveolar rupture.[328] Entry into blood vessels has been demonstrated experimentally in dogs when small lacerations were made in lung parenchyma. Thus, in humans, the application of very high peak inspiratory pressure to a lung of low compliance may lacerate the parenchyma, allowing the passage of air under a high head of pressure into blood vessels.[337] Another possible pathway involves the dissection of air through the subadventitial planes of pulmonary veins, thus producing both air embolus and pneumopericardium.[338]

The appearance of extraneous air, regardless of its location, begins with distal airway or alveolar rupture and air leak. The migration of escaped air ensues through tissue planes that offer the least resistance to extension, thus giving rise to a spectrum of clinical syndromes that range

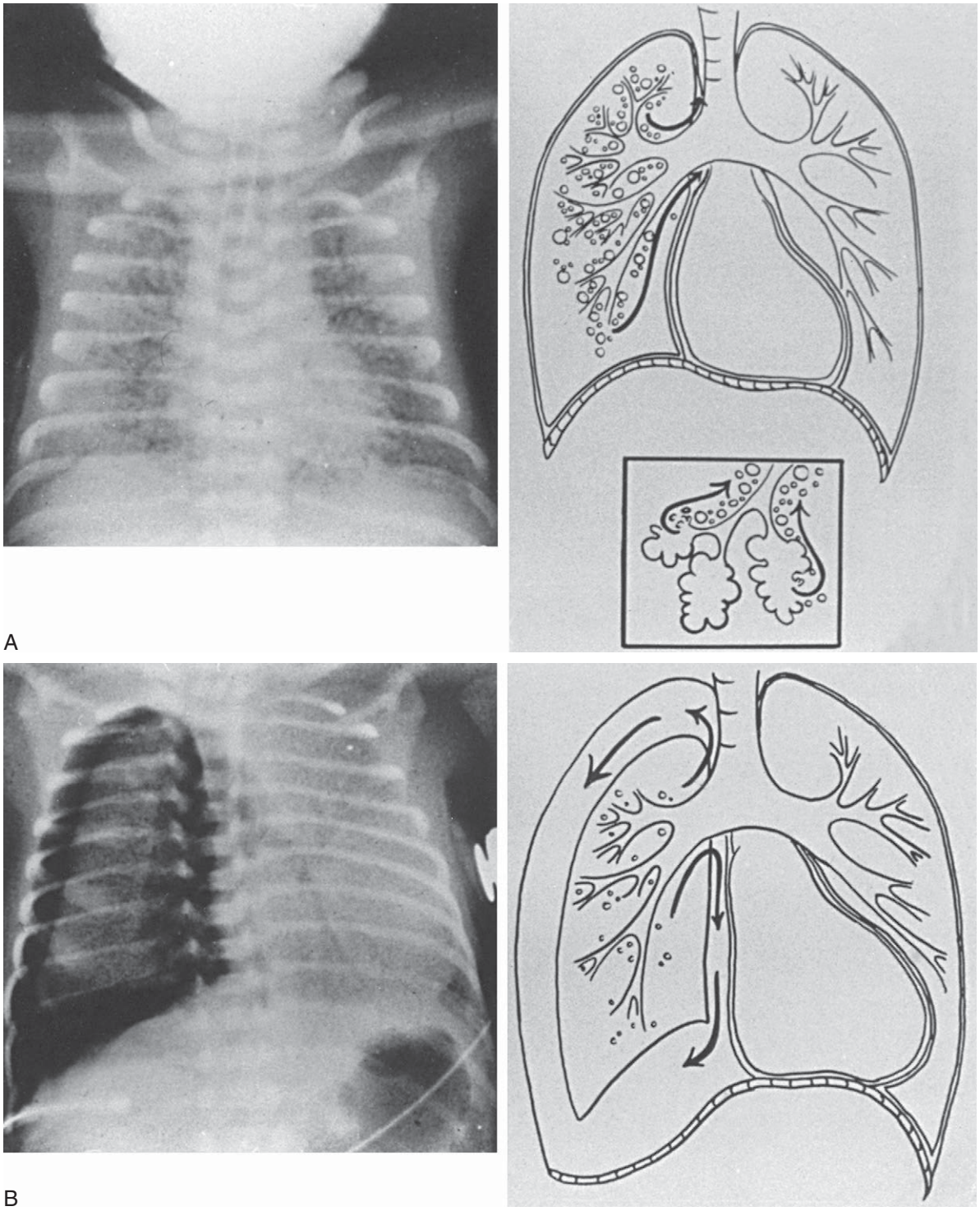
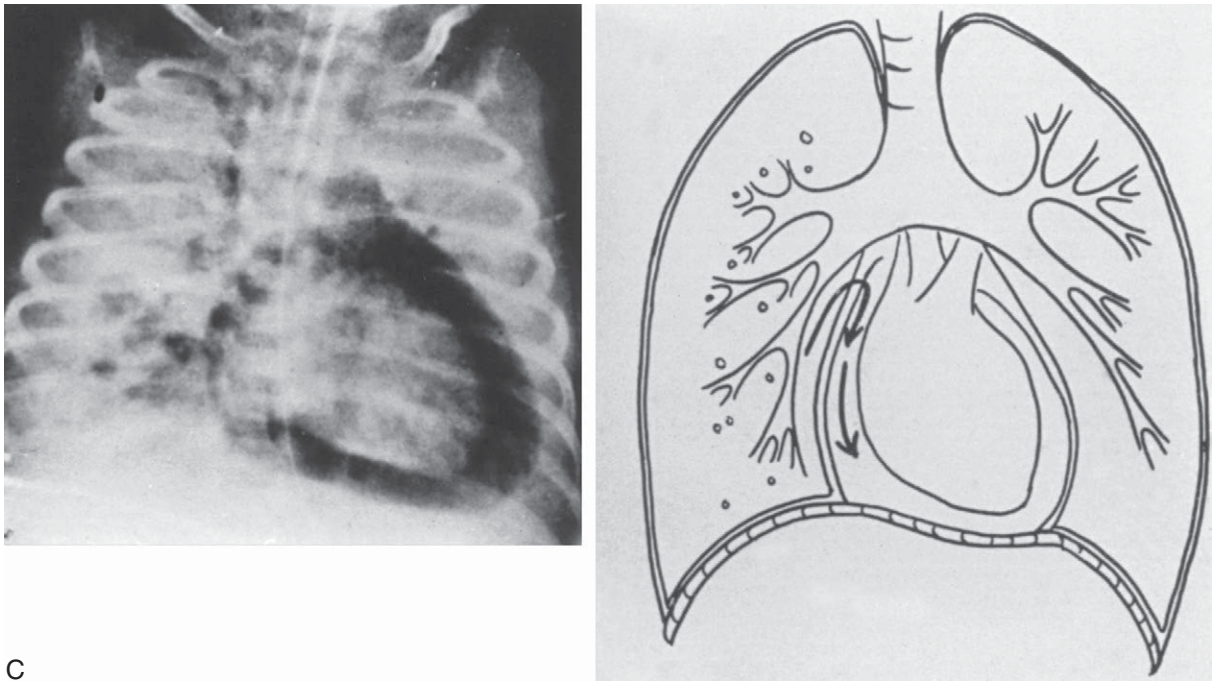


Figure 23-4 ■ **A,** Pulmonary interstitial emphysema. The radiograph shows linear and cystic radiolucencies, which are cast by accumulation of interstitial air. The diagram depicts air leak from a ruptured alveolus (bottom) with escape to interstitial tissue. **B,** Pneumothorax (tension) has compressed a stiff lung, depressed the right side of the diaphragm, and displaced the heart considerably to the left. The diagram indicates a pathway of air from the interstitium into the pleural cavity.

Continued



C

Figure 23-4, cont'd ■ C, Pneumopericardium. Radiograph shows a broad halo of air around the heart. Pulmonary interstitial emphysema affects the right lung. The diagram indicates the path of air from the lung interstitium to the pericardial space. (From Korones SB: High-Risk Newborn Infants: The Basis for Intensive Nursing Care, 4th ed. St. Louis, Mosby, 1986, pp. 252-253.)

from interstitial emphysema and pneumothorax to air embolism and pneumoscrotum.

Clinical Aspects of Extraneous Air Syndromes

Of the 12 syndromes listed in 23-2, only pneumothorax and pneumopericardium require remedial action within minutes lest death or brain damage ensue. On rare occasion, pneumomediastinum and pneumoperitoneum require the same urgent attention. Interstitial emphysema is a serious manifestation of air leak that is associated with a high rate of mortality. Although several treatment modalities have been proposed, no consistently effective treatment is presently available. Air embolus is a fatal event for which no effective therapy exists.

Pulmonary Interstitial Emphysema

Pulmonary interstitial emphysema (PIE) is a consequence of the overdistension of distal airways, and it usually occurs in the smallest babies with the most immature lungs. Ruptured ducts provide a pathway for leakage into connective tissue sheaths that envelop the airways.[331-333] When air accumulates in sheaths, PIE is the result. An alternate description of the distribution of interstitial air was demonstrated by Boothroyd and Barson.[339] Although they could not identify sites of entry, they did demonstrate that the interstitial air largely resided in lung lymphatics.

The onset of abnormal clinical signs is relatively gradual. Most infants develop PIE during administration of mechanical ventilatory support. Oxygen requirements increase, and CO_2 retention may be relentless. Death eventually results from failure to adequately ventilate the baby. The extent to which death is attributable to vascular compression, particularly at the hilum, is unknown. Noncompliant overexpanded lungs impair cardiac venous return because they increase pleural pressure, which may be a reason for the increased incidence of intraventricular hemorrhage in babies with PIE.

Approximately 50% of pneumothoraces are associated with antecedent recognizable PIE. Campbell[340] observed progression to pneumothorax in 13 of 14 infants in whom the preexistence of PIE was unquestionable. Emery[341] noted that PIE was associated with pneumothorax in 11 of 13 necropsied infants. All of the infants studied by Campbell had RDS. All of the babies studied by Emery were born at term and were otherwise well. Mechanical ventilatory assistance was not a factor in either of these studies. In an analysis of 311 infants who received ventilatory assistance over a 12-month period, the author identified 22 infants who had PIE with and without other sites of extraneous air. The gestational age of all 22 infants was 33 weeks or less. Watts et al.[342] noticed a high incidence of PIE during the first 24 hours of life among infants who later developed BPD.

Campbell[340] has clearly described the radiologic appearance of PIE. It is characterized by two basic features: radiolucencies that are linear and those that are cystlike. The linear radiolucencies vary in width; they are coarse and they do not branch. They are seen in the peripheral as well as the medial lung fields. Boothroyd and Barson[339] described the radiologic appearance of lymphatic gas as disorganized and haphazard in distribution. At autopsy, variable distension of lymphatics was microscopically prominent. Medium-sized pulmonary arteries were frequently enveloped by markedly dilated air-filled lymphatics.

Air bronchograms on chest x-rays must be differentiated from interstitial air. Air bronchograms are smooth

branching. They usually are seen toward the hilar regions, particularly in the lower lobes. The cystlike radiolucencies of PIE vary in diameter from 1.0 to 4.0 mm. In some instances, they are oval or lobulated. They may be so numerous that they impart a spongy appearance.

PIE may involve only one lobe, one lung, or more usually, both lungs. It appears within 96 hours of birth in babies who are receiving ventilatory assistance. Attempts should be made to minimize peak inspiratory pressure, shorten inspiratory times, and reduce distending pressures. Usually the development of PIE itself imposes a need for more vigorous therapy. Intubation of the contralateral bronchus when only one lung is involved and "positional therapy" (with the affected lung down) have been used successfully in the management of unilateral PIE. High-frequency ventilation often alleviates PIE within 24 to 48 hours of treatment onset.

Pneumothorax

Pneumothorax can occur spontaneously (no iatrogenic factors implicated), as a result of ventilatory assistance, or rarely as a complication following certain procedures. The incidence of pneumothorax has declined dramatically with the use of surfactant therapy and lower ventilator pressures.

Spontaneous pneumothorax usually occurs during the first few breaths soon after birth. The vast majority of infants are asymptomatic. Radiologic surveys have demonstrated an incidence of 1.0% to 2.0% of all live births;[343] symptomatic pneumothorax, however, has been noted in only 0.05% to 0.07% of live births.[335,344-346] Most investigators have found a higher incidence of spontaneous pneumothorax in full-term infants.[344-346]

In the presence of spontaneous pneumothorax, distress is generally evident in the delivery room or soon after arrival in the nursery. Tachypnea is a universal occurrence. Malan and Heese[346] stressed the frequency and prominence of chest bulge on the involved side. Grunting, retractions, and cyanosis in room air have been noted in virtually all affected infants. As a rule, symptomatic infants have abnormal chest findings that are attributable to lung underexpansion and to displacement of the heart away from the affected hemithorax. Spontaneous pneumothorax is sometimes a manifestation of serious lung disease. It has long been observed in association with meconium aspiration, RDS, transient tachypnea of the newborn, pneumonia, pulmonary hypoplasia with renal anomalies, and diaphragmatic hernia. It has been identified in infants who had RDS syndromes type II (transient tachypnea). Although spontaneous alveolar rupture is sometimes a portent of serious underlying pulmonary disease, most infants have otherwise normal lungs. Approximately 80% to 90% are mildly ill and require no therapy other than O_2 supplementation.[335] Spontaneous pneumothorax and pneumomediastinum often occur in otherwise well babies, most of whom are large and are born at term.

During ventilatory assistance, when pneumothorax occurs, tension pneumothorax is common. Vigilance by expert personnel, particularly nurses, is effective for early detection; a significant number of pneumothoraces can be predicted. Early gestational age, RDS, and high ventilatory pressures are the most significant risk factors. Their presence imposes a high risk for air leak. Predictions based on chest film review are more specific. PIE is a frequent precursor. Campbell and Hoffman[320] reported 31 babies with RDS; PIE preceded pneumothorax in 15 (50%). The shortest interval between radiologic demonstration of PIE and the appearance of pneumothorax was 2 hours; the longest interval was 72 hours. Ogata et al.[321] reported virtually identical observations. Pneumomediastinum is another predictor that has long been identified as an occasional precursor of pneumothorax. Changes in oscilloscopic tracings of cardiac activity are often valuable signs.

Identification and relief of pneumothorax can be accomplished within a few minutes after detection of abnormal signs. Tension pneumothorax produces abrupt duskiness or cyanosis. Ogata et al.[321] described significant declines of arterial blood pressure, heart rate, respiratory rate, and pulse pressure in 77% of their infants. They did not detect the expected abnormal chest signs. Detection of diminished breath (and heart) sounds, bulging of the affected hemithorax, and mediastinal shift to the unaffected side nevertheless are valuable early indications.

The definitive treatment of tension pneumothorax is placement of a chest tube and application of continuous suction (−10 cm H_2O), particularly if PEEP is used for ventilatory assistance. Recurrence of pneumothorax during chest drainage is frequent. Yu et al.[318] described recurrence in 9 of 14 infants. In such circumstances, the existing tube must be replaced if it is demonstrably occluded; if the tube is not blocked, a second one must be inserted.

Pneumothorax as a result of certain procedures is rare. Leake et al.[347] reported a pneumothorax that became evident 3 hours after birth in a term infant. The mother had amniocentesis shortly before the onset of labor and several hours before the infant's birth. They also summarized three previous reports of pneumothorax, all attributable to entry of the amniocentesis needle into the fetal chest. Anderson and Chandra[348] described three infants who developed pneumothorax after perforation of segmental bronchi by suction catheters.

Pneumopericardium

Pneumopericardium usually occurs in association with one or more of the other extraneous air syndromes. It is rare in the absence of mechanical respiratory support. In most instances, very high ventilatory pressures are used for adequate therapy. The first sign of onset is often a sudden appearance of cyanosis. Heart sounds are muffled or inaudible. Reduced cardiac voltage is evident on the oscilloscope or electrocardiograph. If sufficient air accumulates in the pericardial space, pressure within it increases and eventually stroke volume diminishes (tamponade). Arterial blood pressure falls, and in the extreme case, peripheral pulses are not palpable. Metabolic acidosis develops in response to hypoxemia and to the generally diminished tissue perfusion that results from low cardiac output caused by tamponade. The most distinctive features that suggest the onset of tamponade are the abrupt appearance of cyanosis, hypotension, inaudible heart sounds associated with diminished cardiac activity visible on the electrocardiograph or the oscilloscope, and persistent pulsations of fluid in the umbilical artery catheter.[322] Radiographic diagnosis is definitive. A broad radiolucent halo completely

surrounds the heart, including the inferior (diaphragmatic) surface (see Fig. 23-4, *C*). In the lateral projection, a broad area of radiolucency separates the anterior surface of the heart form the sternum, and to a lesser extent, from the diaphragm.

Pneumopericardium varies widely in severity. We have made the diagnosis serendipitously on a routine chest film of a baby who had no abnormal cardiac signs. The pericardial air disappeared spontaneously in an x-ray taken 6 hours later (Fig. 23-5). In a review of the literature, Brans et al.[324] described 57 cases, adding 6 of their own. Approximately 60% of the infants survived. Of those infants who were treated with pericardiocentesis, 79% survived. Conservative management was associated with 32% survival. These authors thus made a case for aggressive management with needle aspiration or catheter insertion. On the other hand, Pomerance et al.[349] and Varano and Maisels[350] opted for conservative management. The latter authors would maintain conservative therapy until cardiac tamponade is indicated by a decrease in aortic blood pressure.

Treatment may consist of multiple pericardial taps, as indicated for the accumulation of air, or the insertion of a pericardial tube for continuous drainage. The incidence of reaccumulation after initial pericardiocentesis was reported to be 53% in one review.[351]

Pneumomediastinum

Pneumomediastinum is a common isolated disorder when it occurs spontaneously in otherwise healthy infants by the same mechanisms that have been described for spontaneous pneumothorax. It also occurs spontaneously in RDS, after resuscitation at birth, and during ventilator therapy. Morrow et al.[352] found that spontaneous "silent" pneumomediastinum occurred at a rate of 25 per 10,000 live births. As observed in spontaneous pneumothorax, postmature infants were more vulnerable than others, presumably for the same reason: a higher incidence of meconium aspiration.

When pneumomediastinum occurs in otherwise normal infants at birth, it is often asymptomatic. In other circumstances, it produces mild-to-moderate abnormal clinical signs. Tachypnea, a bulging sternum, muffled heart sounds, and cyanosis occur with varying frequencies. The chest film is diagnostic in the lateral projection.[353] Anteroposterior projections often appear spuriously normal. In the lateral view, air is seen as a clear inappropriately radiolucent area behind the sternum or in the superior portion of the mediastinum if the infant is upright. Occasionally, the thymus is visible above the heart. In the anteroposterior view, a radiolucent halo may be seen around the heart; this halo does not extend to the heart's inferior (diaphragmatic) border. Sometimes the halo is so broad that it extends toward the lateral reaches of the thorax. The spinnaker sail sign is commonly apparent in this projection. It is produced by lifting of the thymus from the heart by the air beneath it (Fig. 23-6, *A* and *B*). This sign (also called the *bat-wing* or *angel-wing sign*) should not be confused with the sail sign, a normal triangular shadow in the upper mediastinum in which there is no separation of the "sail" from surrounding structures by radiolucent air. Pneumomediastinum resolves spontaneously with rare exceptions. Careful observation is essential, but nothing more aggressive than supplemental oxygen is indicated.

Pneumoperitoneum

Free air in the peritoneum usually suggests perforation of an abdominal viscus, which requires immediate laparotomy; however, in a number of reports, pneumoperitoneum was shown to follow a pulmonary air leak. Air migrates through the diaphragm[326,328,354] to retroperitoneal space and then to the peritoneal cavity. The principal difficulty of this situation is the need to exclude the possibility of gastrointestinal perforation. The simultaneous presence of aberrant air in the chest suggests that the situation is not primarily gastrointestinal. The absence of peritoneal fluid, normal thickness of the bowel wall, and the absence of

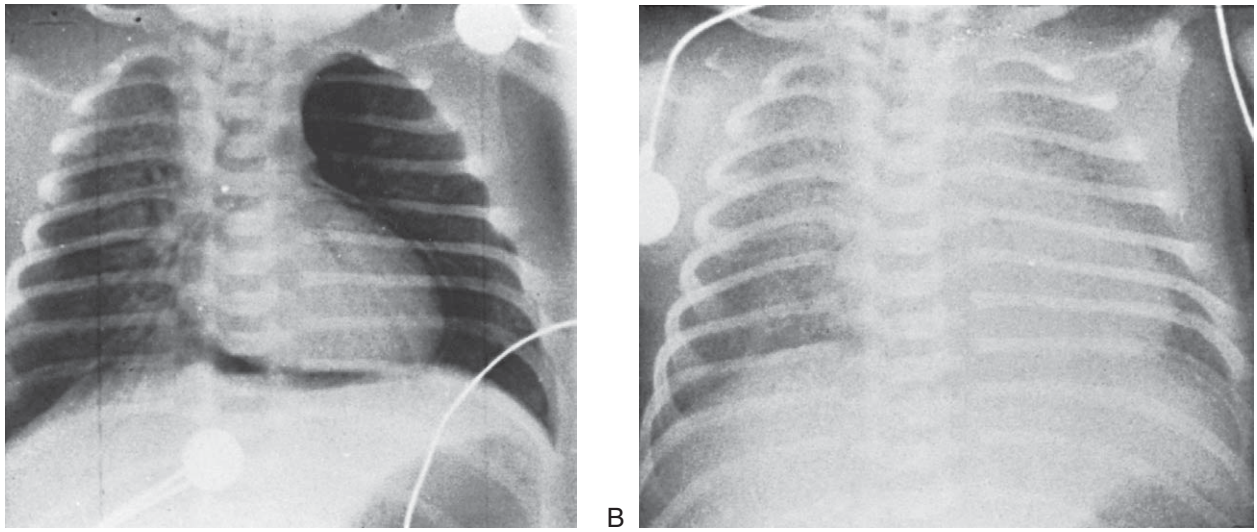
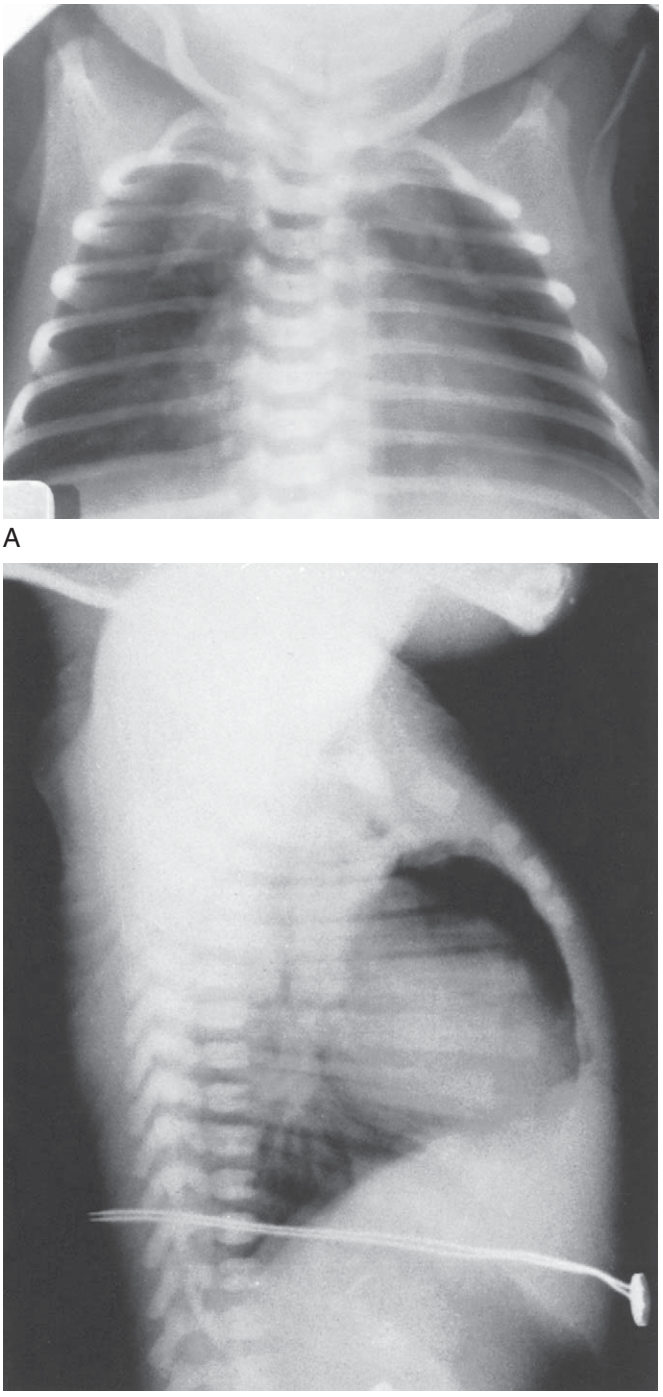


Figure 23-5 ■ Pneumopericardium diagnosed incidentally on a routine chest film in an infant being ventilated for respiraory distress. **A,** A thin halo of air surrounds the heart and delineates the pericardium as a thin white line against air-filled lung. **B,** Spontaneous clearing of pneumopericardium 6 hours later.



A

B

Figure 23-6 ■ **A,** Anteroposterior portion of a pneumomediastinum, which has lifted both thymi lobes to produce the "spinnaker sail sign." **B,** Lateral view shows air beneath the sternum in the superior mediastinum. (From Korones SB: High-Risk Newborn Infants: The Basis for Intensive Nursing Care, 4th ed. St. Louis, Mosby, 1986, p. 257.)

air-fluid levels are further evidence of the nonsurgical nature of the condition. Figure 23-7 demonstrates a curious variation of pneumoperitoneum in which air envelops the scrotum. Occasionally, massive pneumoperitoneum may compress the inferior vena cava, resulting in decreased blood return to the heart, hypotension, metabolic acidosis, and anuria.

Air Embolus

Air embolus, a relatively rare condition, is the most sinister of the extraneous air syndromes. It occurs when extremely high pressures are required to ventilate extremely stiff lungs. Parenchymal tears probably occur, and as a result, air is injected into the pulmonary vasculature. In the infant described by Gregory and Tooley,[337] inflation pressures up to 50 cm H_2O were necessary to provide a satisfactory tidal volume. Lubens et al.[355] had to use a peak inspiratory pressure of 55 cm H_2O in the 800-g infant whom they reported. Bowen et al.[356] encountered a similar situation in the infant they studied, who developed intravascular air. Siegle et al.[357] described two infants with air embolus who were managed in their unit. Each had antecedent PIE. The clinical presentation of infants with air embolus is a catastrophic event. Sudden cyanosis and circulatory collapse become evident. The heart slows, but with each beat the air-blood mixture crackles and pops, as they are heard through the stethoscope. Withdrawal of blood from the umbilical artery catheter yields bubbles of air, similar to what one would expect if a stopcock connection were loose. Radiography reveals the bizarre picture of intracardiac and intravascular air throughout the body. Figure 23-8

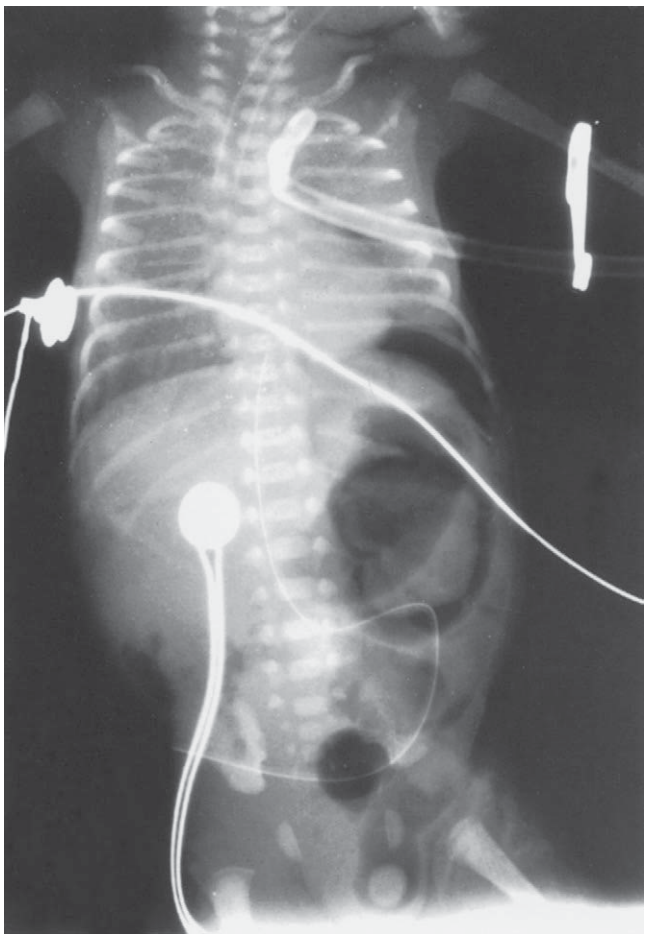


Figure 23-7 ■ Pneumoperitoneum, pneumoscrotum. Air is evident in the peritoneal space, processus vaginalis, and the scrotum. Note also the free air beneath the left diaphragm. (From Korones SB: High-Risk Newborn Infants: The Basis for Intensive Nursing Care, 4th ed. St. Louis, Mosby, 1986, p. 260.)

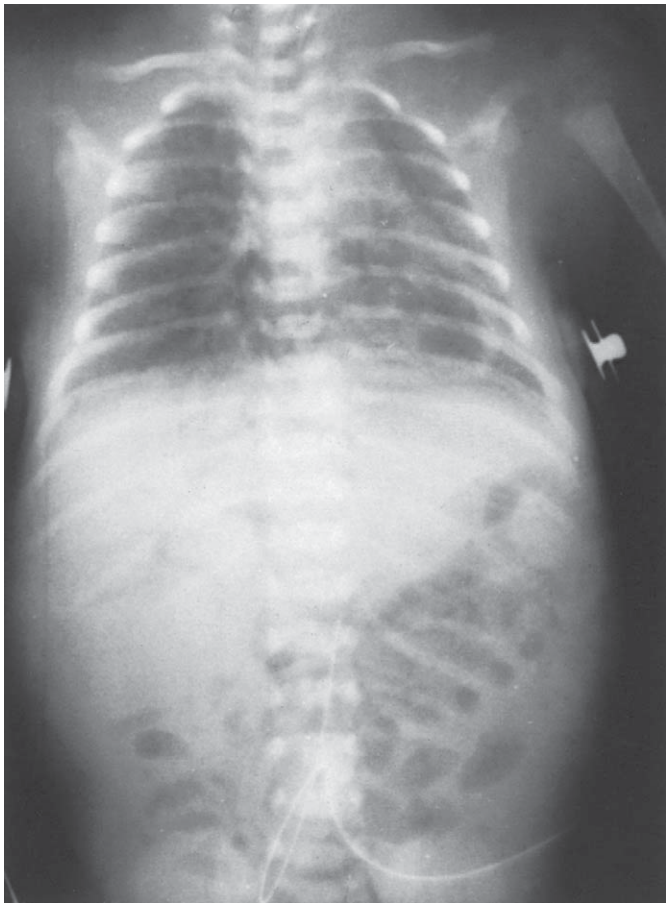


Figure 23-8 ■ Air embolus. The heart is filled with air, which can also be seen in the portal vessels in the liver. (From Korones SB: High-Risk Newborn Infants: The Basis for Intensive Nursing Care, 4th ed. St. Louis, Mosby, 1986, p. 261.)

shows air in the portal vessels as well as in the heart. There is no helpful treatment for air embolism.

Retinopathy of Prematurity

ROP was first described in 1942 by Terry[358] in five premature infants, each of whom had a "grayish-white, opaque membrane behind each crystalline lens." The disorder was then named *retrolental fibroplasia*. Although Terry first described the disease, it was Clifford, a Boston pediatrician, who first called attention to it. Clifford recognized unanticipated blindness on routine examination of a 4-month-old infant during a house call in the Roxbury section of Boston.[359]

Over the next decade, a long list of postulated causes accumulated, but later (between 1952 and 1955), three controlled studies strongly suggested that excessive use of O_2 was associated with the development of ROP.[360-362] As a result, the routine administration of high concentration O_2 to premature infants was considered untenable. It should be realized that these studies addressed restrictions of FIO_2; blood gas determinations were not clinically feasible at the time.

The epidemic of blindness that had transpired during the 1940s and the early 1950s receded remarkably after the widespread restriction of O_2 use. However, in the early 1960s increased mortality and a heightened incidence of cerebral palsy were attributed to the O_2 restriction.[363,364] There followed an era of regulated O_2 administration based on blood gas determinations (PaO_2). This technique was later replaced by transcutaneous O_2 monitoring, which in turn was superseded by O_2 saturation measured by pulse oximetry.

Although O_2 concentration was monitored assiduously with advanced technology, in 1981 Phelps[365] reported that there nevertheless was an apparent resurgence in the incidence of ROP. A "new epidemic" had materialized, and it was attributed to a remarkable increase in the survival of very small infants (less than 1000 g). With increased survival of the smallest babies, despite careful monitoring of blood O_2 levels, the incidence of ROP increased significantly.[365,366] It became apparent that hyperoxia was not the sole cause of ROP.[1,367]

Etiology

Controlled clinical trials in the early 1950s demonstrated that supplemental O_2 administration may be a causative factor. In a cooperative study, Kinsey and Hemphill[360] reported an incidence of 71% for active ROP with the liberal use of O_2 versus an incidence of 33% with the curtailed use of O_2 in a large group of matched infants. Other studies came to the same conclusion.[361,362] However, cases had previously been reported in term infants,[368] in premature infants never exposed to O_2,[368] in infants with cyanotic congenital heart disease,[369] and in term infants who received exchange transfusions.[370]

The assumption that hyperoxia in premature infants is the sole cause of ROP has been virtually discarded.[1,371] Reexamination of the original studies,[372] and accumulated evidence from numerous reports since the original studies, have produced a perspective that becomes possible after years of studied experience. Although the important role of O_2 is evident from the earlier investigations, interpretations of the data have tended to overlook the substantial number of infants who developed ROP despite the assiduous control of low ambient O_2 concentrations. Also overlooked were the impressive number of infants in whom no disease was present despite their exposure to high O_2 concentrations. Furthermore, over 60 infants born at term are known to have developed ROP, and the majority did not receive O_2. In a similar context, 95 low-birth-weight infants who had never received supplemental O_2 were reported to have retinopathy.[1] The disease has been reported in 11 anencephalic infants, 10 of whom either were stillborn or did not survive for longer than a few days.

The issue of causation is further confused by data suggesting that retinal hypoxia may cause the neovascularization that characterizes ROP. Several studies indicate that the infants who develop ROP have more complicated courses, more hypoxemic episodes, and overall lower arterial O_2 levels.[373-376] In 1953, Szewczyk[377] reported a favorable experience with severe ROP when O_2 was gradually rather than abruptly withdrawn. Bedrossian et al.[378,379] also reported fewer cases of ROP when O_2 was gradually withdrawn. These clinical experiences, as well as evidence from

animal studies,[380] eventually motivated a controlled multicenter clinical trial comparing the impact of O_2 saturation at 96% to 99% versus 89% to 94% on progression to threshold ROP in infants identified with prethreshold ROP (Stop-ROP Study). The study sought to determine whether the higher O_2 saturations would diminish progression of the disease to the proliferative stage. The rates of ROP progression did not differ between the two groups.[381]

In summary, views on the etiologic significance of O_2 therapy have changed remarkably since the original studies of the 1950s established a rigid therapeutic approach that was applied for more than 3 decades. The present epidemic of blindness differs from the first one of the 1950s.[365] It affects a population of considerably smaller infants whose birth weights are less than 1000 g. In these infants a particularly direct association between the use of O_2 and the development of retinopathy is questionable. Risk factors in various studies of ROP include prematurity, O_2 administration, vitamin A deficiency, inositol deficiency, indomethacin therapy for prevention of patent ductus arteriosus, vitamin E deficiency, exposure to light, intravenous lipid administration, apneic episodes, transfusions of adult blood, elevated or depressed $PaCO_2$, intraventricular hemorrhage, and septicemia. None of these factors has been identified as a direct cause of ROP. Newer studies examining O_2 saturation targets only suggest that lowering O_2 saturation targets may reduce the incidence of ROP in the most susceptible infants without increasing neurologic dysfunctional outcomes.[180-183,381]

Incidence

All large studies to date reveal that like BPD, the incidence of ROP varies inversely with birth weight, gestational age, or both.[382] This finding supports the evidence that disease originates in the nonvascularized portion of the retina and that vascularization of the retina progresses linearly with increasing gestational age. Kingham[383] found a 13% incidence of ROP in 810 infants discharged from an intensive care nursery. He concurred that the incidence of ROP was greatest in the least mature infants. Two thirds (71/107) of all cases were infants less than 29 weeks' gestation. Kingham found no permanent scarring in any infant weighing more than 1500 g, and spontaneous resolution occurred in 75% of all infants with evidence of ROP at discharge.

Flynn[384] examined 639 infants whose birth weights were 1500 g or less and who survived at least 28 days. The infants were admitted to the intensive care unit from 1975 to 1981. Acute proliferative disease was found in 67% of infants who weighed from 600 to 999 g, 36% of infants who weighed from 1000 to 1249 g, and 13% of infants who weighed from 1250 to 1500 g. Univariate and multivariate analysis indicated that birth weight was the most powerful predictor of disease. Duration of ventilation, particularly for infants weighing more than 1000 g, also was predictive. Oxygen therapy apparently was not predictive for the smallest infants (i.e., those weighing from 600 to 999 g), but there was a strong association between oxygen and ventilation therapy in infants in the higher-weight groups (i.e., those weighing greater than 1250 g). Shohat et al.[385] reported acute disease in 52% of infants whose birth weights ranged from 501 to 1250 g and who were discharged from their intensive care unit from 1977 to 1980.

The CRYO-ROP Study reported that most infants less than 27 gestational weeks had ROP (less than 90% at 25 or fewer weeks). The LIGHT-ROP Study, 10 years later, reported a similar incidence.[372]

Pathogenesis

The completely vascularized retina is not affected by ROP. At 15 to 18 weeks' gestation, vascularization of the fetal retina begins.[386] Vessels grow outward (forward) from the optic disc toward the nasal and temporal periphery of the retina ultimately reaching the ora serrata. As gestation advances, the area of avascular retina diminishes progressively, whereas vascular tissue spreads forward.[387] Rarely, the human retina may not be completely vascularized at term, a fact that probably accounts for the rare occurrence of ROP in full-term infants. Moreover, the human fetus lives in an environment of relatively low oxygenation with PaO_2 from 25 to 35 mm Hg in the umbilical vein. At birth, the retina is thus exposed to relative hyperoxygenation, even when no supplemental O_2 is given.

Retinal vessels are first formed by a process called *vasculogenesis* and later by the process of *angiogenesis.* Vasculogenesis entails developmental progression from the most primitive pluripotential cells to endothelial cells that form cord-like structures. These soon canalize to form structural primitive capillaries. The primitive capillaries are embellished by the addition of smooth muscle cells and pericytes to form arterioles and venules. New vessels evolve from the existing ones by the process of angiogenesis, which entails the formation of additional vasculature to the existing network.

Vascular tissue enters the retina from the optic disc and by the early process of vasculogenesis. They migrate from the posterior pole to the ora serrata, which is the anterior terminal site of advancing retinal vasculature, the mark of retinal maturity. Until vascularity reaches this structural site, the retina remains divided into a posterior vascularized portion and an anterior avascular zone that awaits maturational vascular advance.

Among the cytokines and growth factors involved in the development of retinal vessels, vascular endothelial growth factor (VEGF) is of noteworthy importance. It has been identified in the anterior avascular retina at the forward edge of the advancing vascular tissue.

The forward movement of newly formed blood vessels is a response to up-regulated VEGF expression induced by the physiologic hypoxia in the anterior avascular retina.[388] Neural development and increased metabolic activity of the unperfused retina result in physiologic hypoxia, which up-regulates expression of VEGF. The increased VEGF induces anterior extension of blood vessels from the forward margin of the vascular retina.[388,389] Throughout normal retinal maturation, forward extension of blood vessels continues until the ora serrata is reached. Although VEGF is thus up-regulated by a metabolic need for oxygen, it also can be down-regulated by hyperoxia. Pierce et al.[388] demonstrated that this down-regulation results in the obliteration of immature retinal vessels. The authors successfully inhibited vascular obliteration by administering VEGF.

Normal function of VEGF depends on the presence of insulin-like growth factor (IGF-1). Studies of premature infants indicate that ROP does not develop if IGF-1 levels are sufficient to support normal VEGF function.[390] If IGF-1 levels are low, vascular growth is halted even in the presence of VEGF; absence of sufficient vascular supply causes cumulative hypoxia in the avascular retina, and as a result, VEGF increases to levels that can induce robust neovascularization when sufficient IGF-1 is ultimately formed. IGF-1 permits normal vessel formation. In its absence, VEGF does not elicit an angiogenic response even though it continues to accumulate in the vitreous and avascular retina.

IGF-1 is a pivotal somatic growth factor that apparently comes to the fetus from the placenta and amniotic fluid. Like so many other developmental phenomena, accumulation of fetal IGF-1 is accelerated between the second and third trimesters.[390] Premature birth thus precludes the continued normal increase of IGF-1. Hellstrom et al.[391] have shown that among infants with ROP (also BPD, IVH, and NEC), low serum levels of IGF-1 persist for extended periods of time. Persistent paucity of postnatal serum IGF-1 suppresses normal VEGF function and inhibits vessel growth even though VEGF continues to accumulate in the presence of retinal hypoxia.

When IGF-1 belatedly reaches a level that permits VEGF function, proliferative retinopathy is initiated by the inappropriate excess of VEFG.[389-392] Hellerstrom et al.[389] demonstrated in human infants that prolonged durations of low IGF-1 levels after birth were associated with ROP. In the absence of ROP, mean duration for low IGF-1 levels (less than 30 ng) in 10 infants was 19 days, whereas in the presence of ROP, functional IGF-1 levels first occurred at a mean of 58 days. The authors have suggested that if IGF-1 increases rapidly after birth to permit normal vascular development, ROP does not occur.[389] The therapeutic implications of this suggestion are of major significance.

Progression of ROP

The initial ophthalmologic finding is an abnormal terminal arborization of retinal vessels, which produces a distinct line of demarcation between the vascular and avascular portions of the retina. This line of demarcation is at first on the same plane as the retina. Later, a ridge of neovascularization at the junction of the vascularized and nonvascularized retina is produced by the outward growth of these vessels through the inner limiting membrane of the retina into the vitreous. The creation of an arteriovenous shunt accounts for the finding of dilated tortuous vessels on the retina posteriorly ("plus" disease).

At this point, the disease may take one of two pathways. In most infants, these vascular abnormalities resolve and vision is normal or only slightly impaired. Unfortunately, a few cases progress to yield an exudative response, which when organized leads to the formation of membranes between the retina and vitreous that produce retinal traction and detachment. At approximately 6 months of age, cicatricial changes begin in severely affected infants. This process may be compounded by temporal traction of the new vessels as they leave the optic disc. Concurrently, fibrous tissue continues to proliferate immediately behind the lens, producing leukoria (opaque, white pupils). Partial or total retinal detachment is the endpoint of the cicatricial process, resulting in severely impaired vision or total blindness.

Classification

Classification and screening schedules were slightly revised in 2006 in a statement from the International Committee for Classification of Retinopathy of Prematurity.[393]

Location

Location is expressed as zone 1, 2, or 3 (Fig. 23-9).[394] Each zone is centered on the optic disc because normal retinal vascular growth progresses peripherally from the disc toward the ora serrata.

Zone 1: Posterior pole or inner zone. Extends in all directions from the optic disc to a distance twice that between the disc and the macula.

Zone 2: From the edge of zone 2 peripherally to a point tangent to the nasal ora serrata and an area near the temporal anatomic equator (Landmarks of equator are obscure; therefore, precisely defined locations are difficult to identify).

Zone 3: Remaining crescent of the fundus anterior to zone 2. This zone is the last to be vascularized.

Extent of Disease

The real extent of the disease is expressed in reference to the aggregate number of clock hours occupied by ROP changes (see Fig. 23-9).

Staging of Disease: Proliferative Phase

In addition to the location and extent of the disease, the stage of advancement is also described as follows.

Stage 1: Demarcation Line

The demarcation line is a flat white line within the plane of the retina that clearly delineates the vascularized posterior retina from the avascular anterior portion. Abnormal branching or arcading of vessels is recognizable immediately posterior to the demarcation line.

Stage 2: Ridge

The ridge is an expanded demarcation line that has three dimensions because it has grown in height and width, rising above the plane of the retina. The color may be white to pink. Small tufts of new vessels may lie on the surface of the retina posterior to the ridge.

Stage 3: Ridge with Extraretinal Fibrovascular Proliferation

In addition to the structure of stage 2, extraretinal fibrovascular tissue is present. This tissue may (1) be continuous with the posterior aspect of the ridge, causing a ragged appearance; (2) be immediately posterior to the ridge but not connected to it; or (3) extend into the vitreous perpendicular to the retinal plane.

Stages 4 and 5

Changes of stage 3 are complicated by retinal detachment that is caused by the effusion of fluid, traction, or by both. Serial examinations may be required to ascertain true detachment. Stage 5 indicates a more extensive retinal detachment than stage 4.

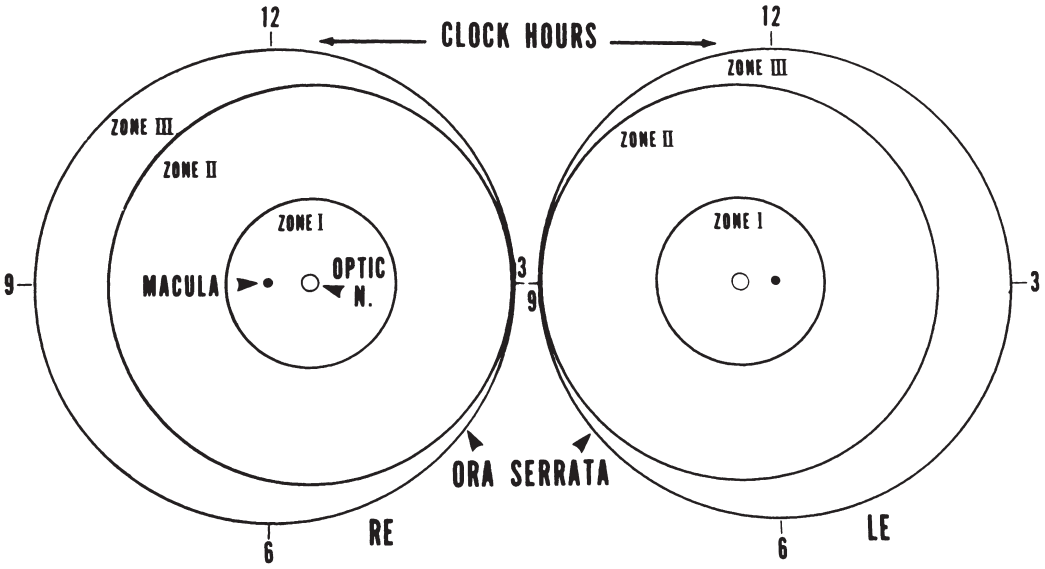


Figure 23-9 ■ Schematic drawing of the retinas of the right eye (RE) and the left eye (LE) showing zone borders. Clock hours are used to decribe the location and extent of retinopathy of prematurity. (From Garner A, Ben-Sira I, Deutman A, et al: Pediatrics 74:127, 1984. Reprinted by permission of *Pediatrics*.)

Plus Disease

For stages 2 and 3, add a plus sign (+) if the posterior veins are clearly enlarged and arterioles unequivocally tortuous. Thus stage 2 ROP with posterior vascular dilation and tortuosity would be written "stage 2+ ROP."

Aggressive Posterior ROP

Aggressive posterior ROP (AP-ROP) is a rapidly progressive, severe form of ROP with prominent plus disease, posterior location, and rapid advancement. The term previously applied was *Rush disease*, to indicate its rapid progress to retinal detachment.

Threshold ROP

Threshold ROP refers to zone 1 or 2 changes that occupy a minimum of the five contiguous (uninterrupted) clock hours or an aggregate of eight clock hours of involved areas that are separated from each other.

Prethreshold ROP

The term *prethreshold ROP* refers to any ROP change that is less extensive than threshold in zone 1. In zone 2, ROP at stage 2 with plus disease or at stage 3 without plus disease is *prethreshold*.

Staging of Disease: Cicatricial Phase

The published statement recommends use of the Reese classification of cicatricial disease. Table 23-3 lists the cicatricial changes.

Treatment

Cryotherapy and laser therapy are presently the only effective treatments available. In the STOP-ROP Study,[381] 82% of the treated eyes had good anatomic outcomes, that is, there was no retinal detachment, folds, or dragged discs. The recommendations of the multicenter trial reported in 1988[382] indicate that therapy should be applied when stage 3 is identified in more than five contiguous clock hours or when more than eight total clock hours (noncontiguous) are involved in zones 1 or 2, including the presence of plus disease.

The Early Treatment of Retinopathy of Prematurity Study was reported in 2003.[395,396] It indicated that earlier treatment of selected infants with prethreshold ROP resulted in better outcomes than treatment at threshold. A clinical algorithm based on these data was developed to deal with changes in examination schedules and with altered indications for ablation of the peripheral retina (Box 23-3).[395-397]

Box 23-3 CLINICAL ALGORITHM FOR ROP DIAGNOSIS

For Continued Serial Examinations

Any eye with type 2 ROP

1. Zone 1, stage 1 or 2 ROP without plus disease
2. Zone 2, stage 3 ROP without plus disease

For Consideration of Retinal Ablation

Any eye with type 1 ROP

1. Zone 1, any stage ROP, plus disease
2. Zone 1, stage 3 ROP, with or without plus disease
3. Zone 2, stage 2 or 3 with plus disease

TABLE 23-3 Classification of Cicatricial Disease in Retinopathy of Prematurity

Grade	Fundus Changes
I	Small areas of retinal pigment irregularities; small scars in retinal periphery
II	Disc distortion
III	Retinal fold
IV	Incomplete retrolental mass; partial retinal detachment
V	Complete retrolental mass; total retinal detachment

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24 Ventilator-Associated Pneumonia

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Philip L. Graham, III, MD, MSc

Ventilator-associated pneumonia (VAP) is defined by the Centers for Disease Control and Prevention (CDC) as pneumonia in individuals who had a device to assist or control respiration continuously through a tracheostomy or by endotracheal tube within the 48-hour period before the onset of infection.[1] Hospital-acquired pneumonias are estimated to affect 250,000 patients each year in the United States.[2,3] Children who are immunocompromised and intubated for extended periods of time are at especially high risk. Neonates requiring intensive care represent a particularly vulnerable population because of their frequent need for intubation (as part of resuscitation), prolonged mechanical ventilation, and susceptibility to other hospital-acquired infections. Hospital-acquired infections in neonates increase costs, prolong hospitalization, and are major causes of morbidity and mortality.[4-7] In adult patients, VAP is the second most commonly occurring health care–associated infection. However, the rate of VAP in infants and neonates, especially those with underlying pulmonary disorders, is not as clear. Moreover, radiologic identification of pneumonia is difficult and procedures commonly used in adults (e.g., bronchoscopy, lung biopsy, protected brush specimen, and bronchoalveolar lavage) are rarely used in the neonatal population. This chapter reviews the epidemiology, pathogenesis, diagnosis, prevention strategies, and treatment of VAP in the newborn infant.

Epidemiology

Although the incidence of VAP is likely underreported, surveillance studies indicate that pneumonia comprises 6.8% to 32.3% of hospital-acquired infections in the neonatal intensive care unit (NICU).[8] The most recent National Nosocomial Infections Surveillance (NNIS) System data[9] indicate a pooled mean rate varying from 1.4 to 3.5/1000 ventilator days (Table 24-1). However, studies from individual centers suggest a much higher incidence (Fig. 24-1). For example, Apisarnthanarak et al.[10] reported a VAP incidence of 6.5/1000 ventilator days in infants less than 28 weeks gestational age. The occurrence of VAP in this study was strongly associated with an increased likelihood of mortality, (odds ratio [OR] 3.0; confidence interval [CI] 1.2, 12.3). Similarly, studies from Switzerland, Brazil, Turkey, Taiwan, and The Netherlands indicate rates varying from 12.5/1000 patient days to 52/1000 ventilator days.[11-17]

Critically ill neonates are at high risk for hospital-acquired infections. The increased susceptibility is multifactorial and includes immunocompromise (particularly infants weighing less than 1500 g), invasive monitoring, need for central catheters, prolonged intravenous alimentation, and mechanical ventilation. Inconsistent hand hygiene practices and overcrowding contribute to the high incidence of health care–associated infections. In the adult population, a number of risk factors for VAP have been identified. These include advanced age, duration of mechanical ventilation of 7 or more days, witnessed aspiration, the presence of central nervous system disease, supine positioning, use of paralytic agents, underlying respiratory or cardiac disease, exposure to antibiotics, prolonged intensive care unit (ICU) stay, the presence of invasive devices, and treatment with antacids and histamine type 2 (H2) receptor blockers.

There have been a number of recent studies examining risk factors for VAP among critically ill neonates.[10,12] Yuan et al.[12] conducted a retrospective cohort study in 259 patients who were ventilated more than 48 hours. By logistic regression analysis, the following variables independently predicted VAP: reintubation (OR 5.3; CI 2.0, 14.0), duration of mechanical ventilation (OR 4.8; CI 2.2, 10.4), treatment with opiates (index of response [IR] 3.8; CI 1.8, 8.5) and frequency of endotracheal suctioning (OR 3.5; CI 1.6, 7.4). After adjustment for the duration of endotracheal intubation, Apisarnthanarak et al.[10] found a preceding bloodstream infection (with an unrelated organism) to be an independent risk factor for VAP (OR 3.5; CI 1.2, 12.3), probably signifying a subpopulation of infants who are more immunocompromised. In a large prospective surveillance study, Van der Zwet et al.[13] identified low birth weight (OR 1.37; CI 1.01, 1.85) and mechanical ventilation (OR 9.69; CI 4.60, 20.4) as risk factors for pneumonia. Interestingly, intravenous antibiotics were protective, (OR 0.37; CI 0.26, 0.56). Hentschel et al.[14] also documented a difference in the hospital-acquired pneumonia rates between intubated infants and those receiving nasal continuous positive airway pressure (nCPAP) (12.8 versus 1.8/1000 ventilator or nCPAP days).

Pathogenesis

The pathogenesis of VAP is illustrated in Figure 24-2.[18] Ventilator-associated pneumonia occurs when bacterial,

TABLE 24-1 **Pooled Means and Percentiles of the Distribution of Device-Assisted Infection Rates, by Birth-Weight Category, HRN* Component, January 2002 through June 2004**

VENTILATOR-ASSOCIATED PNEUMONIA RATE†				PERCENTILE				
Birth-weight category	**No. of HRNs**	**Ventilator days**	**Pooled mean**	**10%**	**25%**	**50% (median)**	**75%**	**90%**
≤1000 g	102	204,117	3.5	0.0	0.0	2.4	5.8	8.5
1001–1500 g	91	50,204	2.4	0.0	0.0	0.0	3.2	8.0
1501–2500 g	86	39,957	1.9	0.0	0.0	0.0	1.5	6.1
>2500 g	90	55,038	1.4	0.0	0.0	0.0	0.9	3.2

Data from National Nosocomial Infection Surveillance System: National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004, issued October 2004. Am J Infect Control 32(8):470-485, 2004. Used with permission.

*High-risk nurseries.

†$\frac{\text{Number of ventilator-associated pneumonia}}{\text{Number of ventilator days}} \times 1000$

fungal, or viral pathogens gain entrance to the normally sterile lower respiratory tract. Only rarely does the organism gain entry to the lung through hematogenous dissemination or by bacterial translocation from the gastrointestinal tract.[19,20] Pathogens responsible for VAP originate from exogenous sources (other infants in the nursery or health care workers) or endogenous sources (contaminated equipment or solutions). The organism gains entry to the respiratory tract by colonizing the endotracheal tube and the upper airway, by tracheal suctioning, or by direct aspiration of gastrointestinal contents. Unlike care measures for older children and adults, cuffed endotracheal tubes are not generally used in the NICU. This practice provides easier access for microorganisms to the lower respiratory tract of neonates. Furthermore, microscopic aspiration may be more common than previously appreciated.[21-23] Farharth et al.[22] quantified pepsin in tracheal aspirate samples from 45 ventilated newborn infants. Pepsin is thought to be a reliable marker of microaspiration. Pepsin was detected in 92.8% of tracheal aspirate samples. The mean concentration of pepsin was significantly lower when the infants were unfed (Fig. 24-3). Methylxanthines increased tracheal aspirate pepsin levels,[22] and infants who developed bronchopulmonary dysplasia (BPD) or developed BPD/died before 36 weeks' gestation had significantly higher levels (Fig. 24-4).[23] Pepsin levels were also higher in infants who developed severe BPD, versus those with moderate BPD (Fig. 24-5).

Microbiology

In surveys of adult and pediatric hospitals, *Staphylococcus aureus* and gram-negative microorganisms (*Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Enterobacter* sp., and *Acinetobacter* sp.) represented the most common pathogens. Apisarnthanarak et al.[10] recovered gram-negative microorganisms from the respiratory secretions of 94% of VAP episodes (Table 24-2). *S. aureus* was recovered in about one quarter of infants with VAP, and multiple organisms were recovered from the airway in 58% of episodes. Yuan et al.[12] recovered gram-negative bacterium in the majority of infants with VAP; however, most health care–associated pneumonia is felt to be polymicrobial in nature.

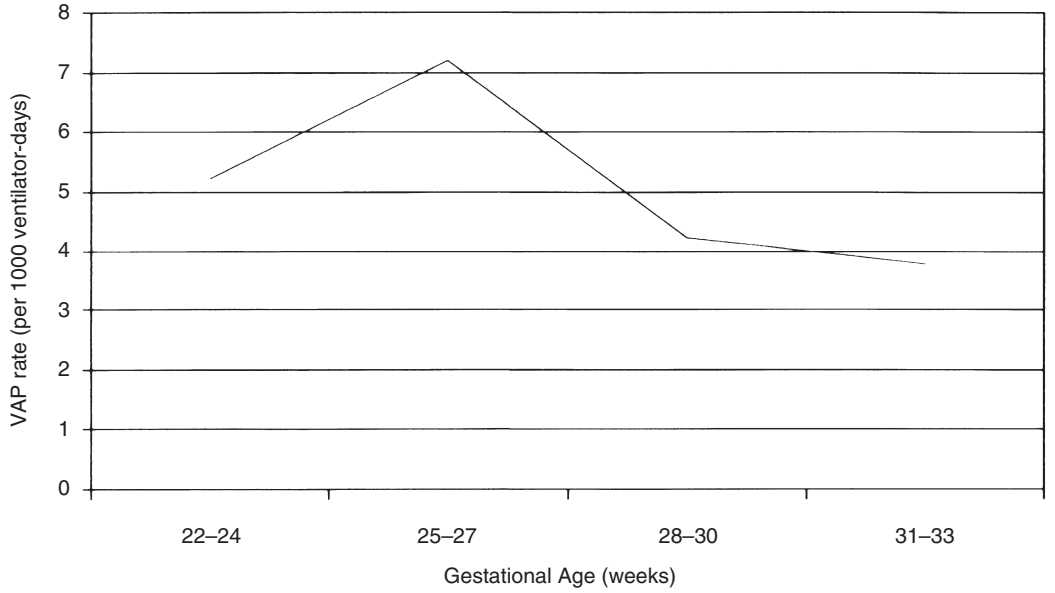

Figure 24-1 ■ Distribution of VAP rates per 1000 ventilator days among neonates with gestational ages of 22 to 33 weeks. (From Apisarnthanarak A, Holamann-Pazgal G, Hamvas A, et al: Pediatrics 112:1283-1289, 2005.)

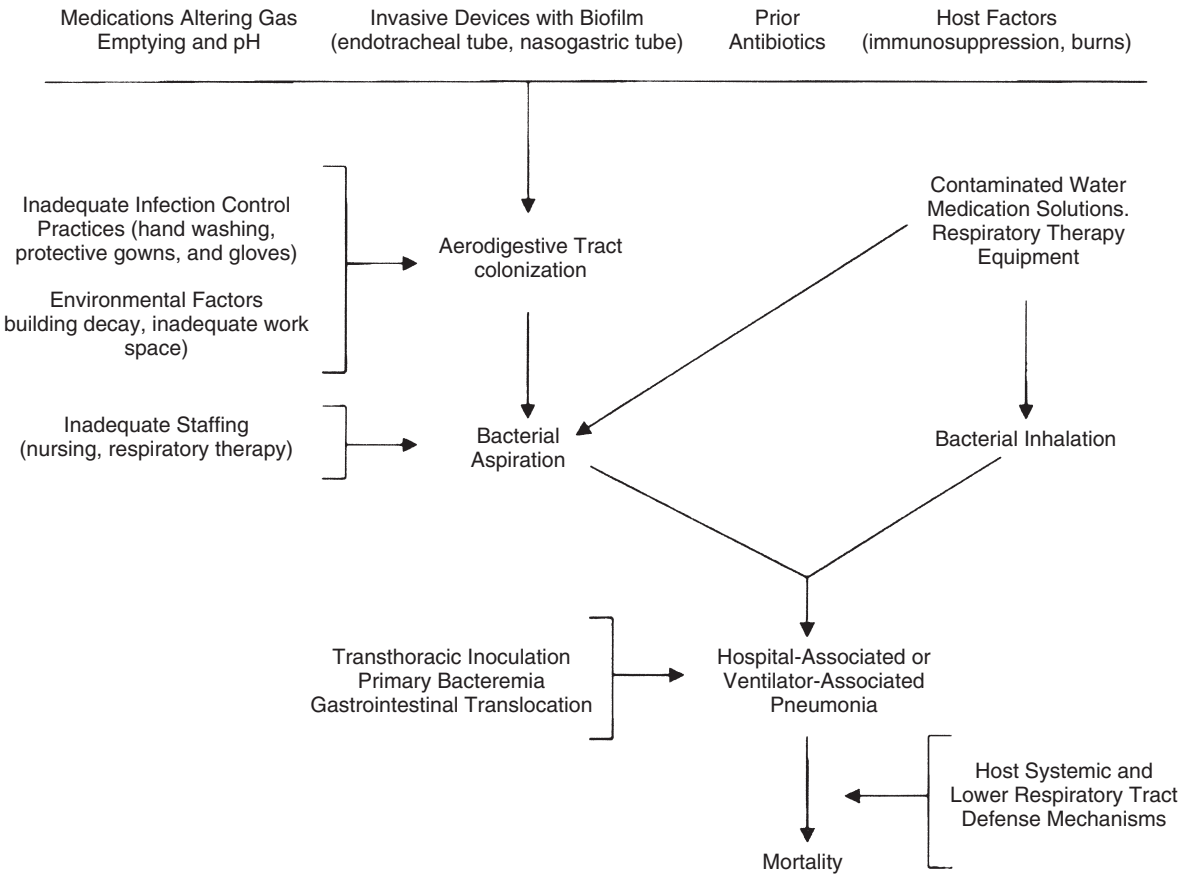

Figure 24-2 ■ Pathogenesis of bacterial hospital-associated and ventilator-associated pneumonia. (From Kollef MH: Crit. Care Med 32:1396-1405, 2004.)

TABLE 24-2 **Microorganisms Recovered from Respiratory Secretions of VAP**

Organisms	Total Population* (*n* = 26; %)	Extremely Preterm Patients* (*n* = 19; %)
Gram-negative Rods		
Pseudomonas aeruginosa	10 (38.4)	8 (42)
Enterobacter spp.	10 (38.4)	8 (42)
Klebsiella spp.	6 (23)	5 (26)
Escherichia coli	4 (15.4)	3 (15)
Acinetobacter spp.	3 (11.5)	2 (10.5)
Proteus spp.	2 (7.7)	2 (10.5)
Citrobacter spp.	2 (7.7)	2 (10.5)
Stenotrophomonas maltophilia	1 (3.8)	1 (5.2)
Gram-positive Cocci		
Staphylococcus aureus	6 (23)	5 (26)
Enterococcus spp.	4 (15.4)	3 (15)
Group B *Streptococcus*	1 (3.8)	1 (3.2)

From Apisarnthanarak A, Holamann-Pazgal G, Hamvas A, et al:. Pediatrics 112:1283-1289, 2005. Used with permission.

*Total episodes of VAP. Because most patients had polymicrobial microorganism, the sum of all percentages is greater than 100%.

Diagnosis

The diagnosis of VAP is problematic.[24] The NNIS and CDC definition requires at least 48 hours of mechanical ventilation accompanied by new and persistent radiographic infiltrates after the initiation of mechanical ventilation. In addition to these criteria, infants less than 1 year must exhibit evidence of worsening gas exchange and at least three of the following: (1) temperature instability with no other recognized cause, (2) leucopenia less than 4000/mm^3 or leukocytosis greater than 15,000/mm^3, (3) change in the character of sputum or increased respiratory secretions or increased suctioning requirements, (4) apnea, tachypnea, nasal flaring, or grunting, (5) wheezing, rales, or rhonchi, cough, and (6) bradycardia (less than 100 beats/min) or tachycardia (greater than 170 beats/min).[1] Baltimore,[25] however, has pointed out that the CDC definitions were developed for epidemiologic surveillance and have not been validated for clinical diagnosis. Complicating this issue is that most infants with suspected VAP have underlying lung disease that predisposes them to atelectasis and episodes of clinical deterioration. Additionally, it is not uncommon for general radiologists to "identify" the presence of an infiltrate on a chest radiograph in an otherwise asymptomatic infant.[15]

In adults with fever, pulmonary infiltrates, and clinical criteria for VAP, only 42% had a definitive diagnosis of

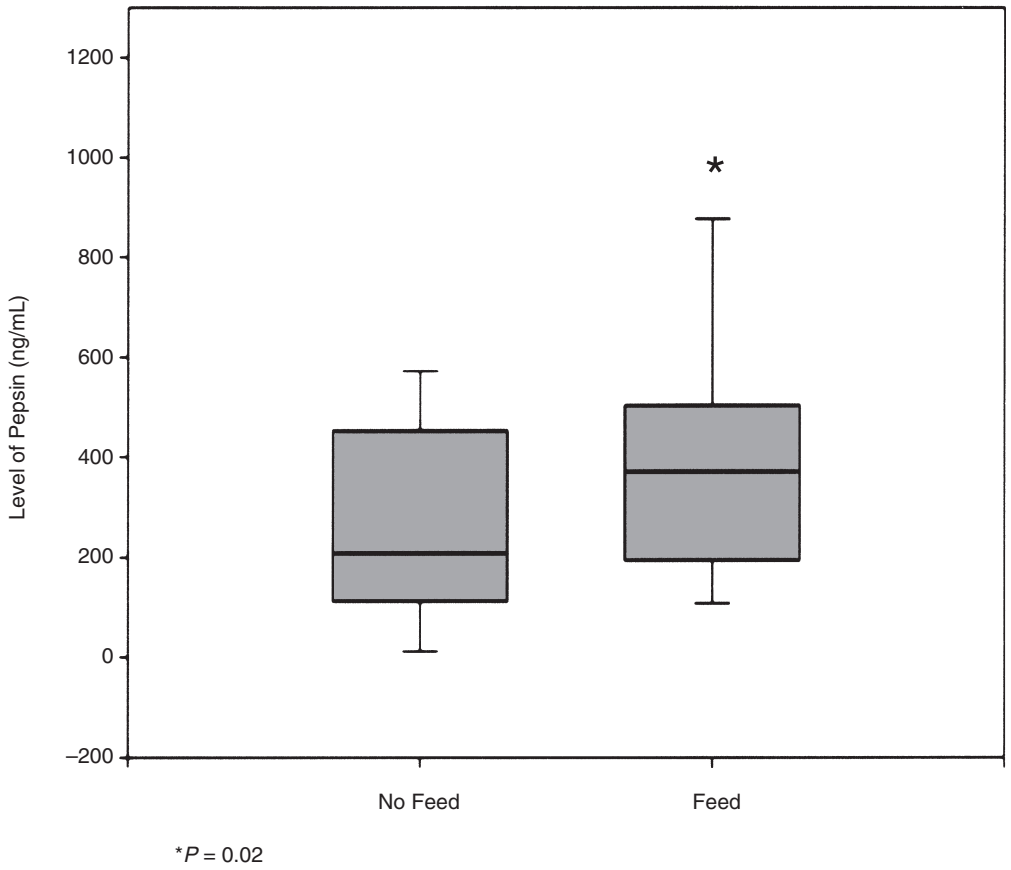

Figure 24-3 ■ The levels of pepsin when infants were unfed and during the feed. Median concentration of pepsin was significantly lower when unfed state was compared with concentration during feeding. (From Farhath S, Aghai ZH, Nakhla T, et al: J Pediatr Gastroenterol Nutr 43:336-341, 2006.)

pneumonia and 66% had a noninfectious etiology.[26,27] Moreover, postmortem examinations demonstrated that only 35% of patients with a new or progressive infiltrate had histopathologic evidence of a pneumonic process.[28,29] In ventilated adults, invasive techniques have been used to quantify the bacterial load as a way to distinguish infection from colonization. The airway of the newborn infant is colonized with a variety of potential pathogens, and a specimen taken from the endotracheal tube will not differentiate colonization from infection. The American Thoracic Society and Infectious Diseases Society of America guidelines[30] suggest using a threshold of 10^3 for quantitative culture from a protected specimen brush sample, 10^4 for quantitative culture of bronchoalveolar (BAL) lavage fluid, and 10^5 or 10^6 for quantitative culture of tracheal aspirates. A meta-analysis of 23 studies of quantitative BAL cultures and 18 studies of protected specimen brush cultures suggested the diagnostic value of these methods.[19,31] However, they have not been shown to decrease mortality. If antibiotics have been given in the preceding 24 to 48 hours, quantitative cultures may be invalid. The collection of BAL fluid or protected brush specimen cultures without bronchoscopic methods (i.e., blindly) has an 80% concordance with bronchoscopic methods.[32] However, the use of quantitative cultures has been criticized because it may delay initiation of antibiotic therapy and there is the possibility of a false-negative test. In adults, the use of BAL may permit discontinuation of antimicrobial therapy.[24]

Köskal et al.[33] obtained bronchoalveolar lavage specimens from 145 intubated newborn infants and did quantitative counts and smears for white blood cells on the BAL fluid. Using CDC criteria for VAP, 44 infants (30%) were diagnosed as infected and 90% of those infants (n = 40) had positive BAL cultures. The percentage of neutrophils containing intracellular bacteria was significantly higher in infants with VAP (versus colonized, asymptomatic infants) as was the presence of leukocytes in BAL fluid (84% versus 26%). Quantitative cultures (greater than 10^5 colony-forming units [cfu]/mL) also distinguished infants with VAP from colonized asymptomatic infants. The sensitivity and specificity of intracellular bacteria and quantitative cultures were 94% and 90% respectively. In contrast, Cordero et al.[34] demonstrated that the majority (71%) of infants with purulent "tracheal aspirates" were asymptomatic. Furthermore, radiologically documented VAP occurred in 7% of very-low-birth-weight (VLBW) infants who never had a purulent tracheal aspirate and in 5% who did. Purulence on a tracheal smear was directly related to the duration of endotracheal intubation. Tracheal aspirates in infants with suspected VAP are important in identifying the organisms colonizing the infant's airways and in making sure they are sensitive to the chosen antimicrobial therapy.

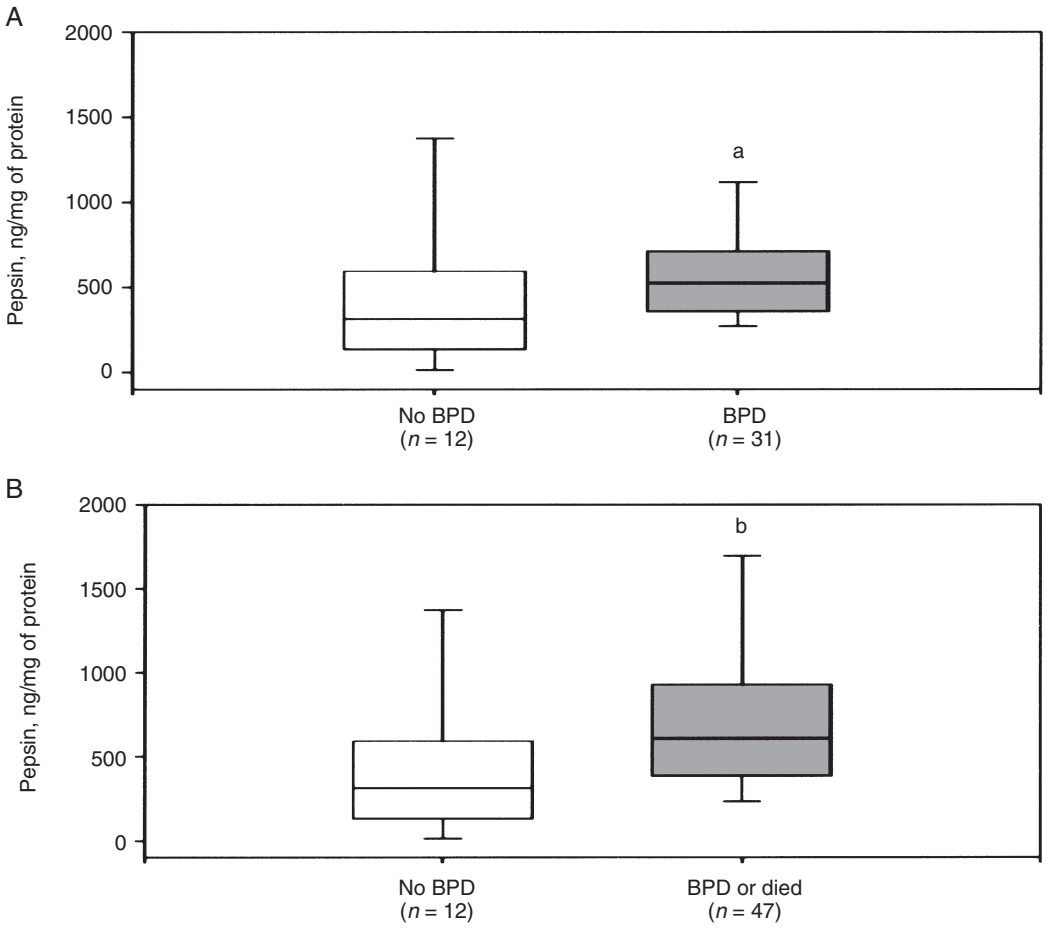

Figure 24-4 ■ Mean pepsin concentration from tracheal aspirates in infants with no bronchopulmonary dysplasia (BPD) and from infants with BPD or with BPD or who died before 36 weeks' gestation. (From Farhath S, Zhaoping H, Nakhla T, et al: Pediatrics 121:e253-259, 2008.)

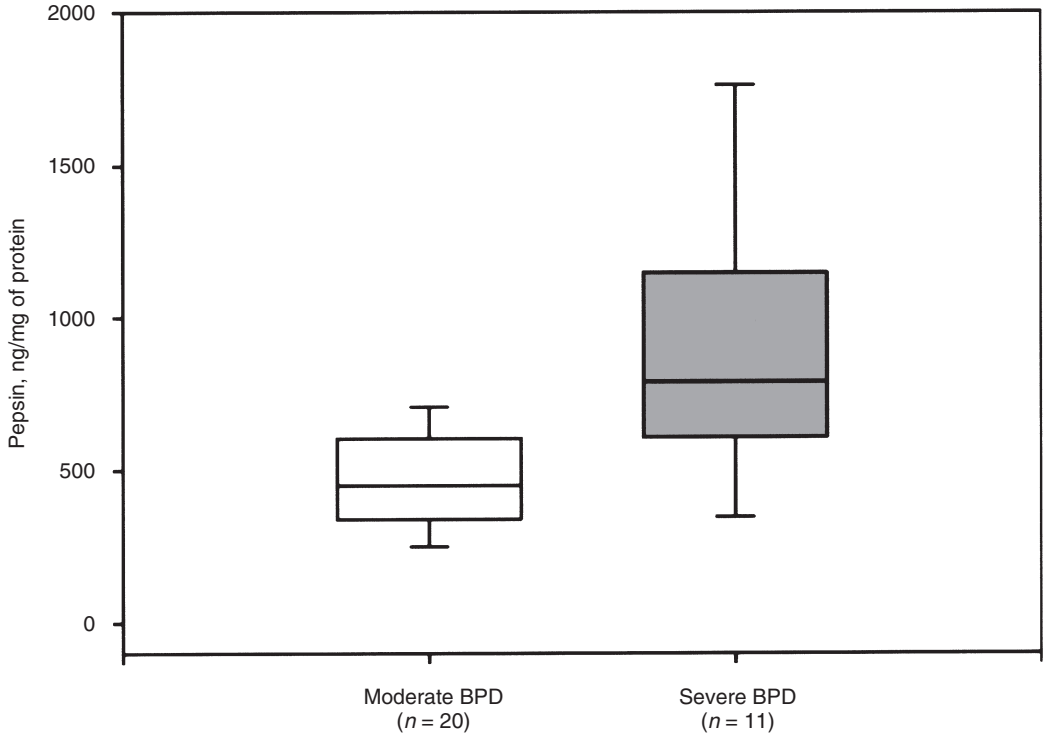

Figure 24-5 ■ Mean pepsin concentration in preterm infants with moderate bronchopulmonary dysplasia (BPD) and severe BPD. (From Farhath S, Zhaoping H, Nakhla T, et al: Pediatrics 121:e253-259, 2008.)

The use of an antimicrobial regimen that is incorrect has been associated with a significantly greater risk of death in adults.[35,36]

The use of biochemical markers (e.g., c-reactive protein and procalcitonin) has been investigated in adults,[37] but there are no data to assess their utility in neonates. Traditional markers (neutrophil indices and acute phase reactants) are of value in infants who are bacteremic, but that represents a minority of the infants with VAP.

Prevention

Prevention of VAP in adult populations has been primarily achieved by the "bundle approach." This involves the simultaneous application of several prevention strategies for all patients, often aided by tools such as checklists. In some cases there is only theoretical evidence or biologic plausibility for one or more of the elements of the bundle being effective, but application of these bundles is widely used and has been highly successful.[8] Prevention strategies for VAP in adult populations generally include elevation of the head of the bed, daily "sedation vacations" and assessment of readiness to extubate, peptic ulcer disease (PUD) prophylaxis, and deep venous thrombosis (DVT) prophylaxis.[38] Additional strategies recommended by the CDC) include staff education, surveillance and feedback of VAP rates to clinicians, ensuring proper sterilization of reusable respiratory care equipment, using sterile water in humidification systems, periodic drainage of condensate from breathing circuits, hand hygiene before and after contact with a patient who has an endotracheal tube, as well as before and after contact with respiratory equipment, vaccination against pneumococcal and influenza disease, prevention of aspiration by avoiding intubation using noninvasive ventilation and elevating the head of the bed, as well as implementing a comprehensive oral-hygiene program. The CDC guidelines do not recommend changing the breathing circuit unless it is visibly soiled or mechanically malfunctioning; do not recommend PUD prophylaxis or selective digestive tract decontamination (SDD); nor do they make a recommendation for a preference between closed or open suction catheter systems.[39] Although many health care institutions have developed VAP prevention "bundles," where several of the above interventions are simultaneously and reliably used for all mechanically ventilated patients, no single set of VAP prevention interventions has been adequately studied in the neonatal (or pediatric) population.

Head-of-the-bed elevation has shown dramatic effect in reducing VAP in adult populations, presumably by reducing reflux and aspiration. The only pediatric trial of this intervention showed no effect, but was underpowered and has been presented only in abstract form.[40] The logic of head-of-the-bed elevation is sound and it is found in almost every VAP reduction bundle, but the physical characteristics of neonates and their support equipment may make implementation challenging.

Another positioning strategy has been proposed, based on an animal model, where intubated neonates are positioned in the lateral, rather than supine, position. One group of authors hypothesized that such positioning would make use of gravity to help to avoid tracheal contamination from oral secretions. In a prospective randomized trial, they demonstrated a 50% lower incidence of positive tracheal cultures in the lateral position group.[41] Whether the optimal position of the intubated neonate is with the head of the bed up, lateral, or positioned otherwise, needs continued study.

Daily "sedation vacations" and assessment of readiness to extubate is standard in most VAP reduction bundles. Some variation on this practice is reasonable for the neonatal population. In almost all cases, practitioners would agree that extubation is a critical goal, and obviously VAP will not occur in the absence of mechanical ventilation. The role of "sedation vacations" is less clear in neonates. Many centers use minimal to no sedation for their intubated premature infants. In situations where sedation is needed, the risk of unplanned extubation must be considered when sedation is periodically withdrawn. Given that reintubation has been found to be a risk factor for VAP, overzealous weaning of sedation could actually become a risk factor for VAP.[12] Noninvasive respiratory support such as nCPAP is becoming more common and its use should reduce VAP rates.[14]

DVT prophylaxis is considered to be standard of care in sedentary adult patients to avoid the complications of thromboembolism, and it is included in most adult VAP reduction bundles. Although these bundles have significantly reduced VAP rates, there is no indication that DVT prophylaxis has a role in this process and is often justified as being included as a general "best practice." DVT prophylaxis is not used in the NICU.

PUD prophylaxis is another standard intervention in adult VAP reduction bundles. Applying peptic ulcer disease prophylaxis is considered an appropriate intervention in the ICU setting because of the higher incidence of stress ulceration in critical illness. In addition, increasing the pH of gastric contents may protect against a greater pulmonary inflammatory response to aspiration of gastrointestinal contents, because the effects of aspirating acidic contents may be worse than those with a higher pH. H2-receptor blockade is often used in neonates who are not yet being enterally fed (for gastric protection) and also in those infants who are thought to have significant gastrointestinal reflux. However, H2 blockade in neonates is not without risks. Normally acidic stomach contents are thought to decrease colonization with bacteria; reversing this innate defense has potential to cause harm. There have been several studies in adult populations examining the use of sucralfate, which provides gastric protection, but does not change pH. Very little data exist on the question of PUD prophylaxis reducing VAP in pediatric populations and none in neonatal populations. Data from the pediatric population show no change in VAP rates between pediatric intensive care unit (PICU) patients treated with an H2-receptor antagonist, sucralfate, or placebo.[42] Additionally, H2 blockade has been shown to be associated with increased rates of gram-negative bacteremia in the neonatal population.[43] At this time, there can be no recommendation for routine use of PUD prophylaxis for the purpose of VAP reduction in the neonatal population.

Selective decontamination of the digestive tract involves the enteral administration of nonabsorbable

antimicrobials for the purpose of decreasing gastrointestinal colonization, and therefore, potentially decreasing respiratory infections because aspirated gastric contents would be less likely to carry contagion. SDD has also been proposed as a preventative strategy for many infections: sepsis, surgical site infections, and others. Although data in adult ICU populations are generally supportive of the role of SDD in VAP reduction, pediatric data are less robust. A prospective randomized trial of colistin, tobramycin, and nystatin administered orally in a PICU population demonstrated a lower rate of pneumonia (VAP was not separated from other types of pneumonia) in the treatment group.[44] A smaller trial of severely burned PICU patients showed no efficacy for a polymyxin E, tobramycin, and amphotericin B regimen.[45] The only study of neonatal patients was a prospective nonrandomized trial of polymyxin E, tobramycin, and nystatin; the treatment group had a statistically significant decrease in infections caused by organisms of intestinal origin; this decrease encompassed respiratory tract infections, sepsis, wound infections, and others. VAP was not reported separately so the results are not clearly indicative of success in its reduction.[46] SDD may have potential in reducing many infections, but carries risk of increased antibiotic resistance and has not been evaluated rigorously enough to consider its use in neonates outside of a clinical trial.

The CDC recommends a comprehensive oral hygiene program to prevent VAP. Several regimens including antimicrobials and chlorhexidine gluconate (CHG) have shown reductions in VAP rates in adult patients. There is no neonatal data on oral hygiene and the risk of VAP, and its pathogenesis may be very different between edentulous neonates and adults who may have gingivitis or other dental disease predisposing them to abnormal oral colonization. In addition, CHG is not licensed for use in children less than 2 months of age.

There is unequivocal evidence that hand hygiene is the most important infection control intervention in all health care settings, but also one of the most difficult infection reduction strategies to maintain. The majority of VAP is polymicrobial and caused by *S. aureus* and a variety of gram-negative organisms. All of these pathogens are carried on the hands of health care workers and are found in the infants' gastrointestinal (GI) tracts. Those sites are likely the reservoir for gram-negative organisms, especially antibiotic-resistant ones, which are spread between patients, first causing colonization and then disease.[47,48] Respiratory care equipment can be colonized with these organisms as well.[49] Hand hygiene (with an alcohol-based hand sanitizer unless hands are visibly soiled) before and after contact with every patient is clearly a practice that will reduce VAP.[50] Given that the organisms that contaminate respiratory equipment are found in the sputum and oropharynx of patients, hand hygiene before and after contact with respiratory equipment and thorough and regular cleaning of the environment and equipment should also reduce VAP.[50]

Improvements to the equipment used to mechanically ventilate patients have potential to reduce VAP. One prospective randomized trial in adult patients demonstrated an approximately 35% risk reduction when a silver-coated endotracheal tube was used compared with a conventional one.[51] The authors hypothesized that the silver coating would reduce biofilm formation and bacterial colonization, thus reducing VAP. Similar changes have been made to central venous catheters to reduce catheter-related bloodstream infections, with generally positive results. This trial showed promise in adult patients, and further study of this and other technologies in pediatric and neonatal populations are needed.

Given the scant literature regarding all of these measures, a neonatal VAP prevention bundle should contain interventions with biologic plausibility and low likelihood of causing harm. Attempting to elevate the head of the bed (reasonable in infants who tolerate that position), consistent hand hygiene practices, and daily assessment of the need for continued mechanical ventilation comprise a reasonable neonatal VAP bundle. Further studies of H2 blockade, sucralfate, and SDD are all warranted in the neonatal population.

Treatment

As with many of the diagnostic and preventative strategies discussed above, there are no clear consensus guidelines or studies as to the optimum treatment for neonatal VAP. Treatment recommendations can be extrapolated from adult guidelines and supported by standard epidemiologic principles. In general, treatment of suspected VAP should start with initial broad empirical therapy. The American Thoracic Society and Infectious Disease Society of America have clear treatment guidelines for VAP in adults.[30] These include early empiric broad-spectrum antibiotics (ideally from a different class than antibiotics that the patient has recently received), the potential use of linezolid in preference to vancomycin for VAP caused by methicillin-resistant *S. aureus* (MRSA), the potential use of aerosolized antibiotics, and narrowing coverage based on culture results and clinical improvement. Early initiation of appropriate therapy for VAP (and most health care–associated infections) is logical and has been shown to improve outcomes. However, the desire to provide early broad coverage carries the risk of overuse and inappropriate use of antibiotics leading to increased resistance, toxicity, and cost. One study in a combined neonatal and pediatric ICU setting demonstrated that antibiotics for suspected VAP accounted for up to one third of inappropriate use in this setting.[52]

When selecting empiric therapy, the likely flora and resistance patterns must be known; local epidemiologic data and known risk factors can inform this selection. Risk factors for infection with multidrug resistant (MDR) pathogens vary amongst adults, children, and neonates but have common themes: prolonged hospitalizations, prolonged mechanical ventilation, prior exposure to broad-spectrum antibiotics, more severe and multisystem illness, and immunosuppressive disease.[8,53] In adult patients, empiric monotherapy is recommended for those with uncomplicated VAP who are unlikely to be infected with MDR pathogens. In contrast, combination therapy is recommended for more complicated disease or in those likely to be infected with MDR pathogens.

Guidelines for adult VAP treatment suggest that initial empiric therapy be tailored or discontinued based on

culture results and clinical status. The technical difficulties of obtaining lower respiratory tract cultures and the general difficulty in diagnosing VAP make this desired deescalation in neonates difficult. The majority of neonates with VAP have multiple risk factors for MDR infection; however, there are no validated clinical scoring systems for VAP severity and improvement. Therefore, despite concerns about antimicrobial resistance, most neonates with VAP will receive a full course of empiric broad-spectrum treatment.

As shown in Table24-2, the majority of neonatal VAP episodes are thought to be polymicrobial; an overwhelming majority involve gram-negative organisms, and approximately one quarter involve *S. aureus*. Empiric therapy needs to address this epidemiology. In general, an antipseudomonal beta-lactam/beta-lactamase combination such as piperacillin-tazobactam or ticarcillin-clavulanate provides excellent therapy for most gram-negative organisms and many gram-positives, and also provides excellent anaerobic coverage. In NICUs with extensive extended-spectrum beta-lactamase–producing organisms, a carbapenem such as meropenem or imipenem/cilastatin would be a more appropriate choice. There is a small amount of evidence that therapy with the fourth generation cephalosporin cefepime provides adequate coverage.[54] It is controversial whether an additional gram-negative agent such as an aminoglycoside is necessary. One way to make this decision is to assess the likelihood of concomitant bacteremia or more severe systemic disease (need for blood pressure support, increased transfusion requirements, elevated inflammatory markers, extremes of white blood cell count). Although deescalating therapy in a neonate with VAP can be difficult, the removal of an aminoglycoside when blood cultures are shown to be negative, is preferable.

The need for dedicated gram-positive coverage for organisms resistant to the above agents is dependent on local epidemiology. If a given NICU has significant numbers of infants colonized or infected with MRSA, then such therapy is indicated. This treatment has traditionally been given as vancomycin, but there is mounting evidence that linezolid results in better outcomes for MRSA pneumonia.[55] It may be possible to discontinue this arm of treatment if no resistant gram-positive organisms are detected, depending on the quality and type of respiratory specimen obtained.

Aerosolized antibiotics are a theoretically attractive therapeutic modality. The only Food and Drug Administration (FDA)–approved aerosolized antibiotic is tobramycin for cystic fibrosis patients. A recent study in adult ICU patients with VAP or "ventilator-associated tracheobronchitis" showed good results with aerosolized vancomycin and/or gentamicin (depending on Gram stain) but there are significant issues with this practice.[56] There is no inhaled vancomycin or gentamicin solution that is preservative free, and a technical report from the American Association of Pediatrics specifically warns of the danger of bronchospasm with antibiotics not specifically designed for aerosolized use.[57] Further study and product development is needed in this area.

Several novel approaches to neonatal pneumonia have been studied including the administration of exogenous surfactant. One study used surfactant and a specific ventilatory strategy to reduce atelectasis and subsequent bacterial growth and translocation in an animal model of group B *Streptococcus* (GBS) pneumonia.[58] In another animal model of GBS pneumonia, exogenous surfactant administration with specific inhaled immunoglobulin was used.[59] Both of these studies showed promising results and deserve further inquiry.

Conclusions

Although the epidemiology of VAP in neonates is less well characterized than in adults, rates of 1.4 to 50/1000 ventilator days indicate a substantial problem. Diagnostic accuracy in neonates (and children) is challenging given that obtaining lower respiratory tract specimens is problematic with currently available equipment. In addition, radiographic studies may be difficult to interpret.

Prevention strategies are less well defined than in adults. A VAP prevention bundle for neonates based on available data, biologic plausibility, and consideration of risk/benefit should include elevating the head of the bed in infants who tolerate that position, consistent oral hygiene, excellent hand hygiene, and daily assessment of the need for continued mechanical ventilation. Further studies of other prevention strategies are clearly warranted.

Treatment with broad-spectrum antimicrobials of a different class than the patient has recently been exposed to for a defined amount of time is a reasonable practice. Changing to more narrowly directed therapy is hampered by the inability to reliably obtain high-quality lower tract cultures. The choice of drugs and the need for MRSA coverage should be informed by local epidemiology.

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25 Surgical Interventions for Respiratory Distress and Airway Management

Robert M. Arensman, MD

The development of neonatal intensive care units and the pediatric subspecialty of neonatology have promoted care and survival of ever increasing numbers of tiny infants and children with a whole host of complex anatomic problems. Consequently, pediatric surgeons face a whole new group of challenges in surgical management of the airway and lungs.

Although most neonates with respiratory difficulties are successfully treated medically, pediatric surgeons, bronchoscopists and otolaryngologists may become involved in the care of an increasing number of these patients (Box 25-1). Our improved ability to intubate, ventilate, and thereby prolong the lives of children who would be victims of neonatal asphyxia, congenital anomalies, or respiratory distress redefines the role of the pediatric surgeon/endoscopist as part of the neonatal management team.

The role of the pediatric surgeon is twofold: (1) as a primary diagnostician and therapist for those infants who manifest respiratory distress from an anatomic problem or who present with congenital airway obstruction (i.e., congenital stridor [Box 25-2]) and (2) as an ongoing consultant for neonates undergoing medical treatment requiring long-term intubation of their airways.

The Pediatric Surgeon as Diagnostician and Therapist

The role of the pediatric surgeon is often defined by the anatomic abnormalities present in any given child. For purposes of organization, material presented here is divided into (1) tracheal obstruction, (2) abnormalities of lung development, (3) abnormalities of the diaphragm, and (4) abnormalities of the skeleton.

Tracheal Obstruction

Nasopharyngeal Obstruction

Because the neonatal airway is quite small and can easily reach the point of critical narrowing, the presence of stridor signals a need for urgent diagnosis and possible intervention. Neonatal stridor may be easily managed medically in some cases, but may represent impending fatal obstruction in others; therefore, the approach to diagnosis is deliberate and timed based on the fear of airway obstruction (Fig. 25-1).

A short list of differential diagnoses for neonatal upper airway obstruction can be formulated by approaching the subject anatomically, beginning in the nasopharynx/oropharynx and progressing down through the respiratory tract.

Choanal Atresia

Choanal atresia, a relatively rare anomaly, with a reported incidence of 1:8000 births, involves occlusion of the posterior nares by a septum with membranous (10%) or bony (90%) constitution (Fig. 25-2). The lesion may be asymptomatic if unilateral but may cause almost total airway obstruction if bilateral because most neonates are preferential nasal breathers. The symptoms are most evident when a baby is at rest, because when agitated and crying, the infant is able to breathe via his oropharynx. Associated anomalies include esophageal atresia, congenital cardiac lesions, colobomata, and Treacher Collins syndrome, and a large number of rarer associations.[1-3] Diagnosis is made by failure to pass a catheter through the nostrils to the oropharynx. Management ranges from simple placement of an oropharyngeal airway to operative opening of the occlusion with placement of stents and rarely to tracheostomy if definitive surgery cannot be done in the neonatal period.[4]

Oropharyngeal Obstruction

Macroglossia

The tongue is often a site of obstruction, causing stridor in a neonate when the tongue is disproportionately larger than the infant's oropharynx. Physical examination confirms the diagnosis. Insertion of an oral airway is usually successful in treating this type of airway obstruction. Several well known syndromes include macroglossia as a component.

Beckwith-Wiedemann Syndrome

Severe hypoglycemia, in many cases secondary to hyperinsulinemia, initially brought these examples of infantile gigantism to medical attention. Other manifestations of this syndrome include macroglossia secondary to muscular hypertrophy, visceromegaly, microcephaly, and a series of

Box 25-1 INDICATIONS FOR NEONATAL BRONCHOSCOPY

- Prolonged intubation (6-8 weeks)
- Repetitive failure of extubations
- Inability to aerate all lobes of the lung (persistent atelectasis)
- Clinical need for cultures or bronchial washings
- Suspicion of necrotizing tracheobronchitis
- Evaluation of stridor

umbilical abnormalities ranging in size from congenital umbilical hernia to omphalocele. Affected infants may also demonstrate a facial nevus flammeus, renal medullary dysplasia, and a characteristic pit on the tragus of the ear. These babies are usually quite large at term and weigh 3.5 to 5.5 kg at birth. The congenital stridor resulting from the enlarged tongue usually resolves rapidly with the insertion of an oropharyngeal airway, and little further diagnostic workup of the airway is necessary if the child can be identified as having this syndrome.[5-9]

Box 25-2 DIFFERENTIAL DIAGNOSIS OF NEONATAL STRIDOR (ANATOMIC APPROACH)

Nasopharynx
- Choanal atresia

Tongue
- Idiopathic
- Beckwith-Wiedemann syndrome
- Metabolic disorders
  - Hypothyroidism/lingual thyroid
  - Glycogen storage disease
- Down syndrome

Oropharynx (Micrognathia and Glossoptosis)
- Pierre Robin sequence
- Treacher Collins syndrome
- Hallermann-Streiff syndrome
- Möbius' syndrome
- Freeman-Sheldon syndrome
- Nager syndrome

Larynx
- Laryngeal atresia
- Laryngeal web
- Vocal cord paralysis
- Laryngomalacia
- Subglottic stenosis
  - Congenital/traumatic
- Laryngocele
- Laryngeal cleft
- Subglottic hemangioma

Trachea
- Intrinsic compression
  - Tracheomalacia
  - Tracheal stenosis
  - Necrotizing tracheobronchitis
- Extrinsic compression
  - Cystic hygroma
  - Vascular rings

Metabolic Disorders

Several neonatal metabolic disorders cause macroglossia and result in congenital stridor, the best known of which are hypothyroidism and glycogen storage disease. The large tongue, high nature of the airway obstruction, and findings consistent with the underlying condition hopefully suggest the diagnosis and appropriate work-up early in the course of the disease. The stridor in these babies is generally mild, usually successfully treated with an oropharyngeal airway, and disappears shortly after birth as these babies adjust to extrauterine life and have the underlying condition successfully treated. Diagnostic evaluation in these patients should be directed to the underlying metabolic disorder; little additional diagnostic work is need for the tracheobronchial tree.

Down Syndrome (Trisomy 21)

Children affected by Down syndrome are easily identified by their constellation of abnormalities. Their relative macroglossia may result in a mild congenital stridor. Because Stewart[10] has reported an association between Down syndrome and congenital subglottic stenosis, endoscopy may be necessary to establish the definitive cause of the stridor.

Lingual Thyroid

Lingual thyroid is a rare condition that can cause oropharyngeal obstruction.[11-13] Stertor in the presence of hypothyroidism, detected by persistent elevation of thyroid-stimulating hormone on routine neonatal screening, raises the suspicion for lingual thyroid, although other lesions are more commonly responsible. This condition occurs in just over 1 in 10,000 births.

Laryngoscopy is performed to confirm a mass. This is further characterized by computed tomography (CT) scan and thyroid scintigraphy to aid in diagnosis. Of note, the thyroid may continue to hypertrophy during early infancy and childhood, and the respiratory complications associated with hypothyroidism, such as respiratory depression, may not occur until later

Severe Bronchopulmonary Dysplasia

Although not generally reported and often not appreciated clinically, macroglossia can develop in infants with severe bronchopulmonary dysplasia and worsen the chronic pulmonary compromise. The obstruction caused by this condition is the result of chronic hypoxia (similar to clubbing of the fingernails) and often heralds a poor outcome. The condition may result in increased respiratory acidosis and is best treated by tracheostomy rather than plastic reduction of the tongue.

Craniofacial Dysmorphology Syndromes

The craniofacial dysmorphology syndromes range from unusual to extremely rare. All have in common an obstruction located in the oropharynx resulting from micrognathia with glossoptosis.[14] The stridor varies from mild to severe, and it is important to identify the underlying problem, which is often genetic. More complete descriptions of these conditions can be found in texts on congenital malformations.

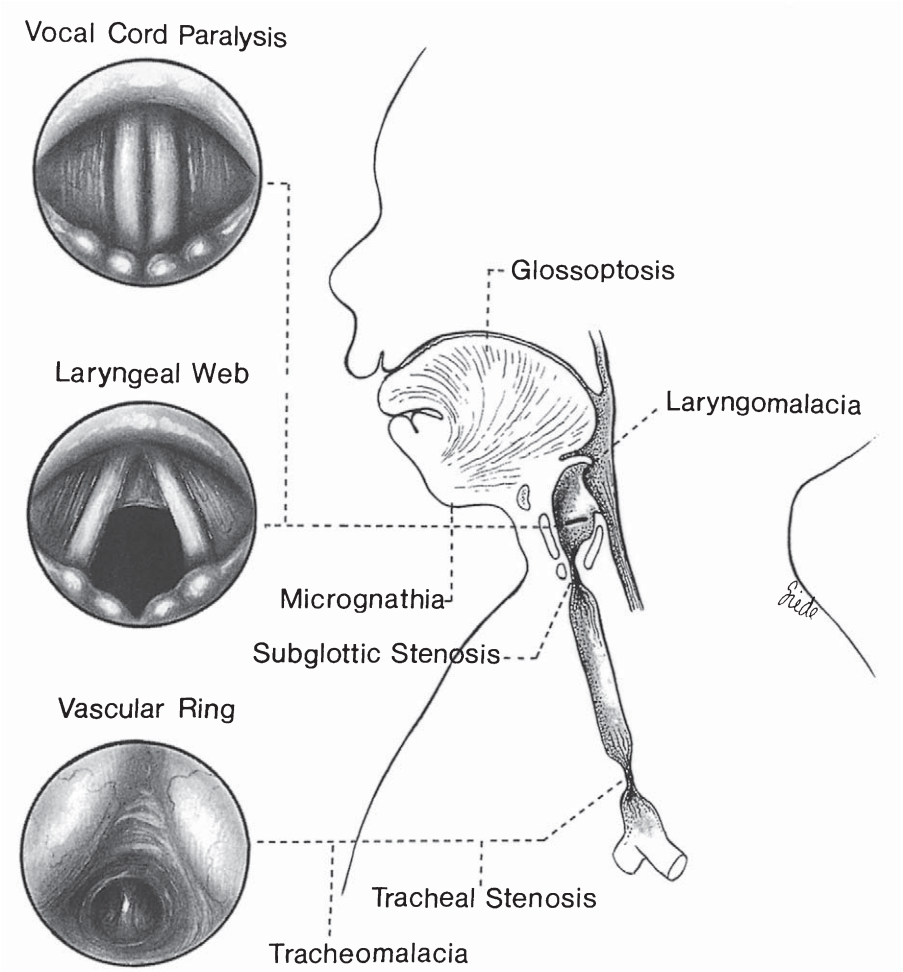
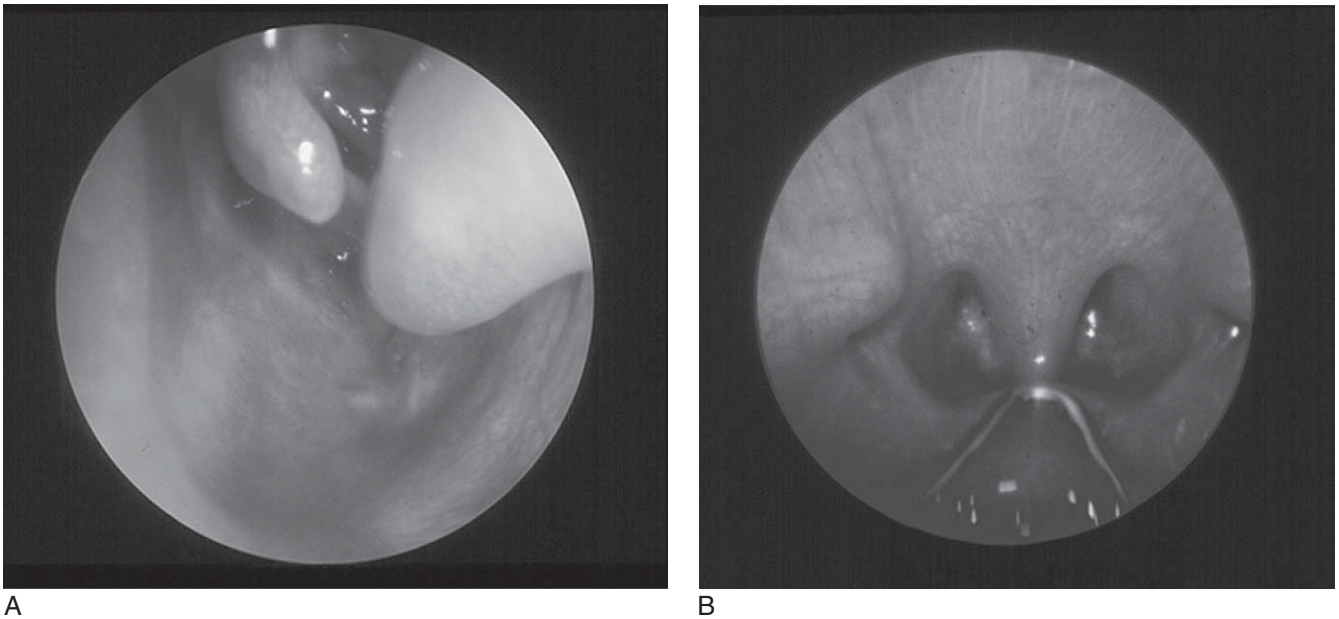


Figure 25-1 ■ Composite diagram of some of the lesions that result in neonatal stridor (proceeding downward through the respiratory passages).



A B

Figure 25-2 ■ Choanal atresia **A,** Endoscopic view. **B,** Nasopharyngeal view.

Pierre Robin Syndrome

Pierre Robin syndrome[15-20] represents the most common dysmorphic situation in this group with micrognathia and glossoptosis. In addition, approximately half of these babies also have cleft palates/cleft lip anomalies, perhaps attributable to protrusion of the tongue between the posterior palatine plates during embryologic development, resulting in failure of normal midline fusion. The tongue often prolapses posteriorly, resulting in partial obstruction of the upper airway. During inspiration, negative pressure in the pharynx further retrodisplaces the tongue and may increase the degree of pharyngeal obstruction. Stridor consequently results in these children with Pierre Robin syndrome, and they have particular difficulty on inspiration. The airway obstruction is usually resolved with insertion of an oropharyngeal airway; the baby also tends to breathe more comfortably in a prone position. Feeding may create further problems for these babies and necessitate special nipples or gavage nutrition.

Tracheostomies are rarely necessary in these cases and are to be avoided if at all possible because of the risks of airway occlusion and death. Surgical procedures such as glossopexy or creation of a lingual flap have been described as alternatives but are also seldom needed except in the most severe cases. The first few months of life are critical in determining the severity of a particular child's anomaly and its importance in the overall prognosis.

Treacher Collins Syndrome

Treacher Collins syndrome,[21] also known as *mandibulofacial dysostosis*, includes an extremely variable and diffuse group of craniofacial anomalies. Babies afflicted may manifest downward sloping palpebral fissures, colobomata of the lower lids, sunken cheek bones, and blind fistulae on an angle between the mouth and ears (Fig. 25-3). Pinnae may be deformed, deafness is common, and micrognathia is part of the syndrome (usually less severe than that seen in Pierre Robin syndrome). The presumed genetic defect is autosomal dominant with *mutation* in the *TCOF1* gene, at chromosome *5-q32-q33.1*.

The hypopharynx is the location of the obstruction in these children (as in children with the Pierre Robin syndrome), owing to the disproportionate relationship between the small jaw and the large tongue. These cases of stridor can most often be managed medically, often with simple insertion of an oropharyngeal airway, and tracheostomy is seldom necessary. Rarely, bronchoscopy may be indicated if associated tracheobronchial tree anomalies are a concern, but these are quite unusual.

Hallermann-Streiff Syndrome

The Hallermann-Streiff syndrome[22,23] is a rare syndrome, or perhaps a rare family of closely related syndromes, that consists of microphthalmia, cataracts, blue sclerae, and nystagmus. Associated anomalies include a pinched nose, micrognathia, and hypertrichosis of the scalp, eyebrows, and eyelashes (Fig. 25-4). Transmission is presumed to be autosomal dominant, although most cases are thought to represent fresh mutations. Congenital stridor in these infants arises from micrognathia with relative glossoptosis, and treatment is similar to that outlined for Pierre Robin or Treacher Collins syndromes.

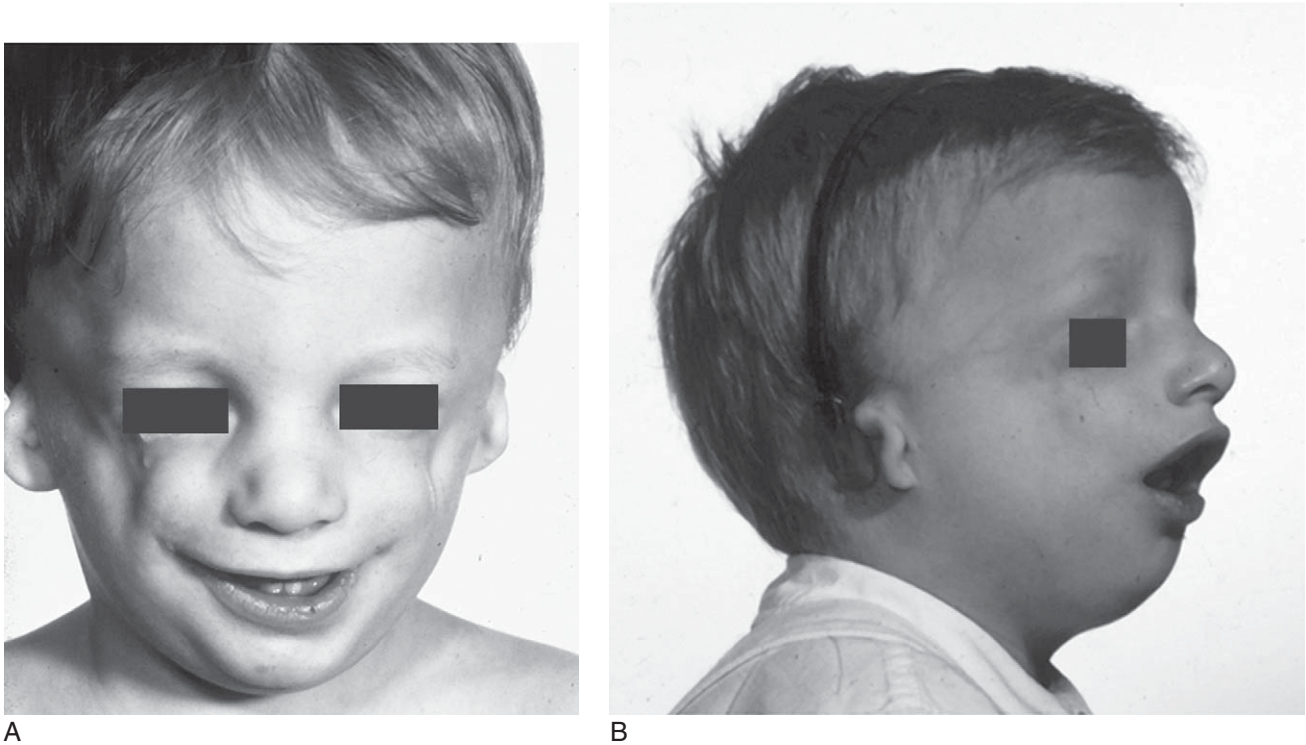


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Figure 25-3 ■ Example of a child with Treacher Collins syndrome demonstrating sunken cheek bones, downward sloping palpebral fissures, and micrognathia.

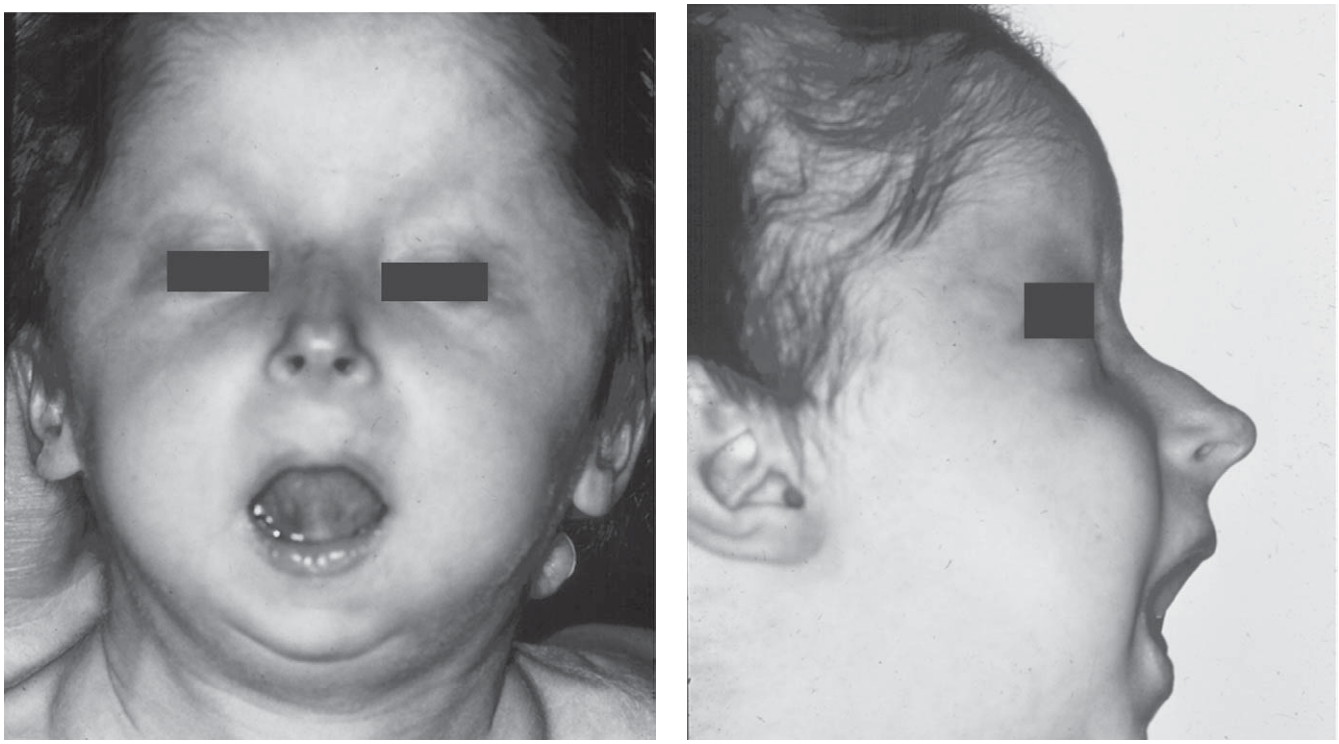

Figure 25-4 ■ Example of an infant with Hallermann-Streiff syndrome demonstrating microphthalmia, pinched nose, micrognathia, and hypertrichosis of scalp.

Möbius Syndrome

Infants with the Möbius syndrome[24-26] have characteristic absence or maldevelopment of various cranial nerve nuclei. The seventh (facial) nerve is most commonly involved, but other cranial nerves (6, 5, and 8) may be affected to various extents. Common physical findings include facial paralysis, ptosis, ophthalmoplegia, clubbed feet, and syndactyly. The presumed mode of transmission is an autosomal dominant defect.

The facial immobility secondary to seventh nerve involvement causes upper airway obstruction and difficulties in chewing and swallowing. Both inspiratory and expiratory components of stridor result from the relatively fixed nature of the obstruction. Judicious placement of a tracheostomy may be required in severe cases. Many children, however, can be successfully treated by parental instruction in very careful feeding techniques.

Freeman-Sheldon Syndrome

Infants with Freeman-Sheldon syndrome[27,28] are often called "whistling faced" children. They have hypoplastic alae nasi, clubbed feet, and masklike whistling facies. Their eyes are deep set with blepharophimosis, ptosis, and strabismus. Transmission is autosomal dominant with some variations that transmit as autosomal recessive. Chromosomal abnormalities have been reported at both *11p15.5* and *17p13.1*. Today these children are classified as having a type of distal arthrogryposis.

Stridor in these children is effectively the result of air forced through a narrow passage, and although the sound may be alarming to family and nursing personnel, it usually does not require immediate intervention.

Nager Syndrome

Nager syndrome[29-34] is a rare acrofacial dysostosis that presents with upper limb malformation, mandibular and malar hypoplasia, downward slanting palpebral fissures, absent eyelashes in the medial third of the lower lids, dysplastic ears with conductive deafness, and variable degrees of palatal clefting. Chromosome 9 abnormalities are suspected in the development of this syndrome. Airway obstruction in these patients is related to mandibular hypoplasia and tongue displacement posteriorly. Acute management often requires early tracheostomy and subsequent mandibular distraction to establish an airway and correct the defect.

Laryngeal Anomalies

An infant's larynx is the next site of possible obstruction and laryngeal anomalies account for the majority of cases of stridor in newborns.

Laryngeal Atresia

The most extreme form of obstruction at this level, laryngeal atresia, results in a desperate emergency during the first few moments of life. This lesion was originally described in 1826, but only 51 cases were reported in the subsequent 160 years. Of children thus affected, few have survived. This low survival rate is attributable to the fact that surgical intervention must occur within 2 to 5 minutes of birth.[35]

The most dramatic physical finding is that the child is aphonic, with absence of any cry or gasp at birth. If the lesion is immediately recognized on direct laryngoscopy, an emergency cricothyroidotomy should be performed. Diagnosis of laryngeal atresia has now been reported prenatally,[36] and in the future, clinicians may be able to prepare for emergent airway management at birth or schedule the child for an ex-utero intrapartum treatment (EXIT) procedure followed by emergent airway opening.

Laryngeal Web

Laryngeal web accounts for approximately 5% of laryngeal anomalies (Fig. 25-5). These lesions arise about the 10th week of intrauterine life and probably represent an arrest of the development of the larynx in the area near the vocal cords. Seventy-five percent of these lesions occur at the level of the cords; the rest are subglottic or supraglottic in about equal numbers. The web generally occurs anteriorly, and the lesions are often asymptomatic if they extend less than halfway back along the cords. Because the glottic area is triangular, these anteriorly placed webs reduce the glottic area by only 15% to 20% and are usually not sufficient to cause stridor.[37]

If the web extends posteriorly, the symptoms may be marked. The stridor is primarily inspiratory but often has an expiratory component. The affected infant's cry is hoarse and weak; the child is rarely aphonic and often is dyspneic at rest.

Laryngoscopy and bronchoscopy should be performed as soon as possible. If a thin, transparent web is encountered at the level of the cords, it may be easily swept away with the bronchoscope, completely correcting the problem. Bronchoscopy should be done for completion to rule out the possibility of associated anomalies beneath the area of the web.

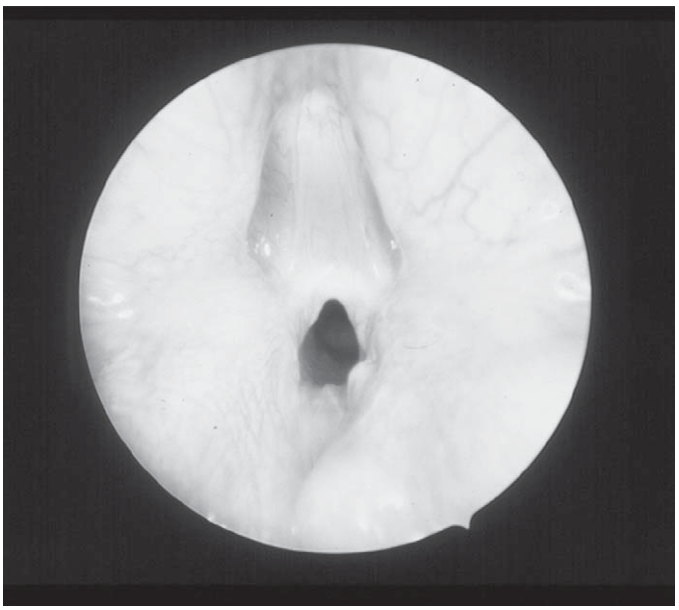

Figure 25-5 ■ Endoscopic view of neonatal larynx with partial laryngeal atresia and a laryngeal web partially obstructing the laryngeal orifice.

If the web is thick and fibrous, no attempt should be made to force the bronchoscope through the area. This kind of web is often encountered in the subglottic region. Tracheostomy is the treatment of choice if the child is dyspneic and unable to tolerate the web. If aeration of the child is satisfactory despite the stridor, as evidenced by arterial blood gas determinations, simple observation may be sufficient management until the baby is able to undergo surgical repair. This is usually deferred until the child is 18 months to 2 years old. The best results to date have been achieved in those children who undergo a meticulous removal of the thick fibrotic web and insertion of a mold during the healing period.[38] Depending on the thickness of the web, laser therapy is an alternative and may yield superior results in the future.

Congenital Vocal Cord Paralysis

Congenital vocal cord paralysis is the second most common cause of congenital stridor. In the past, birth trauma was frequently implicated in the etiology of the paralysis but now appears to be a declining cause. Intracranial lesions and the possibility of congenital cardiac lesions, especially one impinging on the recurrent laryngeal nerve, must be considered.[39]

Fortunately, the paralysis is unilateral in 70% to 80% of cases. Some studies report that both sides are equally involved,[40] but left-sided paralysis is significant in its association with underlying congenital cardiac anomalies. In these infants, the cry is hoarse and weak, and if the paralysis is bilateral, these children may be truly aphonic. The inspiratory stridor is obviously worse in bilateral paralysis. Marked supersternal and intercostal retractions may be present in these children.

Diagnosis is rapidly made by laryngoscopy, and treatment depends on the severity of the problem. In a unilateral paralysis with minimal or no dyspnea, simple observation is appropriate. Bilateral paralysis, generally associated with severe symptoms, necessitates tracheostomy for prevention of impending total obstruction. Once the airway is adequately secured, the cause of the paralysis can be explored. If the causal lesion can be identified and corrected, the stridor may improve. If no lesion can be found or if it cannot be safely corrected, later fixation of the arytenoids with the vocal cord in abduction may result in satisfactory control of the stridor and decannulation of the child.

Laryngomalacia

Laryngomalacia is the most common cause of congenital stridor, accounting for 60% to 75% of cases of stridor in newborns. It also appears to account for three-fourths of the congenital laryngeal abnormalities. The pathophysiology of this condition involves an immature, floppy larynx that is sucked downward into the glottis during each inspiration (Fig. 25-6), producing an inspiratory stridor of varying severity that is often much worse when the child is agitated or screaming. Whether this stridor improves at night is unpredictable. Some children improve at night, but others experience a worsening of their respiratory sounds.

Laryngomalacia occurs with a 2:1 male-to-female predominance and is usually present at birth. In 25% of cases,

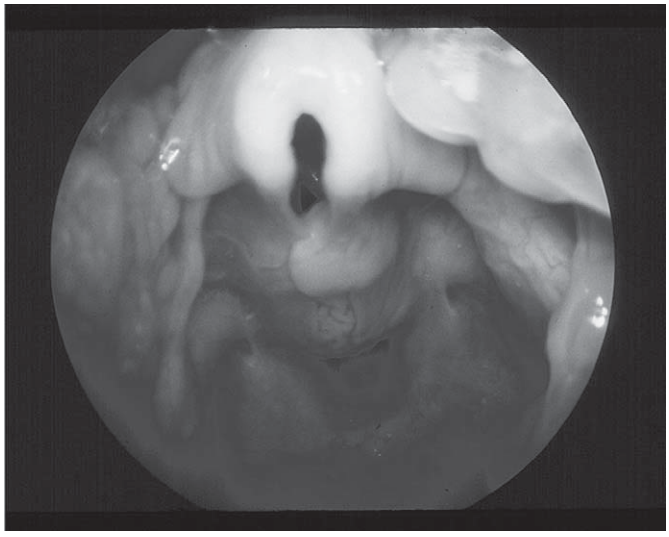

Figure 25-6 ■ Endoscopic view of immature floppy glottis characteristic of laryngomalacia. Dynamic examination demonstrates downward placement of glottis into larynx with inspiration.

however, the first symptoms appear during the first or second week of life. Many cases are reported to have micrognathia, and some may be confused with Pierre Robin syndrome.

Diagnosis is made easily by laryngoscopy, which shows a soft, enfolded epiglottis. The larynx if often difficult to expose and is found high under the tongue. Bronchoscopy should accompany laryngoscopy to rule out associated anomalies or extensive malacia, such as tracheomalacia and/or bronchomalacia.

The prognosis for this condition is excellent, and only on rare occasions are symptoms severe enough to justify tracheostomy. Maturation of the epiglottis by the age of 18 to 24 months results in resolution of the stridor.

Congenital Subglottic Stenosis

The overall incidence of congenital subglottic stenosis is unknown, because many such cases remain unrecognized, although 39% of all subglottic stenoses have been estimated to be congenital (the remaining group being acquired).[41] As a rule, the narrowed area is 2 to 3 mm below the vocal cords and may reduce the subglottic area to 3 to 3.5 mm. The proposed cause of the congenital group is arrested development of the conus elasticus or the cricoid.[42]

The stridor, if present at all, is usually biphasic and sometimes arises during the first or second month of life. More commonly, the presenting symptoms, usually initiated by an upper respiratory tract infection, are respiratory distress and an inability to handle secretions. Affected children are often treated for recurrent pneumonias or prolonged tracheobronchitis. Many cases are not discovered until a severe episode of croup or epiglottitis results in emergency tracheostomy or intubation.

The diagnosis is confirmed by laryngoscopy; bronchoscopy rules out associated defects that may be present.[43] The mild forms of this lesion should be observed, and antibiotic therapy may be added during periods of upper respiratory tract infection. Tracheostomy is necessary in more than half the cases of children with severe stenoses and marked symptoms.[44] Once the tracheostomy is in place, dilation via monthly laryngoscopy under general anesthesia often results in considerable improvement. The dilation must be gentle to prevent further damage or fibrosis of the subglottic region. For more severe degrees of stenosis, open surgical intervention may be necessary. The outcome in this congenital group of subglottic stenosis is quite good, with 82% of patients in one large series successfully decannulated after one procedure.[45]

Acquired Subglottic Stenosis

Acquired subglottic stenosis, most often caused by prolonged endotracheal intubation, is explained by the sequence of events described in the pathophysiology section near the end of this chapter. Because of the increased survival of neonates with respiratory difficulties requiring intubation (especially extremely low-birth-weight infants), this lesion is increasing in frequency as a cause of stridor. A protracted form of acquired subglottic stenosis occurred in 8.3% of neonates surviving a period of endotracheal intubation in one study.[46]

In its mildest form, the stenosis consists of laryngeal edema and has been reported in 30% of infants immediately after intubation. Stridor in these patients is inspiratory and present with the first breaths after tube removal. This stridor usually resolves within 72 hours. During this 3-day period, an infant is sufficiently treated with head elevation, humidified air, racemic epinephrine, nasal continuous positive airway pressure, and occasionally systemic steroids (although the efficacy of steroids has never been conclusively demonstrated by experimental study).

In its most severe form, acquired stenosis is a dense scar of well-organized fibrous tissue. This lesion may require tracheostomy before the actual stenosis can safely be manipulated. Initial treatment includes graded, gentle dilation with or without intralesional steroids. As many as half of the stenotic scars will improve and often stabilize after 4 to 6 treatments. Failure to achieve significant improvement by then indicates the need for more aggressive treatment such as cryosurgery, laser surgery, cricoid split procedure, or resection and reconstruction with stents or keels. There have been reasonable results with cricoid split procedure and intubation during healing rather than recourse to tracheostomy, and this alternative should always be considered.

Laryngeal Cleft

Although laryngeal clefts were once considered extremely rare lesions, they have frequently been reported during the past 25 years.[47] This is probably a result of enhanced endoscopy techniques and improved ability to make the diagnosis in the antemortem period. The lesion seems to result from a failure of dorsal fusion during the chondrification of the cricoid cartilage.[48] A midline cleft thus remains posteriorly and extends down between the arytenoids into the upper portion of the esophagus and trachea. Affected children are often quite stridorous at birth, and many have died in the past because of inadequate resuscitation. In addition to their respiratory difficulties, these children aspirate and develop severe pneumonitis if they are fed without regard for their clefts.

Consequently, they require recognition, intubation, and stabilization. A feeding gastrostomy and possible fundoplication are probably necessary until definitive repair can be performed. Once extubation is accomplished, it is important to observe the child closely to ensure that upper airway secretions do not continuously pass into the lungs. If this proves to be a severe and ongoing problem that precipitates recurrent pneumonia and respiratory distress, it may be necessary to place a tracheostomy until surgical closure of the cleft can be achieved.

Subglottic Hemangioma

Hemangiomas may be another cause of congenital subglottic obstruction. The onset of symptoms is variable, as are the growth and development of these lesions. The lesions are at first quite small and may have a period of rather precipitous growth, followed by a long plateau and slow involution. If the lesion has significant growth during embryonic life, the affected child may display both inspiratory and expiratory stridor at birth. In other babies, the lesions develop shortly after birth, and in some children, several months may elapse before symptoms develop. Hemangiomas on other areas of the body suggest the possibility of subglottic hemangioma; definitive diagnosis is made by laryngoscopic and bronchoscopic examination.[49]

A bronchoscopic finding of a red or purple mass just beneath the cords is generally considered sufficient to confirm the diagnosis. Most pediatric surgeons believe that biopsy is contraindicated when such findings are seen, because hemorrhage necessitating emergent surgery is a distinct possibility after biopsy. Once the diagnosis is established, appropriate therapy is chosen according to the severity of symptoms. If the child is stable and has normal blood gas values at rest, observation is sufficient. If the obstruction is significant enough to result in dyspnea, severe stridor, and possibly abnormal blood gas values, tracheostomy below the lesion should be considered. One must also be aware of the possibility of platelet trapping (Kasabach-Merritt syndrome) before surgical intervention.

It is questionable whether radiation should be used in the treatment of these children today because of the risk of thyroid malignancy. Prednisone, 2 to 4 mg/kg per day, and interferon-alpha are quite beneficial if the hemangioma is growing quickly and causing thrombocytopenia. Dramatic regression of the hemangioma and prompt correction of the thrombocytopenia with the use of these agents have been reported, although both have also been associated with significant side effects.[50]

Tracheal Anomalies

Internal Tracheal Compression

Tracheomalacia

Tracheomalacia results from a failure of the cartilaginous rings to fully support the round shape of the normal trachea. The cartilages are hypoplastic and allow the trachea to collapse, especially during expiration (Fig. 25-7). This condition is commonly seen in babies and children undergoing bronchoscopic evaluation but is only incidentally responsible for stridor in a moderate number of them. Because obstruction of the airway tends to occur as the trachea collapses with expiration, stridor occurs at that time. The condition is diffuse and usually occurs throughout the length of the trachea.

Diagnosis is most simply achieved by bronchoscopy. After the scope is passed through the vocal cords, the trachea assumes a transverse or ovoid appearance, which is accentuated as expiration takes place. It is frequently difficult to see the carina as the scope advances through the trachea because of the collapse of the anterior wall. Despite some rather marked findings in some children, this lesion rarely necessitates any treatment, and it can be expected to resolve spontaneously with growth and maturation.

Tracheal Stenosis

Tracheal stenosis can involve either a short stenotic segment in an otherwise normal trachea or the entire trachea with a cylindrical tapering from the subglottic region (Fig. 25-8).[51] Either form may demonstrate a fixed obstruction resulting in inspiratory and expiratory stridor. Tracheal cartilages are often absent when this occurs, and instability of the tracheal lumen is not uncommon.

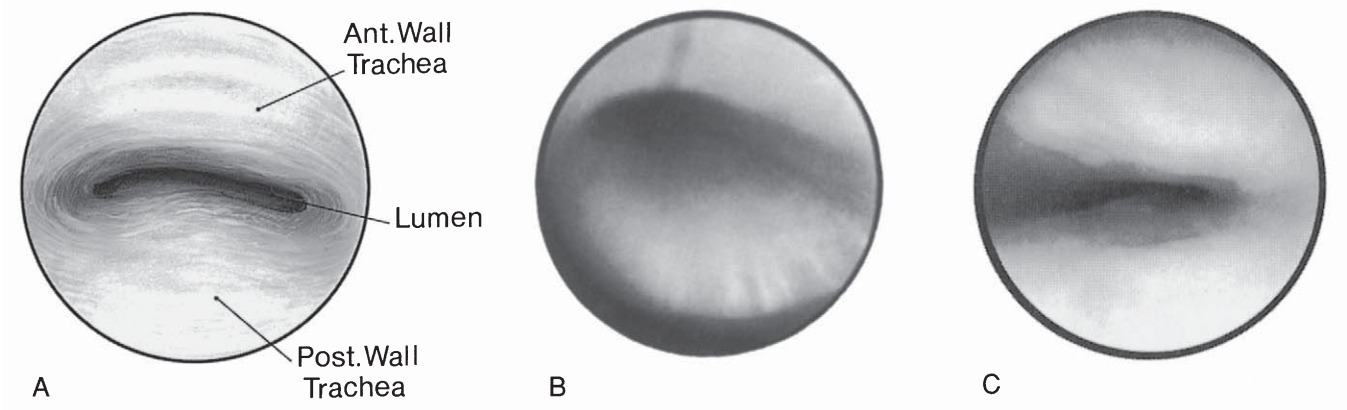

Figure 25-7 ■ Tracheomalacia showing collapse of the trachea on expiration. The lumen is almost obliterated as the anterior wall approaches the posterior wall. **A,** Artist's drawing. **B-C,** Photographs.

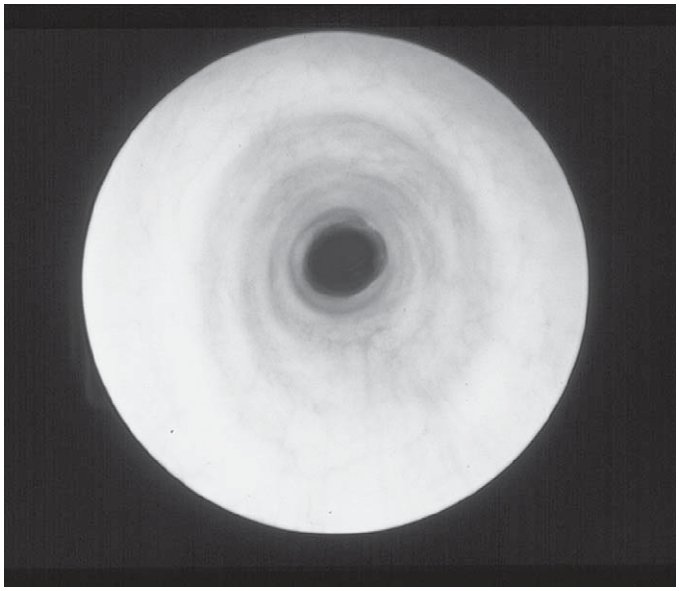

Figure 25-8 ■ Endoscopic view of tracheal stenosis as a result of complete tracheal rings tapering to a narrow lumen.

Depending on the severity of the stenosis and its length, affected children may have severe respiratory distress with cyanosis. Respiratory sounds may be weak, and the danger of sudden and acute obstruction is quite possible. Lateral radiographs or xerograms of the neck and chest may show a stenotic lesion. Otherwise, bronchoscopy is the best study to confirm the diagnosis.

Necrotizing Tracheobronchitis

The necrotizing tracheobronchitis lesion has been reported in two relatively large series from two different institutions, and numerous case reports and a small series have followed.[52,53] It is a necrotizing process that results in sloughing of the tracheal mucosa. The cause is unknown because cultures have consistently failed to reveal a bacterial or fungal infection in the majority of cases. However, it seems to be associated with hypoperfusion (such as a difficult birth requiring extensive resuscitation) and the use of high-frequency ventilators.

Clinical presentation involves deterioration of respiratory status. Affected babies generally manifest sudden carbon dioxide retention that fails to respond to change in ventilator settings, change of endotracheal tube, or intratracheal suctioning. Mortality is high unless suspicion of the lesion leads to bronchoscopy and mechanical clearing of the airway.[54] Moreover, even if a child is able to recover from an acute episode, recurrent necrotizing tracheobronchitis or chronic strictures may result.[55]

External Tracheal Compression

Cystic Hygroma

Cystic hygromas of sufficient size and extension to result in compression of the trachea, resulting in stridor, have been reported.[56] When these lesions are severe enough to result in stridor, they almost always produce respiratory distress and require surgical intervention. The goal of the initial treatment is to relieve the compression, which may be achieved by simple aspiration of fluid from the cyst. This can be followed by bronchoscopy to rule out the possibility of associated laryngotracheal anomaly and by surgical extirpation of the cyst.[57] This is a benign lesion, and critical structures are preserved whenever possible.

Vascular Rings

Vascular rings arise from anomalous formation of the great vessels that cross over or encircle the trachea and the esophagus. The variety of anomalies is quite extensive, but the few categories that commonly occur and lead to problems can be classified under four to six headings. Those structures usually responsible for congenital stridor are the double aortic arch, the right aortic arch with left ductus arteriosus or ligamentum arteriosum, and the anomalous innominate artery. More rarely, an anomalous right subclavian artery (Fig. 25-9), an anomalous left pulmonary artery sling, or an anomalous left common carotid artery may give rise to symptoms. For technical accuracy, only a few of these conditions should be considered true vascular rings that are complete encirclement of the trachea and esophagus by vascular structures. Specifically, these lesions include the double aortic arch and the right aortic arch with left ductus. The others are more correctly referred to as *slings*; because they pass around the trachea or esophagus and compress one or the other, but do not completely encircle them.

Stridor in affected neonates is present at birth or by 1 to 2 months of age. With the fixed nature of the obstruction, stridor is both inspiratory and expiratory. Afflicted children have a brassy, barking cough. If the compression of the vascular anomaly affects the esophagus, as it does in a few cases, the neonate may have associated problems with deglutition, such as regurgitation, vomiting, and aspiration.

Evaluation of these children begins with a barium swallow, which usually shows a single or double oblique indentation on the esophagus.[58] Subsequent bronchoscopy often reveals the pulsatile compressing mass passing over the anterior portion of the trachea on either the right

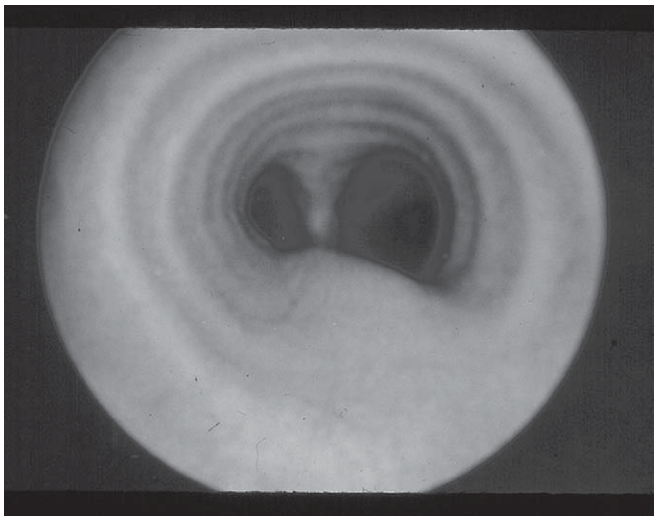

Figure 25-9 ■ Endoscopic view of anomalous right subclavian artery with impingement on the tracheal membrane.

or left side.[59] Depending on the location of the indentation, a presumptive diagnosis can be made. Also, one can occasionally compress the pulsatile area to check for disappearance of pulses to suggest which of the vascular anomalies is present. In most of these cases, computed tomography or magnetic resonance imaging with contrast materials give wonderfully accurate pictures of the exact anatomy.

Treatment of these lesions[60] is essentially surgical division of the ring when one is present. In cases of double aortic arch or right arch with left ductus arteriosus, division of the ring at its narrowest portion or ductal ligation and division usually result in considerable improvement. In the case of sling lesions, the offending vessel may be divided (as in treatment of the anomalous right subclavian artery) with or without reanastomosis. If transection alone does not relieve the obstruction, dissection of the trachea and esophagus with vessel suspension to the anterior chest wall has been performed with considerable improvement of symptoms.

All of these operations may be performed through a standard left thoracotomy, and results have been quite acceptable in several large review series.[61-63] The anomalous left pulmonary artery sling is fortunately one of the rarest of the vascular slings and continues to be the most difficult to handle surgically. This is usually approached through a median sternotomy, although some surgeons have performed it through a left thoracotomy. The left pulmonary artery must be transected, moved from behind the trachea, and reanastomosed anteriorly. This results in a more hazardous surgical undertaking and consequently a greater surgical mortality rate.[64,65]

Families must be warned before surgery that a residual tracheal deformity and tracheomalacia will persist and that symptoms usually do not abate for 6 months to 2 years after surgery. The deglutition problems may rapidly improve, but the stridor wanes much more slowly.

Abnormalities of Lung Development

Pulmonary and Lobar Agenesis

In intrauterine life, an entire lung or a portion of a lung may failure to develop. Etiology is not definitively known, but sufficient cases have been reported in neonates to document that little affect is seen with lobar agenesis. However, a right or left pulmonary agenesis generally creates respiratory distress and has a significant mortality. Interestingly, mortality seems to be greatest when the lung missing is the right lung. Numerous associated anomalies have been reported in all the organ systems.

Generally, a neonate born with this problem requires immediate intubation. Chest radiograph shows an opaque hemithorax with narrowed rib spaces and variable mediastinal shift. If the chest radiograph has been sufficiently penetrating, it may be possible to seen the absence of a carina or a blind-ending bronchial stump. Endoscopy confirms the agenesis.

After intubation and stabilization, attempts are made to wean the neonate from ventilatory support. This may or may not occur. In the event of success and survival, the neonate is at risk for recurrent pulmonary infection.

Pulmonary Hypoplasia

Pulmonary hypoplasia is discussed elsewhere in this text in terms of ventilatory management. However, there are several lesions that are well known to produce pulmonary hypoplasia from lung compression. The most known is the diaphragmatic hernia, but large intrauterine tumors such as tonsillar or head/neck teratomas can produce the same result. In cases such as diaphragmatic hernia, surgical intervention may be necessary, but the airway is usually not involved.

Congenital Lobar Emphysema

Congenital lobar emphysema,[66,67] frequently referred to as *CLE*, is extremely rare, usually present at birth or apparent within the first 6 months, and is of unknown etiology. The mechanism seems to be a ball valve obstruction, often attributed to deficient cartilage formation in the bronchi accompanied by bronchomalacia. However, fully half of the lungs removed as therapy fail to show any significant abnormality other than hyperinflation. Most series report a male preponderance of 2 : 1.

The pattern of involvement is surprisingly consistent, involving the upper lobes; first the left upper lobe (40%-45% of cases), then the right middle lobe (30%-35% of cases), and finally the right upper lobe (20%-25% of cases). Rarely, two lobes are affected at the same time, and a few reports of metachronous involvement of two lobes have been described.

Respiratory distress, possibly with cyanosis, is the presentation. Intubation may stabilize the situation, especially if the intubation is bronchial. In fact, bronchial intubation may result in resolution of hyperinflation that fails to return when the endobronchial tube is removed. Mild cases may be observed, but severe distress requires thoracotomy and lobectomy.

Chest x-ray alone is often sufficient for the diagnosis, based on hyperinflation, widened rib space, mediastinal shift, and collapse of the other lung. Computed tomography and $\dot{V}/\dot{Q}$ scanning have been advocated to confirm the diagnosis and add additional anatomic information, but in most cases recourse to these modalities is not necessary.

Congenital Cystic Adenomatoid Malformation

Congenital cystic adenomatoid malformation (CCAM) is, again, a rare and puzzling pulmonary malformation that affects all lobes, both sexes, and produces nonfunctional pulmonary tissue that has cysts, increased amounts of cellular elements, and abnormalities of cartilage, elastin, and other tissues.[68-70] The cystic component may be microcystic or macrocystic, and this element is often used as a typing criteria. The respiratory compromise is caused by space occupation with nonfunctioning pulmonary tissue that produces respiratory distress or harbors infection (Fig. 25-10). Some major disruption of the developmental interaction between developing airways and mesodermal somites that contribute the alveolar mass probably explains this unusual lesion.

All lobes may be involved with this process; there is no sex preponderance. At least 1 in 4 neonates affected will die from fetal hydrops. Maternal polyhydramnios is common. Some children have no symptoms at birth;

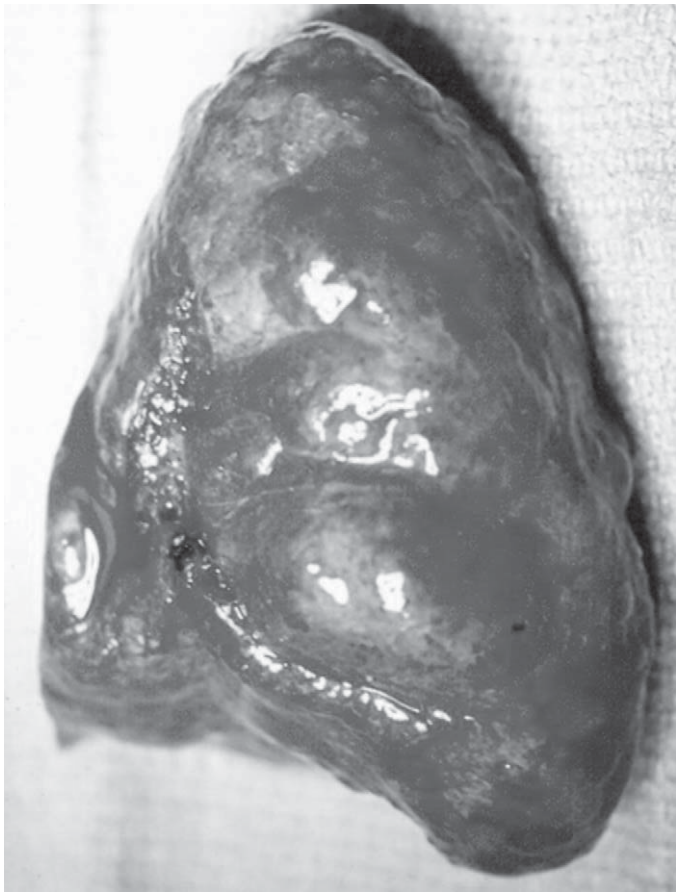

Figure 25-10 ■ Congenital cystic adenomatoid malformation (CCAM)–red, beefy lobe from lung with increased terminal alveolar tissue.

others are severely compromised. Many of these children are now diagnosed with prenatal ultrasound, so planning can be done to support the child at birth in case respiratory compromise is severe.

Space occupation and mediastinal shift may compromise a neonate at birth. Resection and removal may be completely curative therapy, but many of these children have mild or severe pulmonary hypoplasia and pulmonary hypertension. Surgery will not solve these problems, so recourse to extracorporeal life support (ECMO), long-term ventilation, and all the different modalities of ventilation and pharmacologic therapies may be necessary. Despite this gamut of therapies, some children have inadequate lung volume for survival (particularly those with severe mediastinal shift in utero and those with severe polyhydramnios).

Sequestration

Sequestrations[71-74] are masses of pulmonary tissue that do not attach to the bronchopulmonary tree. In other words, they are sequestered segments of mesoderm that should have contributed to the alveolar mass of the lung on the side where they are found. The exact etiology is unknown, but this lesion seems to affect males 3 or 4 to 1 over females, involve the lower lobes more frequently than the upper, have a systemic arterial blood supply, and often an anomalous venous drainage system.

Symptoms occur when these sequestra become infected or attain a size that results in significant space occupation (often because they have become a huge intrathoracic abscess). Antibiotic therapy and fluid resuscitation may be the initial treatments; what is eventually required is a surgical resection.

Sequestration is often divided into two groups depending on the proximity of the sequestered mass to the actual lung. Those immediately adjacent or within a lobe are called *intralobar* (Fig. 25-11). Those more remote and often with a complete pleura covering are called *extralobar.* The latter group is often seen with other anomalies; about half of the extralobar type occur around the opening of a diaphragmatic hernia.

It is well known that these lesions have a systemic arterial blood supply, generally arising as a direct branch from the aorta, and possibly from the thoracic aorta and traversing the diaphragm. This is also frequently seen with CCAM, and the similarity of some of these characteristics has led to the suggestion that these lesions may represent a spectrum of developmental pulmonopathy.

Pulmonary Cystic Lesions

Pulmonary cystic lesions[75-77] may be developmental or acquired. Within the first group are the bronchogenic cysts and the duplication cysts. This differentiation cannot be made if no mucosal lining is found in pathologic examination. In all these lesions, sequestration or maldevelopment of some portion of the tracheobronchial tree or foregut results in the development of a cystic lesion that may grow over time, especially if there is a secretory lining. Obviously, foregut duplication occurs near the native esophagus, and bronchogenic cysts (characterized by their ciliated cuboidal mucosa) occur at or near the carina; the proximity of the origin of these lesions may make them hard to differentiate.

Within the second group (acquired) are the cysts that result from barotrauma secondary to prolonged intubation, ventilation, suctioning, and recurrent infection. Obviously, these often appear later in the neonatal course, having not been evident on x-ray at birth or shortly thereafter.

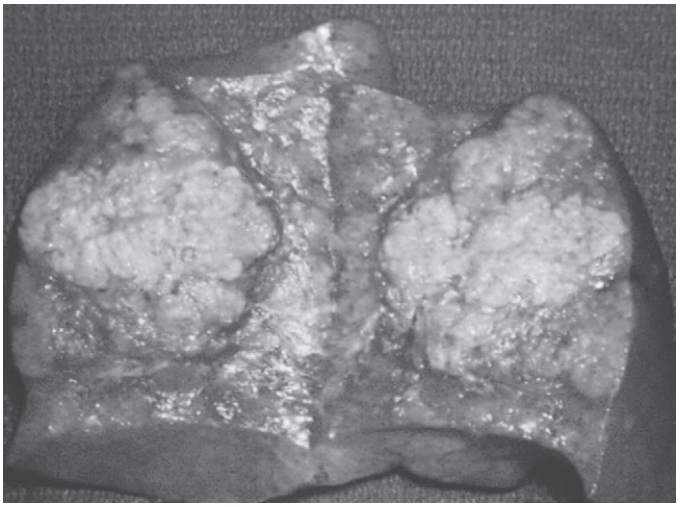

Figure 25-11 ■ Intralobar pulmonary sequestration treated by pulmonary lobectomy.

Size varies from small to enormous, essentially replacing an entire lung. Symptoms result, once again, from space occupation or infection. Often infection creates the increase in size (abscess) that finally leads to the diagnosis of the lesion. Plain radiography is generally sufficient to make this diagnosis, but barium swallow, computer tomography, and magnetic resonance imaging may all occasionally be needed.

Generally, surgical resection is the best solution because it eliminates the chance of infection and prevents any further enlargement and anatomic displacement. If the baby is ventilator dependent on high settings, a ventilation strategy such as low-volume high-frequency ventilation may be necessary to prevent a recurrence in other areas of the lung postoperatively.

Abnormalities of Diaphragmatic Development

Only three conditions need be considered here: diaphragmatic hernia, diaphragmatic paralysis, and diaphragmatic eventration. Clinically only the congenital diaphragmatic hernia of Bochdalek is of concern. Most of the other hernias are rare, and seldom do any of them create major problems in the neonatal period.

Diaphragmatic Hernia of Bochdalek

The posterior-lateral diaphragmatic hernia, most common on the left as described so succinctly by Bochdalek that it has carried his name since, occurs in approximately 1 : 5000 live births.[78-81] Therefore, it is a lesion seen fairly commonly in large metropolitan children's hospitals. The etiology is unclear, although we now have a rat model in which the diaphragmatic defect and the pulmonary hypoplasia can be induced by maternal ingestion of the teratogen, Nitrofan (2,4-di-chloro-phenyl-p-nitrophenyl ether; generic name: nitrofurantoin). The problem is complicated by the serious pulmonary hypoplasia that exists on the side of the diaphragmatic defect, but that is also often found in the contralateral lung.

Many neonates afflicted with this problem have associated anomalies and die in utero. Those who survive to term are generally fairly large and surprisingly free of other problems. Males comprise about two-thirds of the reported cases.

Many of these cases are now diagnosed prenatally, and sufficient data is now available to prognosticate on ultimate outcome in a general fashion. Neonates who have a small chest consistent with pulmonary hypoplasia, large amounts of abdominal viscera within the chest, particularly the left lobe of the liver, and marked mediastinal shift can be expected to have severe problems at the time of birth and often are nonsurvivors. In marked contrast are the babies born without symptoms or babies who are not diagnosed until 1 to 2 months of age. Virtually all of these latter children are survivors.

Presentation is generally some degree of respiratory distress that requires intubation at birth or shortly thereafter. Those who are tolerating the lesions without problems or who have minimal symptoms are brought to elective repair when other anomalies have been excluded and pulmonary hypertension has had a chance to abate. For those that require immediate intubation, a large number of therapeutic ventilation programs with the addition of nitric oxide are available. These have proven quite successful for many of these neonates.

Those who fail these modalities can be taken to extracorporeal membrane oxygenation (ECMO) with ultimate repair on the pump or after successful decannulation (see Chapter 16), although the later approach may have advantages of diminished hemorrhage after completion of anticoagulation. Use of all the modalities has produced survival rates that are near 80% today compared to historical reports of 40% survival.

Diaphragmatic Paralysis/Eventration

Diaphragmatic paralysis and eventration can be lumped together because it is virtually impossible to distinguish them from each other. They look alike and act in a similar fashion. If a neonate has had a traumatic birth and has other neurologic deficits or if the baby has undergone intrathoracic surgery, it is reasonable to assume that the child has paralysis. If those conditions are not met, it is just as likely to be one lesion as the other.

In both conditions, one or both diaphragms assume a high position on chest x-ray and may compromise function of the lung. Fluoroscopy for paradoxical motion suggests paralysis, but a thin, attenuated muscle may give very similar results. In addition to the space problems, the paradoxical motion creates increased work of breathing, tires the baby, and makes effective spontaneous ventilation difficult.

If either of these conditions is present but asymptomatic, the situation can be observed. Obviously, if the baby needs ventilation, some future action may be needed. The literature is replete with recommendations, none based on any good objective data, that suggests diaphragmatic plication be done in 3 to 6 weeks if the neonate cannot be weaned from ventilation. These recommendations do not seem unreasonable because intubation and ventilation are not without their own risks and complications. The folding and suturing of the diaphragm creates a stable platform against which the other diaphragm can effectively achieve normal or near normal breathing.

Abnormalities of the Skeleton

There are a host of skeletal anomalies that result in thoracic asphyxiation at the time of birth or shortly thereafter. These are beyond the scope of this chapter, but the reader should be aware that there are some surgical expansion procedures offered in a limited number of institutions in the United States that can increase thoracic volume and hold some small promise for some of these children.

The Pediatric Surgeon as Consultant

Neonatal Bronchoscopy

The increased frequency of long-term neonatal intubation and the survival of children with severer respiratory difficulties have been associated with increased airway

complications. The pediatric surgeon/endoscopist has an important role in the evaluation of congenital stridor (previously discussed), persistent atelectasis, evaluation of endotracheal tube position or patency, and as an aid to difficult intubations.[82]

Anatomic Considerations

A neonate's air passages are obviously smaller than those of an adult or a larger child, and this increases their vulnerability to obstruction.[83] The mucosa is softer, looser, and more fragile. The location of the epiglottis and larynx of the neonate's airway is more cephalad and anterior than an adult's. Of note, the cricoid cartilage is the narrowest point in an infant's upper airway. This feature not only makes the use of cuffed endotracheal tube usually unnecessary in this population, but it also increases the risk of the complication of subglottic stenosis from pressure during prolonged intubation. Furthermore, at an infant's carina, the mainstem bronchi angulate almost symmetrically, unlike the anatomy in older children and adults.

Pathophysiology

Edema is the minimum adverse effect of endotracheal intubation. If intubation continues for longer than a few hours, acute inflammation becomes superimposed on edema. This proceeds over days and weeks to mucosal ulceration, submucosal inflammation, chondritis, cartilage fragmentation, and tracheomalacia. The body's reparative response to these changes is fibrosis and scarring, which, if severe, results in laryngotracheal stenosis.

To minimize this cycle of destruction when intubation is mandatory, an endotracheal tube of appropriate size is used commensurate with ventilatory control. Fixation should be secure enough to minimize lateral or horizontal motion, and attempts should be made to shorten the time necessary for intubation using such techniques as permissive hypercapnia, nasal continuous positive airway pressure, and noninvasive ventilation. Some clinicians advocate nasotracheal intubation and fixation for prolonged intubation, but this technique also may have serious adverse sequelae.

Evaluation of Intubation

Because the majority of patients admitted to most neonatal intensive care units for intubation and ventilatory support are treated medically, the role of the pediatric surgeon/endoscopist is primarily one of consultation. Improved techniques for endotracheal and nasotracheal intubation and the development of better neonatal ventilators make it quite possible to maintain most children safely on respiratory support for 6 to 8 weeks with minimal concern for permanent pressure damage to the airway. After 6 to 8 weeks of endotracheal intubation, one should consider bronchoscopic evaluation to determine whether damage has occurred and whether continued intubation is appropriate management (see Tracheostomy). For a list of other indications for diagnostic bronchoscopy, see Box 25-1.

Endoscopes

Excellent rigid and flexible endoscopes are now available for examination of the neonatal airway. In addition, ultrathin flexible bronchoscopes are available that allow examination of the tracheobronchial tree through endotracheal tubes. The scopes are available in diameters from 1.3 to 2.7 mm.[84,85] They allow bronchoscopic examination without major disruption to positive-pressure ventilation when a Y-adaptor (Vigo, France) is used between the endotracheal tube and the ventilator. These scopes are easy to maneuver, and serious complications such as perforation are unlikely, making examination in the neonatal intensive care unit possible. However, the majority of these scopes do not provide capabilities for significant lavage or suction, and their resolution is somewhat limited. Furthermore, scopes of sizes smaller than 2.7 mm do not have flexible tips.

One role for flexible bronchoscopy is aiding in difficult intubations of a neonate. With the new ultrathin flexible endoscopes, it is possible to place an endotracheal tube under direct vision by passing the tube over the bronchoscope. This can be particularly useful in neonates with congenital airway obstruction or craniofacial anomalies. The flexible endoscopes can also rapidly provide information about endotracheal tube position and patency. For major diagnostic and all therapeutic procedures, however, rigid bronchoscopy performed by an experienced pediatric endoscopist provides the maximum yield. Performed with appropriate anesthesia, lighting, and suction, it is associated with minimal morbidity and mortality.

Rigid scopes, such as those provided by Storz equipped with Hopkins telescopes, are available for neonates in sizes from 2.5 to 4.0 mm. These provide superb illumination and magnification for inspection as well as an adequate lumen through which to insert tubes or instruments. A technique of using the Hopkins telescope without the sheath but instead inserting it directly through an endotracheal tube via a Y-adapter has also been described and allows continuation of endotracheal intubation and positive-pressure ventilation throughout the procedure.[86]

Both flexible and rigid scopes can easily be used in the neonatal intensive care unit when the condition of a baby precludes moving him/her to the operating room; consequently, it is rare for an infant to be denied an endoscopic examination when diagnostic or therapeutic benefits are likely.

If an endotracheal tube has been in place for several weeks, mucosal edema, petechiae, and erythema are inevitable. Damage greater than this indicates serious consideration for tracheostomy. Mucosal erosion, granulation and early fibrosis, and ultimately stricture are ominous signs and will probably progress if irritation by the endotracheal tube continues.

Tracheostomy

Although physicians at some centers would continue endotracheal intubation if no damage is encountered on evaluation of the airway, many clinicians would proceed with neonatal tracheostomy after prolonged periods of continuous intubation (generally 4-8 weeks). Such a procedure helps respiratory function by decreasing the work of breathing and reducing dead space and makes oral motor activity possible for the baby. Tracheostomy should also be seriously considered for infants who manifest central nervous system failure, severe bronchopulmonary dysplasia,

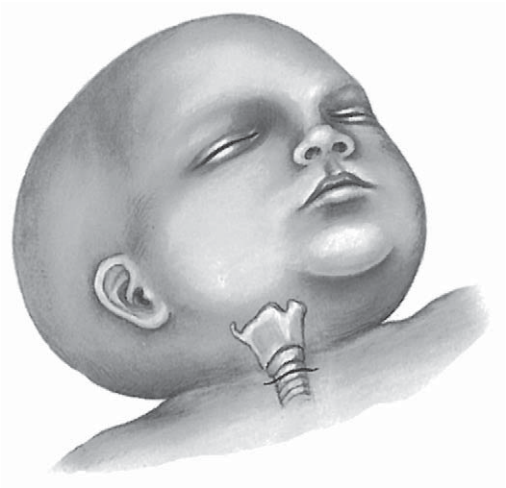

Figure 25-12 ■ Transverse skin incision over tracheal rings (1 to 3).

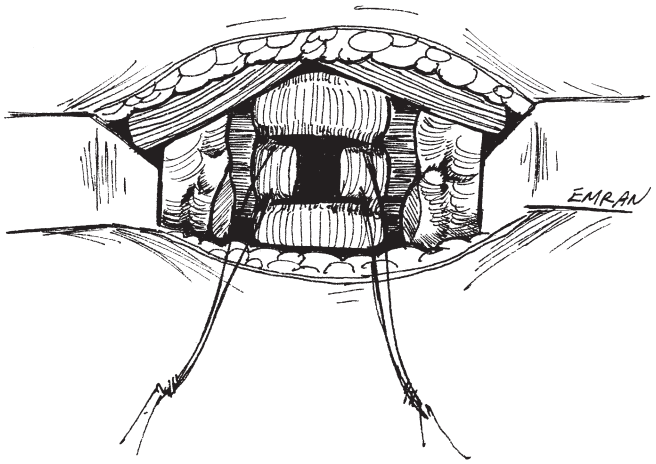

Figure 25-14 ■ The tracheal opening is dilated. Retention sutures are sewn through the cartilages to aid postoperative reinsertion if necessary. No tracheal cartilage is removed at any time.

complex cardiovascular disease, or in whom an endotracheal tube is inadequate for maintaining pulmonary toilet.

The specific technique of neonatal tracheostomy varies little from a well-performed tracheostomy at any age. Except in dire emergency, when a needle cricothyroidotomy is the preferred approach, neonatal tracheostomy should be performed under operating room conditions, and the infant should be intubated before the surgical procedure begins.

Procedure

After the landmarks of the anterior triangle of the neck are well established, a transverse or midline skin incision can be made (Fig. 25-12). The choice of skin incision used appears to make little difference in the overall outcome and should reflect the preference and experience of the operating surgeon. Once the skin and subcutaneous tissues have been opened, midline dissection is mandatory to prevent damage to vascular or neural structures. Division of the thyroid isthmus may occasionally be necessary and can easily be performed with electrocautery (Fig. 25-13). Either a simple transverse[87] or T-type tracheal incision is performed in neonatal cases (Fig. 25-14). Stay sutures, often called "trap door" sutures, are placed through the cartilages of the tracheostomy site at the time the initial incision into the trachea is made. If reintubation in the early postoperative period is necessary, these sutures aid the replacement, decrease the trauma of replacement, and may prevent placement into subcutaneous tissues. At no time should cartilaginous rings or portions of them be removed, because this almost inevitably results in stricture formation if decannulation is successful in the future.[88-92]

Because a neonatal tracheostomy is performed over an endotracheal tube if possible, the endotracheal tube is removed under direct vision as the tracheostomy tube is inserted (Fig. 25-15). This ensures control of the neonatal airway throughout the entire procedure. Finally, fixation of the tube is critical, because dislodgement in the postoperative period can be fatal if experienced personnel are

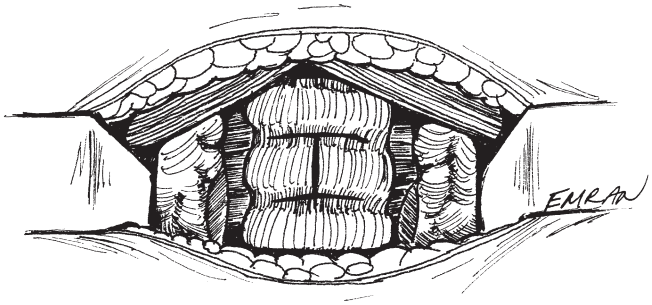

Figure 25-13 ■ Platysma and strap muscles retracted laterally to allow midline dissection to the trachea. The thyroid isthmus is retracted or cut as necessary.

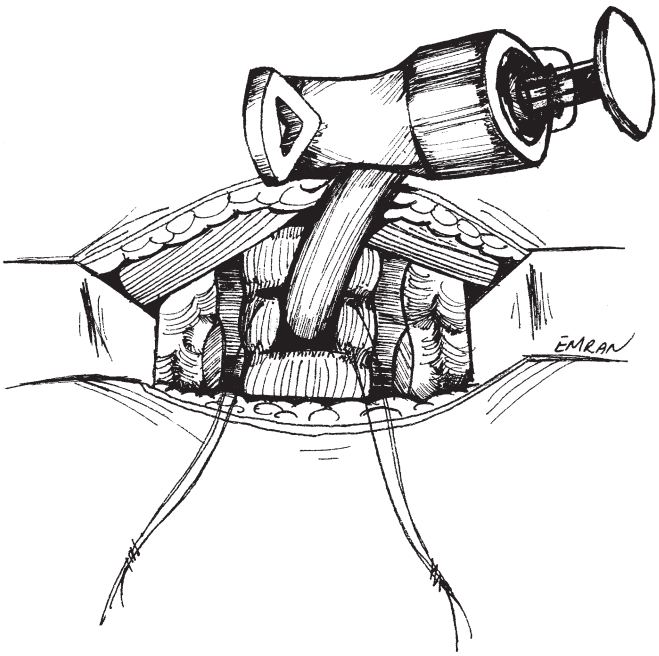

Figure 25-15 ■ Tracheostomy tube is inserted following slow withdrawal of the endotracheal tube under direct vision.

Figure 25-16 ■ Completed tracheostomy with dressing and tapes in place.

unable to reinsert the tube immediately. Consequently, the tube must be tied securely by those familiar with this technique; alternatively, the tube may be sutured directly to the lateral aspects of the neck (Fig. 25-16).

Anterior Cricoid Split Procedure

The improved survival of premature infants who require prolonged intubation has made pressure complications of the airway increasingly common. As an alternative method of management, instead of tracheostomy in neonates with early stages of subglottic stenosis, Cotton and Seid[93] have recommended an anterior cricoid split procedure performed over an endotracheal tube. This procedure involves a transverse skin incision and a longitudinal incision through the cricoid cartilage and upper two tracheal rings as well as through the underlying mucosa (Fig. 25-17). The soft tissues of the neck are then reapproximated over the defect via a single-layer (skin) closure. After this procedure, the patient remains intubated for a period of 7 to 21 days, during which time the mucosa heals by fibrosis, and tracheal stability is reestablished (Fig. 25-18). After this healing has taken place, attempts may be made to extubate the infant.

Experience with this technique during the 20 years since its original description has shown it to be a reasonable alternative in carefully selected patients, resulting in successful extubations in approximately 75% of patients. However, when reintubation and positive-pressure ventilation become necessary in infants who have recently undergone this procedure, complications such as aerocele and persistent fistula at the site of the anterior cricoid split have been reported.[94,95] Thus careful selection of patients for this procedure is essential, and tracheostomy remains the mainstay of initial treatment for the majority of neonates with tracheal pressure complications secondary to prolonged intubation.

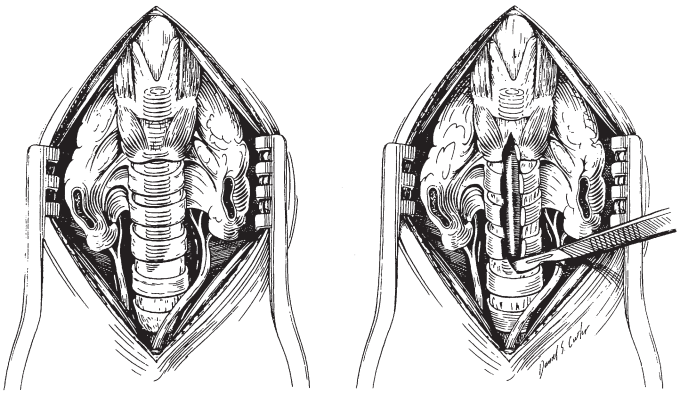

Figure 25-17 ■ Anterior cricoid split procedure. After exposure of the anterior surface of the cricoid cartilage and upper two tracheal rings, a vertical incision is made through the cricoid and tracheal rings. Exposure of the endotracheal tube along the length of the split indicates completion of the procedure. (From Drake AF, Babyak JW, Niparko JK, et al: The anterior cricoid split: Clinical experience with extended indications. Arch Otolaryngol Head Neck Surg 114:1405, 1988. Copyright 1988, American Medical Association.)

Tracheostomy Tubes

The choice of an appropriate tracheotomy tube is as important as the correct technique of tracheostomy placement. The soft, pliable, polyvinyl chloride tubes manufactured under the Shiley and Portex trade names seem best suited for the neonatal airway. The Aberdeen tube, a silicone elastomer tube, is also an excellent alternative but is available in fewer sizes. These tubes remain soft at body temperature and conform well to individual anatomy, thus reducing trauma and risk of subsequent stricture formation. Additionally, the softer tubes are more comfortable for a patient and reduce the chances of cervical skin irritation or abrasions from sharp metal edges. Rigid metal tracheostomy tubes are contraindicated in this population.

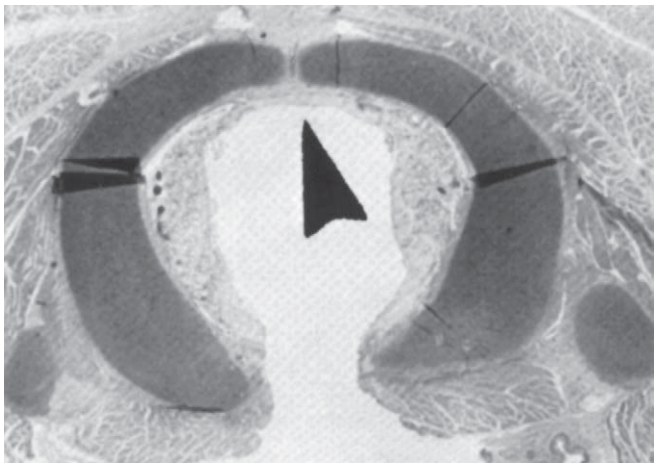

Figure 25-18 ■ Cross-sectional specimen obtained at autopsy from a patient who had previously undergone an anterior cricoid split. The *arrow* indicates the site of the cricoid split (the posterior opening was created by the pathologist during autopsy). (From Cotton RT, Seid AB: Management of the extubation problem in the premature child: Anterior cricoid split as an alternative to tracheostomy. Ann Otol Rhinol Laryngol 89:510, 1980.)

If a patient undergoing tracheostomy has an endotracheal tube in place, the size of the endotracheal tube can be used to guide the selection of a tracheostomy tube of appropriate size. A reasonably reliable rule is that the tracheostomy tube can be 0.5 mm larger than the correct orotracheal tube or 1.0 mm larger than the correct nasotracheal tube. Reference to the comparative table reveals that reasonable choices to fit variation in neonatal airways include Shiley 00, 0, 1, 2, 3; Portex FG 14, 15, 18, 21; and Aberdeen 1 and 3.

Choosing a tube of proper length is usually more difficult than finding the proper diameter. At birth, tracheal length for the normal term birth-weight infants is a maximum of 5 to 6 cm. Even a very short tracheostomy tube may lie dangerously close to the carina, or even in the right or left mainstem bronchus. Alternatively, if the tube is too short and lies high in the neck, the chance of dislodgement is increased. Generally pediatric tubes are 3 to 6 mm longer than neonatal tubes of the same diameter and can be used if the neonatal tube of the appropriate width is too short. Today, all the manufacturers will provide custom constructed tubes, usually with only a 2- to 3-day delay in delivery. Consequently, it is possible to request the appropriate sized tube.

Once a tracheostomy is in place and serous drainage from the wound has ceased, daily changing of the dressing and weekly changing of the tube seem adequate. Generally, it is best to have the surgeon or his service make the first tracheostomy tube change. If in the early postoperative period, the tracheostomy tube accidentally dislodges and the bedside team is unsure that the replacement is in the trachea, the infant can be safely intubated through the oral cavity. Once it has been established that the tract is well healed and tubes can be removed and replaced without major problems, nurse and family members may assume this task. An alternative tube should always be available. This is cleansed with soap and water, stored in a clean container, and used in the event that sudden replacement is necessary. Suctioning is performed as necessary to keep the airway clear of secretions, and details of suctioning are similar to those for endotracheal tubes (see Chapter 6).

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26 Cardiovascular Assessment of the Ventilated Neonate

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In focusing on the obvious respiratory problems of premature and newborn babies, the practitioner must always remember that the lungs are merely half of the cardiorespiratory system that delivers oxygen to tissues and removes carbon dioxide. The cardiovascular component of the system, although essential, is often only considered when a low blood pressure is measured or when the effect of a patent ductus arteriosus (PDA) is considered. However, respiratory disease has an effect upon the heart and postnatal cardiovascular adaptation, just as cardiac dysfunction and maladaptation can exert a deleterious effect upon respiratory function. The two systems are truly interdependent and frequently simultaneously involved in disease states. This chapter addresses the importance of cardiovascular assessment of the ventilated neonate, examines and discusses the available techniques used in assessment, including their limitations, which are often ignored. It offers a logical approach to cardiovascular management while highlighting the need for further research.

Perinatal Cardiovascular Physiology

An understanding of perinatal cardiovascular physiology is essential if subsequent interventions are to be logical rather than merely treating "figures" as is common practice in much intensive care.[1]

Antenatal Physiology

Before birth, oxygenated blood from the placenta passes through the umbilical vein, the ductus venosus, inferior vena cava, and into the right atrium. This blood tends to be streamed by the crista terminalis through the foramen ovale to the left atrium. From the left atrium, the blood passes to the left ventricle and aorta and supplies the brain, which is a major metabolic organ in the fetus. Only about 10% of the total cardiac output crosses the aortic isthmus and returns to the placenta via this route.

Blood from the superior vena cava (relatively deoxygenated) is directed to the right ventricle. Because there is a high pulmonary vascular resistance, most of the right ventricular output is diverted through the ductus arteriosus to the descending aorta and back to the placenta, returning to the left atrium via the pulmonary veins. Pulmonary blood flow increases from 2% to 4% of the total cardiac output early in pregnancy to approximately 8% to 10%[2] near term. The volume of blood pumped by the right ventricle near term is thought to be approximately 65% of combined output of both ventricles. Pulmonary vascular resistance early in gestation is extremely high relative to that in the infant and adult, probably because of the reduced number of small arteries. During the last half of gestation, new arteries develop, the cross-sectional area increases, and pulmonary vascular resistance falls progressively; however, baseline pulmonary vascular resistance is still much higher than after birth.[3,4] Therefore, when babies are delivered prematurely, pulmonary resistance will fall more slowly than at term because of both physical and pathologic factors.

Postnatal Adaptation

After birth there is a decrease in pulmonary vascular resistance due to aeration increasing the arterial pO_2,[5,6] and to an increase in peripheral vascular resistance caused by removal of the low-resistance placenta and exposure to the outside environment. Ventilation of the newborn mammal which does not change the oxygenation level produces only partial pulmonary vasodilation, whereas ventilation with air or oxygen produces increased pulmonary vasodilation.[7] The exact mechanisms of oxygen-induced pulmonary vasodilation during the transition remain unclear. The increase in alveolar or arterial oxygen tension may decrease pulmonary vascular resistance, either directly by dilating the small pulmonary arteries or indirectly by stimulating the production of vasodilator substances such as phosphoglucose isomerase (PGI), bradykinin, or more importantly, nitric oxide.[8,9]

More blood flows through the lungs as it returns to the left atrium where the pressure rises causing the foramen ovale to close, usually within minutes of birth. The ductus arteriosus initially remains open with flow first ceasing and then reversing (left-to-right) when systemic pressure exceeds pulmonary pressure. This is the postnatal part of the transitional phase of the perinatal circulation. Perinatal insults may cause a failure of this transition giving rise to a pulmonary pressure maintained higher than systemic pressure (a pathologic state that is commonly called *persistent pulmonary hypertension of the newborn* [PPHN] or more inaccurately *persistent fetal circulation*). Although most of the decline in pulmonary vascular resistance occurs in the first day at term, it may not be complete for several weeks.[9-12]

Ductal Closure

Closure of the ductus is normally initiated by constriction of the spiral medial muscle layer with shortening and thickening of the ductus, disruption of the intima, and formation of intimal cushions.[13] Intimal cushions, which

are identifiable by echocardiography as echo-dense protrusions into the ductal lumen, have been shown to be the first signs of impending ductal closure. Lack of these protrusions within the first few hours of life is associated with ductal patency.[14] The sequence of closure usually starts at the pulmonary end. Functional closure is usually complete by 72 hours of age in healthy term infants[15,16] but may take longer in the preterm infant.[17-19] In normal newborn infants over 36 weeks' gestation, functional PDA closure has occurred in 42% by 24 hours after birth; 78% by 40 hours; 90% by 48 hours, and in all by 96 hours.[16] Closure is often delayed in preterm babies, and 48% of prematures with a birth weight under 1000 g have a symptomatic PDA.[17]

It is important to realize that functional closure of the ductus arteriosus may predate anatomic closure by several weeks. Early ductal closure is initiated after birth by a complex interaction between oxygen, local and circulating neurohumoral factors, and the ductus smooth muscle. Increased oxygen tension causes ductal constriction, and hypoxemia causes ductal relaxation.[20] This sensitivity to oxygen is greatest at term and diminishes within 24 hours of birth.[21] As the fetus approaches term, the duct becomes less sensitive to the dilating effects of prostaglandins.[22-25] In contrast, the preterm infant demonstrates increased sensitivity even after initial constriction,[26] and paradoxically, there is some evidence that oxygen metabolites may stimulate prostaglandin E2 production and ductus dilation.[27]

Cardiac Function

The right ventricular dominance that is present at birth gradually subsides and develops into the left ventricular dominant picture of the adult over the first 3 to 6 months of life as the ventricles become remodeled in response to decreasing right and increasing left ventricular pressure work. These anatomic changes are reflected in the neonatal electrocardiogram (ECG), which has some important differences when compared to ECGs of older children and adults. However, the ECG is rarely used in the cardiovascular assessment of the ventilated neonate and therefore is not discussed further in this chapter.

In preterm and full-term infants, cardiac output is higher than in adults (200 mL/kg/min versus 100 mL/kg/min). Cardiac output is the product of heart rate and stroke volume, and stroke volume depends on myocardial contractility, preload, and afterload (Frank-Starling mechanism). In newborns, the myocardium contains less contractile tissue and more connective tissue than in adults, with myofibrils being relatively disorganized.[28] This lowers the compliance of the relaxed ventricles and limits the role of preload in determining stroke volume. However, afterload is also low due to poorly developed sympathetic tone.[29] Sympathetic tone increases with age in parallel with an increase in systemic blood pressure (see below). Initial animal studies on lambs suggested that in neonates the resting stroke volume remains fairly constant, and the higher cardiac output is achieved mainly by an increase in heart rate (average 140 beats per minute [bpm] at birth falling to 70 bpm by puberty).[30] However, echocardiography has demonstrated that the normal cardiac output in neonates without significant ductal shunting may vary from 158 to 325 mL/kg/min (Box 26-1).[31,32] Left ventricular stroke volume increases in the first 2 to 5 hours after birth followed by a fall in output by 24 hours of age,[33] but the significant increases seen with ductal shunting are mainly mediated via an increase in stroke volume.

Blood Pressure

Blood pressure is widely monitored in preterm and term babies receiving intensive or high dependency care. Initial normative ranges were reported for small selected groups of babies in the first 12 hours of life[34-38] with no long-term outcome data. The Northern Neonatal Nursing Initiative in the north of England has published population-based normative data for systolic blood pressure for the first 12 days of life (Fig. 26-1, *A, B,* and *C*).[39] This data was obtained from 398 babies less than 32 weeks' gestation at birth who were free from severe disability at 2 years of age and is the best normative population data available with known outcomes. It confirms the direct relationship between systolic blood pressure and gestational age or birth weight (Fig. 26-2).[40]

Systolic blood pressure often changes rapidly in the period immediately after birth. Pressure in term babies is nearly always high in the first 2 to 3 hours of life,[41-43] even after delivery by caesarean section,[42] and pressure is particularly high in babies showing signs of moderate asphyxia.[42] Blood pressure is lower in the quiet baby. Conversely, preterm babies often have low pressure immediately after birth, which rises spontaneously before

Box 26-1 ECHOCARDIOGRAPHIC RANGES AND INDICATORS

Left Ventricular Output (± one standard deviation)	
Overall normal range	158-325 mL/kg/min
Term	236 ± 47 mL/kg/min
Preterm	221 ± 56 mL/kg/min
Indicators of Low Right Ventricular Output	
RVO	Lesss than 150 mL/kg/min
PA Vmax	Less than 0.35 m/sec
SVC Flow	
Low flow associated with adverse outcome	Less than 40 mL/kg/min
Fractional Shortening	
Term	25%-41%
Preterm	25%-40%
Signs of Ductal Shunting	
LA:Ao ratio	Greater than 1.5 after first 24 hours
Ductal dimension	Greater than 1.5 mm in first 30 hours
LVO	Greater than 300 mL/kg/min or 60% increase in LVO
Continuous left to right ductal flow with higher systolic and low end-diastolic velocities	
Descending aortic retrograde flow greater than 30% of forward flow	
Retrograde diastolic mesenteric flow	
Intra-atrial septum bowed left to right	

LA:Ao, Left atrial to aortic root ratio; *LVO,* left ventricular output; *PA Vmax,* pulmonary artery maximum velocity; *RVO,* right ventricular output; *SVC,* superior vena cava.

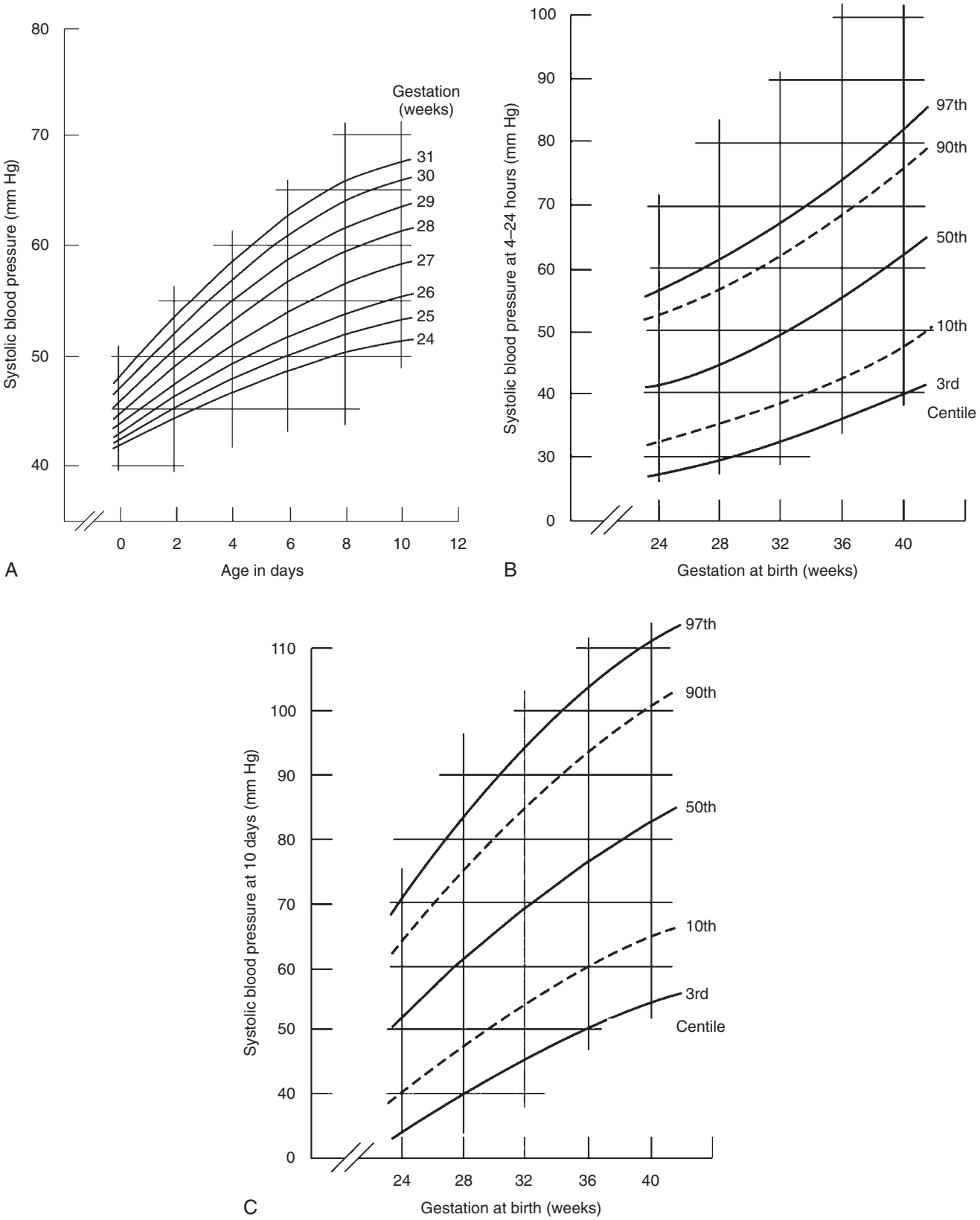


Figure 26-1 ■ **A,** Relation between mean systolic blood pressure and gestational age in babies of 24 to 31 weeks' gestation in the first 10 days of life. To calculate the 3rd and 97th percentiles, subtract or add 35% from the mean value shown. Range of systolic blood pressure seen in babies of 24 to 40 weeks' gestation when **(B)** 4 to 24 hours old and **(C)** 10 days old. (From Northern Neonatal Nursing Initiative: Arch Dis Child Fetal Neonatal Ed 80:F38-F42, 1999.)

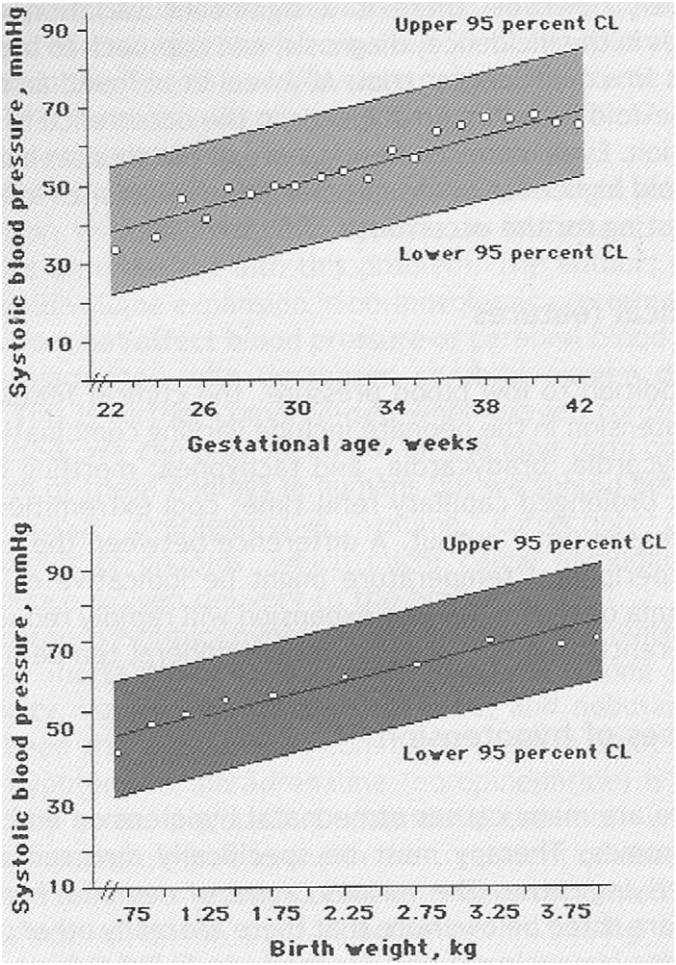


Figure 26-2 ■ Systolic blood pressure in 608 infants with 24,052 measurements. Values for gestation and birth weight are shown. (From Zubrow AB et al: J Perinatol 15:470-479, 1995.)

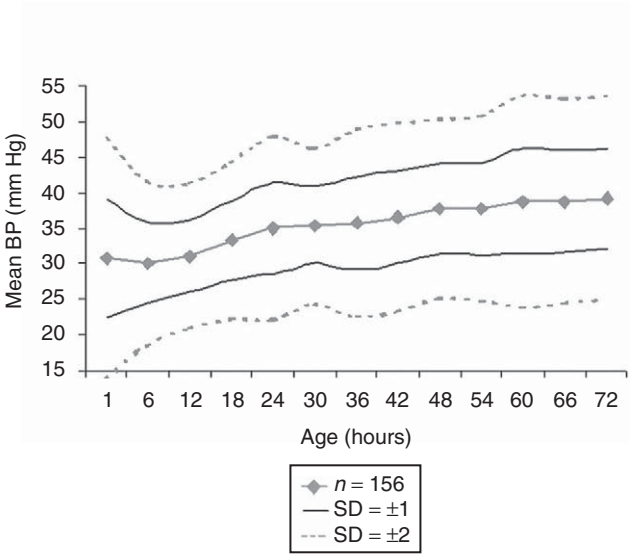


Figure 26-3 ■ Mean blood pressure of all infants 401 to 1000 g during the first 72 hours of life. (From Fanaroff et al: Pediatrics 117(4):1131-1135, 2006.)

stabilizing by about 6 hours.[37,39] Blood pressure in the preterm baby with a low Apgar score can be particularly low in the first few hours of life.[38]

Although the data has been of poorer quality, mean blood pressure has been widely measured because it can be obtained by oscillometry, and if measured invasively, is thought to be free of artefacts caused by resonance, thrombi, and air bubbles. Normative data is limited by the need to have invasive monitoring unless oscillometry is used, which correlates less well with systolic measurements than other techniques.[39] Most studies show trends for mean arterial blood pressure that are similar to those for systolic pressure,[1,44-50] but these studies are of selected subjects and not population based. However, all mirror the spontaneous increase in the first days of life in preterm babies (Fig. 26-3).[50]

Many studies demonstrate that blood pressure measurements stabilize in the first 4 to 6 hours of life and that early measurements are highly variable and difficult to interpret.[41-50]

Cardiovascular Adaptation and Respiratory Disease

The purpose of the cardiorespiratory system is to supply tissues with oxygen and remove carbon dioxide. Its effectiveness is dependent upon the respiratory system, the oxygen content and carrying capacity of the blood, the volume of blood passing through pulmonary and systemic circulations, and the tissues of the body. The provision of nutrients and removal of waste is also part of the function of the cardiovascular component.

Cardiovascular Effects Related to Preterm Delivery

The first 24 hours after premature birth are a period of particular circulatory vulnerability. Low blood pressure and fluctuations in systemic and cerebral blood flow have all been associated with ultrasound evidence of brain injury and poor neurodevelopmental outcome.[51-56] However, causality has not been proven, and all babies adjust their blood pressure after birth, with an increase in pressure seen in those born prematurely.[39-43] Many babies who develop symptomatic cardiovascular problems have indicators of cardiac dysfunction within the first day of life.[57] This may be partly an ischemic or hypoxic problem, but the myocardium is also immature[28,29] and must deal with an unexpectedly early increase in afterload.

Administration of surfactant has been linked to patency of the ductus arteriosus in one study of natural surfactant treatment of established respiratory distress syndrome (RDS),[58] but subsequent meta-analysis of this and 12 other trials found no effect.[59] Clearly the incidence of ductal patency is inversely related to gestational age as is the likelihood of the neonate requiring assisted ventilation. A significant ductal shunt increases cardiac output and pulmonary blood flow[60,61] and may be associated with the need for increased ventilatory requirements and inspired

oxygen concentration. Increasing left ventricular output can predict future symptomatic ductal shunting.[62]

Surfactant deficiency and ventilation have been associated with a delay in the fall of pulmonary resistance,[63] and this is one of the factors that governs the symptomatic presentation of ductal patency. However, although high pulmonary artery pressure is a feature of RDS, it does not correlate with the severity of the disease, nor does it usually require treatment.[63,64] Pure right-to-left ductal flow, which occurs when pulmonary arterial pressure is higher than systemic arterial pressure throughout the cardiac cycle (found in persistent pulmonary hypertension of the newborn [PPHN]) is rare in respiratory distress syndrome.[63-65] Severe or fatal RDS is more commonly associated with generalized circulatory failure, biventricular dysfunction, and systemic hypotension than with increased pulmonary vascular resistance.[57,63,64,66,67] In fact, most infants with RDS have coexistent predominantly left-to-right ductal and atrial shunts.[63-65]

Systemic hypoperfusion is often exacerbated by ductal "steal," where aortic blood flow destined for the descending aorta is "stolen" into the pulmonary circulation through the arterial duct, particularly during diastole.[68] This occurs because pulmonary vascular resistance is falling and is *lower* than systemic vascular resistance, and it results in *high* pulmonary blood flow.

A study of human infants with RDS showed that half had significantly increased pulmonary blood flow secondary to left-to-right ductal shunting during the first 48 hours of life.[69] This increase in pulmonary blood flow through the duct maintains a high pulmonary artery pressure (PAP) at the expense of a reduction in both systolic and diastolic aortic pressure.[70] *High* rather than low total pulmonary blood flow is therefore a characteristic feature of RDS, and interventions to increase total pulmonary blood flow further are unlikely to be helpful in most infants with this disease.

Surfactant administration has also been associated with a short-term decrease in blood pressure and cardiac output in animal models.[71] This is presumably due to improvement in pulmonary compliance and increased perfusion of the lungs.

Ventilation Effects

Airway pressure during ventilation can alter both left and right ventricular output.[72,73] This is associated with increased mean airway pressure, positive end-expiratory pressure, and oscillation[72-74] and is thought to be an effect upon venous return to the heart. The style of ventilation may also have an effect because even a 1 kilopascal (kPa) rise in carbon dioxide (1 kPa = 7.5 mm Hg) may cause an increase in blood pressure and a fall in cardiac output.[75]

Assessment of the Cardiovascular System

Clinical Assessment

Assessing clinical signs is part of any medical or nursing training. Heart rate, skin temperature, and blood pressure are standard nursing observations. However, in the critical, ventilated neonate, it is desirable to identify cardiovascular dysfunction before it becomes irreversible. Capillary refill time is a poor predictor of cardiovascular function in adults,[76] children,[77] and neonates[78,79] and cannot be recommended as an important sign. An increase in heart rate was once thought to be the major mechanism for increasing cardiac output, but this is now known to be incorrect in human neonates. Increasing heart rate will still often increase cardiac output, but a tachycardia has a low specificity for predicting cardiovascular compromise. Similarly, evidence of reduced urine output and a baby's decrease in spontaneous activity may be important elements of an overall evaluation but are not individually predictive. Moreover, base deficit on blood gases are none-specific indicators of problems in which cardiovascular dysfunction may be primarily or secondarily involved. Lactate can predict poor outcome but as yet is not useful in directing any intervention,[80] although future research incorporating other parameters with serial lactate measurements may be more helpful.

Hypotension

Systemic blood pressure is the product of left ventricular cardiac output and the systemic vascular resistance. It is relatively easy to measure and therefore has been used as an indicator of cardiac output and tissue perfusion. This concept was reinforced by the association of a mean arterial blood pressure below 30 mm Hg with cranial ultrasound abnormalities and poor outcome,[52] as well as suggestions that cerebral autoregulation fails below this level.[81] Some practitioners therefore act to keep the blood pressure above this level,[1] whereas others look for corroborating evidence of low flow. The British Association of Perinatal Medicine recommends keeping mean arterial pressure in mm Hg at or above gestational age in weeks based on normative data from well babies.[82] However, there is equally compelling evidence that cerebral blood flow depends more on left ventricular output than on blood pressure,[83,84] and mean blood pressures below 25 mm Hg are neither uncommon nor associated with adverse outcome in extremely low gestational age babies.[85] Research has shown that blood pressure is a poor predictor of systemic flow.[79]

Obviously, a single value defining hypotension such as 30 mm Hg is difficult to justify for all gestations and ages. It is hardly surprising that 95% of all hypotension occurs in the first 24 hours of life given such definitions[1] because the natural course is, as described previously, to stabilize at 4 to 6 hours and then rise in the preterm baby.[37,39,44-50] A mean blood pressure of 30 mm Hg is above the 50th percentile for infants of 25 weeks' gestation at 6 hours of age, which would prompt treatment in many centers. There is no dependable evidence from which to define a blood pressure threshold for intervention[85] and no evidence that intervention at any threshold improves outcome.[85] Current definitions of hypotension do not predict abnormal cranial ultrasound findings in preterm infants.[86] Furthermore, there is some evidence that simply increasing blood pressure may actually reduce tissue perfusion in some instances[87] and may be the cause of adverse events.[88] Therefore, before treatment is considered, more information regarding the clinical condition of the baby should be obtained.[89]

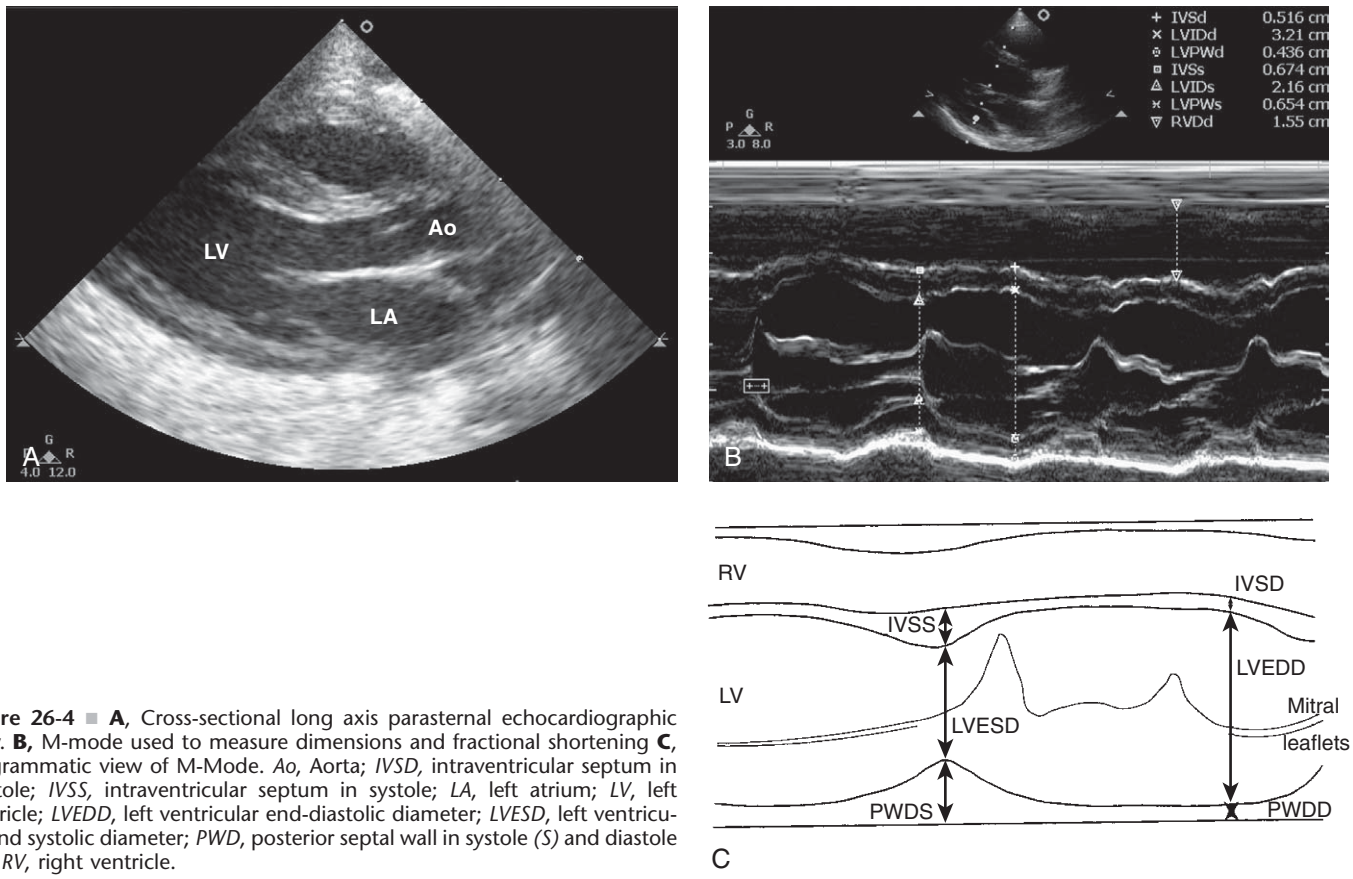


Figure 26-4 ■ **A**, Cross-sectional long axis parasternal echocardiographic view. **B,** M-mode used to measure dimensions and fractional shortening **C**, Diagrammatic view of M-Mode. *Ao*, Aorta; *IVSD,* intraventricular septum in diastole; *IVSS,* intraventricular septum in systole; *LA*, left atrium; *LV*, left ventricle; *LVEDD*, left ventricular end-diastolic diameter; *LVESD*, left ventricular end systolic diameter; *PWD*, posterior septal wall in systole *(S)* and diastole *(D)*; *RV*, right ventricle.

Echocardiography

Echocardiography not only offers a direct view of the cardiac structure including the ductus arteriosus but also offers increasing amounts of functional information. Until relatively recently, functional echocardiography was used mainly as a research tool and although the effects of therapeutic interventions have been reported,[90,91] it remains to be shown whether it can be used to alter neonatal outcomes. However, as a technique, it offers the possibility of delineating clinical situations to test commonly used treatments in randomized controlled trials. First, there must be an understanding by clinicians of what can be measured and assessed, followed by the ready availability of the skills in the neonatal intensive care unit.[92] Although all ultrasound measurements have an intrinsic error ranging from about 10% for intraobserver variability up to 15% to 20% for interobserver variability,[93,94] this is similar to other noninvasive measurements such as assessment of cardiac output by thermodilution.[95]

Cross-sectional echocardiography is used to assess anatomy, to allow accurate positioning of an M-mode cursor, continuous or pulsed-wave Doppler cursor, and to obtain a subjective impression of ventricular function. It can also demonstrate rare cardiac complications of intensive care such as intracardiac thrombus and pericardial effusions secondary to long line extravasations.[96] In the latter case, early diagnosis can be life saving. The standard views are the long axis parasternal view (Fig. 26-4, *A* and *B*), the short axis parasternal pulmonary view (Fig. 26-5), the four-chamber apical view (Fig. 26-6, *A* and *B*), the suprasternal view, and the subcostal view. These views, with minor modifications, are used to assess ventricular measurements and function, ventricular output, volume loading, pulmonary pressure, superior vena caval (SVC) flow, intra-atrial flow, and to assess the size and flow through the patent ductus arteriosus.

Ventricular Function

It is important to remember that ventricular function (or myocardial fiber shortening) and ventricular output are not the same although they are clearly related. Ventricular function and cardiac output need to be measured and considered separately while also assessing preload and afterload to gain a more complete hemodynamic picture.

Fractional shortening (FS) is the most reproducible and commonly used assessment of left ventricular contractility. It is assessed in the long axis parasternal view using M-mode echocardiography (see Fig. 26-4, *B* and *C*).

$$FS(\%) = \text{Left ventricular end diastolic diameter} - \text{Left ventricular end systolic diameter} \times 100$$

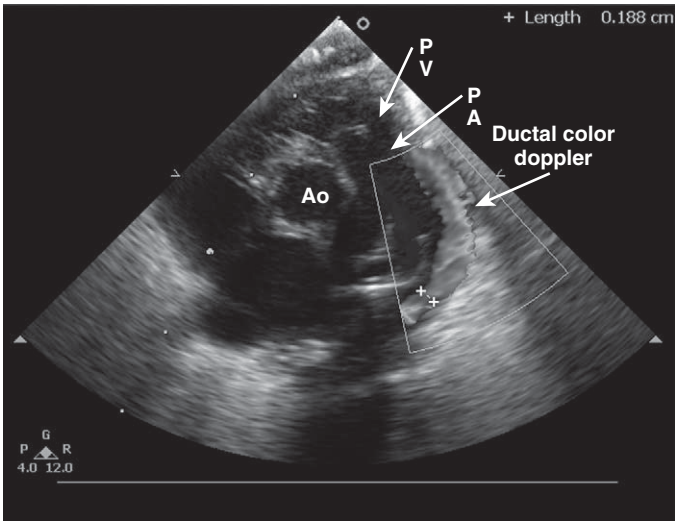
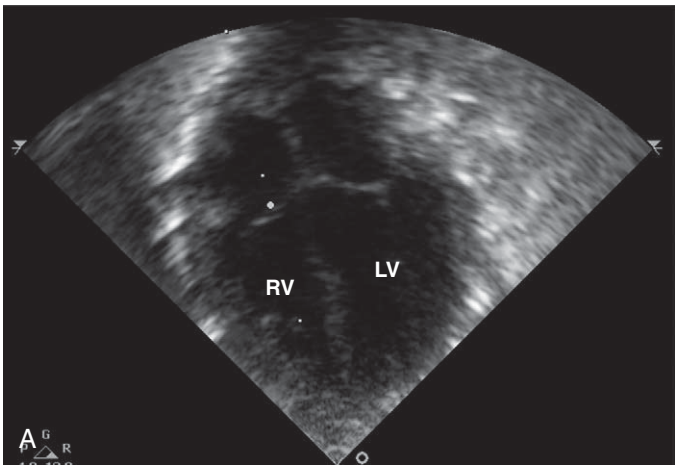
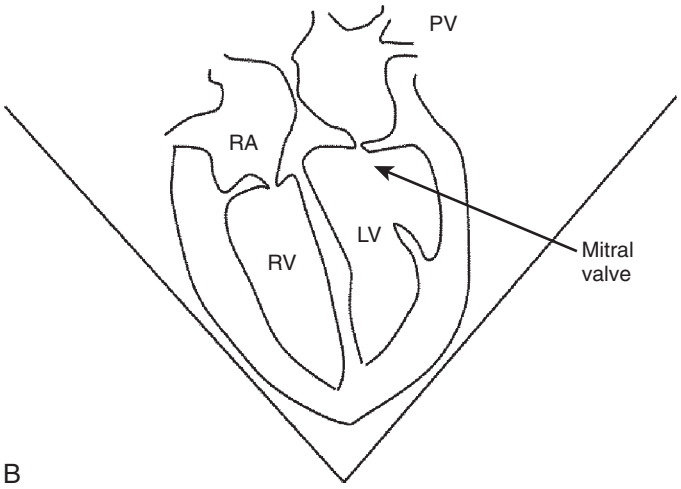


Figure 26-5 ■ Short axis parasternal with left to right ductal flow seen in orange. *Ao*, Aorta; *PA*, pulmonary artery; *PV*, pulmonary valve.





B

Figure 26-6 ■ **A,** The four chamber apical view. **B,** Diagram of four-chamber apical view. *LV*, Left ventricle; *RV*, right ventricle.

Left ventricular end-diastolic diameter

The normal range of left ventricular end diatolic diameter (LVEDD) for preterm neonates is 25% to 40% (95th confidence limits).[97] However, this measurement is affected by both preload and afterload.[98] Errors may also occur because of the distortion of the left ventricle in the preterm infant and paradoxical septal wall motion associated with right ventricular dominance.[99] Mean velocity fiber shortening (velocity of circumferential fiber [VCF]) is an alternative measurement of contractility that is less sensitive to minor dimension discrepancies and involves no assumption about ventricular shape. However, it is also influenced by volume loading of the ventricle, which tends to increase both measurements.

Tissue Doppler imaging is a relatively new ultrasound technology that derives measurements of contraction and relaxation velocities directly from the myocardium. As a direct measurement, it is affected less by preload and afterload, and normal values have been documented[100]; however, as yet it can only be seen as an area for further promising research in the neonatal population.

Cardiac Output

Left and right ventricular output can be measured echocardiographically[95] by measuring the annulus of the aortic or pulmonary valve and the velocity/time integral of the Doppler waveform of the flow through those valves. The stroke volume is calculated and multiplied by the heart rate. Echocardiographically derived left ventricular output has been shown to correlate closely with Fick-derived measurements.[96] The normal values are known in neonates (see Box 26-1)[31,32]; changes in cardiac output can be monitored when instituting supportive treatment with fluid boluses or the administration of inotropes.

Left ventricular output (LVO) does not necessarily equate to systemic flow. Flow through the coronary arteries is lost, but in the presence of a left-to-right ductal shunt, LVO cannot be used as a reliable reflection of systemic blood flow and oxygen delivery. If such a shunt exists, changes in LVO could reflect changes in systemic flow, ductal shunting, or a combination of the two.

Assessments of systemic flow, which are theoretically unaffected by ductal shunting, are right ventricular output (RVO) and SVC flow. However, turbulence in the pulmonary artery from ductal flow can disturb the flow pattern making accurate determination of RVO difficult. LVO is increased by ductal shunting, but RVO may be decreased because of reduced systemic venous return. RVO is also affected by interatrial shunting across the often patent foramen ovale. Low RVO values below 150 mL/kg/min are found particularly in hypoxemic infants; infants with PPHN and high values may be found with large interatrial shunts. However, in the first 48 hours after birth, significant interatrial shunting is uncommon, and maximum velocity in the main pulmonary artery is the main determinant of RVO. Pulmonary artery maximum velocity (PA Vmax) can therefore be used as a screen for low RVO in the first 48 hours of life with a velocity of less than 0.35 m/sec being indicative of an RVO of less than 150 mL/kg/min.[93,101,102] Evans has recommended measuring the RVO and SVC flow in all babies with a PA Vmax of less than 0.45 m/sec.[95]

SVC flow less than 40 mL/kg/min in the first 24 hours of life has been associated with late intraventricular hemorrhage that tended to occur as perfusion improved.[101] In 126 infants it was also significantly associated with death or disability at 3 years of age and an abnormal development quotient at 3 years.[103] A randomized controlled trial of intervention with either dopamine or dobutamine in infants with an SVC flow of less than 41 mL/kg/min demonstrated that although dopamine was more effective at raising blood pressure, dobutamine produced a significantly greater increase in blood flow than dopamine. However, there was no difference in short-term mortality or morbidity.[90] There was no difference between the two groups at 3 years of age for incidence of combined death or disability.[90] However, survivors in the dopamine group had significantly more disability and a lower Griffiths general quotient, and those in the dobutamine group had reduced rates for late severe periventricular/intraventricular hemorrhage.[104]

Volume Loading

Measurements of the left atrium (LA) and left ventricular end-diastolic dimension (LVEDD) in comparison to the size of the aorta can give some indication of the volume loading of the heart as can "eyeballing" the heart in the four-chamber view. The LA tends to be larger with significant ductal shunting, and an LA to aortic ratio greater than 1.4 : 1 (Fig. 26-7) is associated with at least a moderate ductal shunt but is not sufficiently predictive to guide treatment, especially in the first 24 hours.[105-107] An LVEDD to aortic ratio of more that 2.1 : 1 is associated with large shunts[106] and with such a volume-loaded left ventricle that hypotension is unlikely to respond to treatment with a fluid.[108]

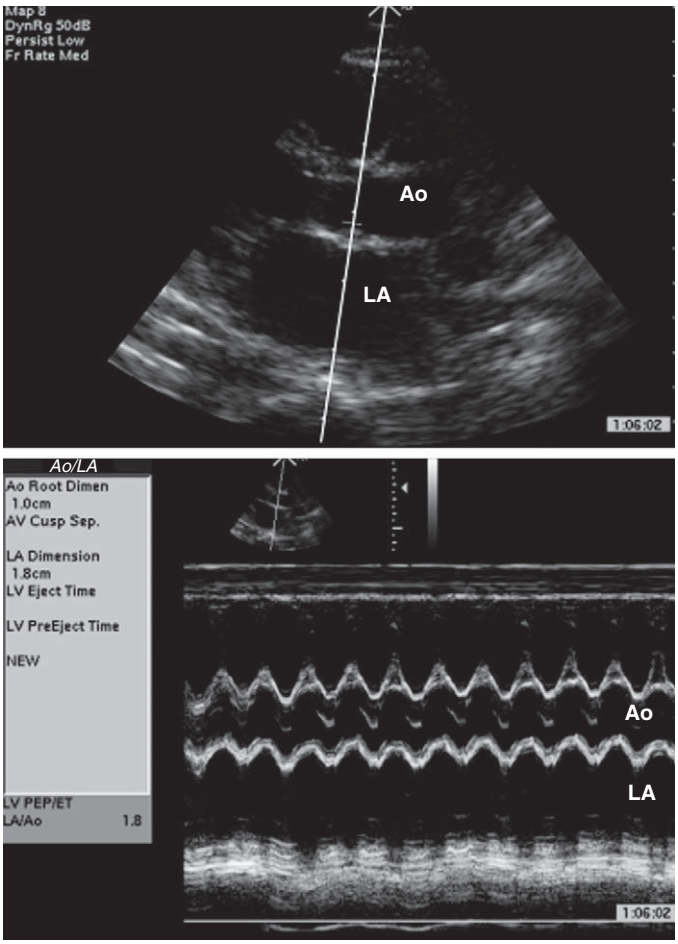


Figure 26-7 ■ Large left atrium (LA) measured with M-mode.

Pulmonary Pressure Measurements

The most accurate and reproducible method for assessing pulmonary artery (PA) pressure is measurement of the velocity of tricuspid regurgitation (TR) (Fig. 26-8) and application of the modified Bernoulli equation (pressure = 4 V^2).[109] TR has a direct relationship to pulmonary artery pressure but is not always present, and both ductal velocity and the ratio between the pulmonary time to peak velocity and right ventricular ejection time can also be used. These have an inverse relationship and the latter is less useful in the presence of a large patent duct. The ratio between the right ventricular preejection period and right ventricular ejection time has a direct relationship with PA pressure but has poor repeatability.

Information about PA pressure in relation to systemic pressure can also be derived from the ductal flow pattern and direction. Pure right-to-left flow occurs in PPHN with the pulmonary pressure greater than systemic throughout the cycle (Fig. 26-9). Bidirectional flow occurs normally during postnatal adaptation but can also be seen in response to treatment of PPHN. Continuous left-to-right flow means that pulmonary pressure is lower than systemic throughout the cycle.

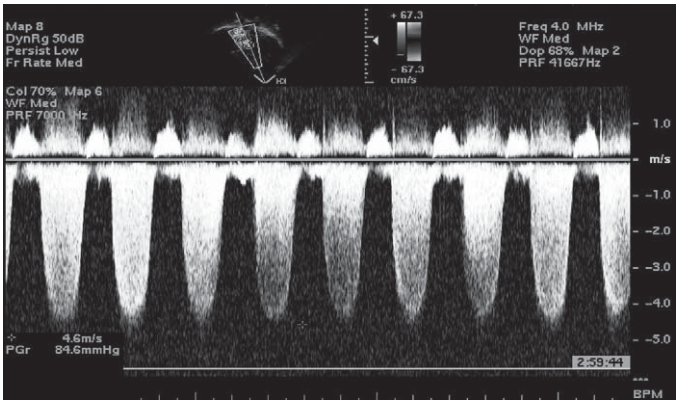


Figure 26-8 ■ Tricuspid regurgitation with raised pulmonary pressure.

Patent Ductus Arteriosus

In premature infants receiving intensive care, the incidence of patency in the ductus arteriosus is high as discussed previously.[17] Unless prophylactic treatment is employed, the decision to treat is based upon whether the duct is thought to be hemodynamically or clinically significant. This is a clinical decision that cannot be based on a single echocardiogram or the presence or absence of a murmur. Indeed, clinical signs of a duct, if present, appear on average 72 hours after echocardiographic signs.[62]

Echocardiography can reveal whether shunting is present, the size of the duct, and circulatory side effects

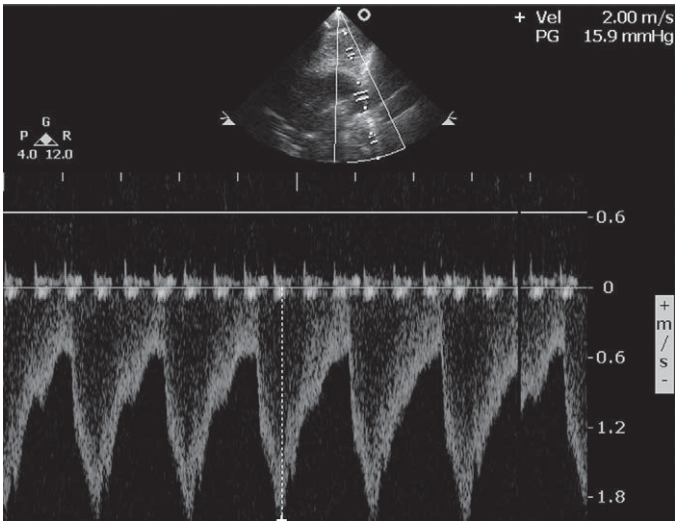


Figure 26-9 ■ Pure left to right flow in patent ductus arteriosus (PDA) caused by persistent pulmonary hypertension of the newborn (PPHN).

such as reduced diastolic flow in systemic arteries. In the presence of a large left-to-right shunt, the left atrial and left ventricular enlargement may be marked. The degree of left atrial enlargement depends not only on the size of the duct but also the size of the foramen ovale. LV function appears hyperdynamic and fractional shortening may be above the normal range.[110]

Measuring the size of the duct using cross-sectional echocardiography is inaccurate. The most reproducible technique is to measure the ductal dimension using the width of the color Doppler jet. Kluckow and Evans[107] found a measurement of greater than 1.5 mm taken within the first 31 hours of life in infants less than 29 weeks' gestation to be the best early predictor of hemodynamic significance with a sensitivity of 83% (confidence index [CI] 71%, 94%) and a specificity of 90% (CI 81%, 98%). However, this is from a single unit and it is difficult to extrapolate because other units report less intervention and the results have not as yet been reproduced elsewhere.

The direction and pattern of ductal flow is determined with pulsed and/or continuous-wave Doppler. Large left-to-right shunts characteristically have continuous left-to-right flow, but instead of continuous high-velocity flow seen in healthy babies before the duct closes, the higher velocity is found in late systole, and the velocity at end diastole tends to be low (less than 1 m/sec and less than half the peak velocity in systole). This flow pattern suggests that the aortic and pulmonary pressures are nearly equal at the end of diastole, which is not seen in healthy infants.

Left ventricular output is also raised with large left-to-right shunts[60-62] and can also predict ducts that prompt intervention.[62] Theoretically the right and left outputs could be compared to assess shunt, but this is complicated by variable intra-atrial shunting.

Diastolic aortic pressure is low with a large left-to-right ductal shunt due to "ductal steal" and low systemic resistance. Blood passing down the descending aorta during systole reverses at some stage of diastole, flowing across the duct and into the pulmonary arteries. This causes underperfusion of systemic arteries. It is important to realize that a large shunt may reduce the systolic as well as diastolic blood pressure.[111] Pulsed-wave Doppler can assess this in the descending aorta or mesenteric arteries. Using these techniques, ductal shunting can be separated into small, medium, and large, but at present action will depend upon local practice until accepted values for treatment are tested in a multicenter trial.

Clinical Situations

Hypotension and Shock

As mentioned above, 95% of hypotension is diagnosed in the first 24 hours of life in preterm babies.[1] There is clearly no consensus about timing of intervention and no evidence of efficacy on clinically important outcomes. Many infants who are hypotensive have normal systemic blood flows, are clinically well perfused, and can have good short- to medium-term outcomes.[1,39,85,86,104] Although goal-directed intervention in adults with septic shock has improved outcomes,[112] there is evidence from animal models that neonatal responses may be different and that extrapolation from adult treatments may once again be inappropriate.[113]

Treatment of hypotension in the newborn cannot be justified based on a mean value below the gestational age.[1,82] There is a need for interventional studies, but the definition of hypotension is at present inadequate. Such definitions as do exist may be helpful in prompting further thought and investigation as to the reason for the low systemic pressure in individual cases. It is clear that normal variation, patent ductus, sepsis, and rarely hypovolemia must all be considered if inappropriate and potentially harmful treatment is to be avoided.[87,88,101] It is therefore logical to use echocardiography (if available) to base any therapy on a more complete understanding of the underlying hemodynamic situation. For this to occur, neonatologists must be able to perform functional echocardiography,[114,115] but recent studies would suggest that this occurs in less than 23% of neonatal units in the United Kingdom prior to treatment. Generally, a fluid bolus is administered as an initial treatment (67%), and inotropes are still given empirically.[1,116]

In the absence of echocardiography documenting decreased cardiac output or signs of shock, a conservative approach to treatment of low blood pressure should be followed. If treatment is started, then the administration of volume is rarely justified without evidence of hypovolemia and has been associated with poor outcome.[117] Dobutamine will increase blood pressure in many babies, and although not as effective at this as dopamine,[118] it is better at improving systemic blood flow.[90,118] In the first 24 hours, when systemic flow is likely to be low, there is a logic in using dobutamine with vasopressors such as dopamine and adrenaline (epinephrine) being reserved as second-line therapy. However, the risks of afterload compromising flow and perfusion due to vasoconstriction must be considered.[118]

If echocardiographic information is available, then it may be appropriate to keep SVC flow above 50 mL/kg/min or RVO or LVO above 150 mL/kg/min. Dobutamine is

more effective than dopamine at achieving the former.[90] At least, one should consider screening for a PA Vmax less than 0.35 m/sec, which is predictive of a low SVC and RVO flow. However, functional echocardiography in infants with low blood pressure or shock offers the ability to describe clinical situations sufficiently for randomized interventional studies to assess clinically important outcomes. This may finally change the treatment of neonatal low blood pressure and low systemic blood flow from art to science.

Persistent Ductus Arteriosus

The many and varied criteria used for diagnosis and assessment of PDA constitutes a problem in standardizing an approach to treat. Typical clinical findings of continuous or systolic murmur, hyperactive precordium, bounding pulses, and hepatomegaly may be specific but are not sensitive for PDA.[119] Tachycardia, tachypnea, and a requirement for ventilatory support are sensitive but not specific.[119] This lack of sensitivity has been described as the "silent PDA,"[120] with neonatologists disagreeing as to whether treatment can be based upon purely clinical signs or whether echocardiographic information is needed to inform the decision.[121-124] However, reliable early diagnosis of PDA in the first 4 days of life depends upon echocardiography; using clinical signs alone often results in misdiagnosing ductal status.[123] After that time, a cardiac murmur is the most reliable of the clinical signs in diagnosing PDA,[123] but in the premature population, echocardiography is still the gold standard.

After diagnosis, the decision to treat is made by assessing the overall clinical effect of the PDA. "Significant" or "hemodynamically significant" are terms that are used to justify treatment. but the definition of these terms varies among neonatologists and should be avoided.[125] Despite this, as well as the clinical course of the infant, certain measurements described above will help identify those PDAs that are likely to cause problems. In babies less than 1500 g at birth requiring ventilation, a ductal dimension greater than 1.5 mm in the first 30 hours of life is the best predictor for PDA requiring treatment.[107] After the first day of life, a left atrial to aortic root ratio (LA:Ao) of greater than 1.5 : 1 has a sensitivity of 88% (CI 81%, 95%) with a specificity of 95% (CI 93%, 97%).[126] Left ventricular end-diastolic diameter to aortic root ratio can also be a useful indicator when greater than 2.1 : 1, as can left ventricular output when greater than 300 mL/kg/min. However, these latter measurements are not as sensitive, although an increase in left ventricular output of 60% has been shown to predict the development of symptomatic ductal shunting.[107,124,126,127] Doppler flow information may also be helpful. The classical pattern of ductal flow with a large shunt is high in systole and very low in diastole, but information about aortic diastolic flow can also assist in assessment of the effect of the PDA.[107,125,128,129]

Unless prophylactic treatment is used, which may treat up to more than 64% of babies unnecessarily,[107,130] treatment must be targeted. Early intervention can only be justified based on echocardiographic criteria, which at present would be based on ductal diameter, but the clinical situation is still relevant, because if the baby is not ventilated, then the measurement cannot be interpreted. Later intervention must take into account the clinical situation with echocardiographic estimates of the size of the duct.

Cyanotic Infant Without Structural Heart Disease

Cyanosis can be difficult to identify shortly after birth because most babies are born with some degree of cyanosis, and even healthy term babies may take up to 55 minutes to achieve saturations greater than 95%.[131] However, once identified, persistent cyanosis is a diagnostic emergency. Respiratory causes are most common and the easiest to detect clinically. Congenital heart disease is excluded by echocardiography, which has an important role in the assessment and evaluation of management of the hypoxemic infant. It is important not to let a diagnosis of "*persistent pulmonary hypertension of the newborn*" stop thought processes. The infant may have a primary problem with high pulmonary vascular resistance leading to extrapulmonary right-to-left shunting and poor pulmonary blood flow; however, other problems may produce a similar picture. Systemic hypotension may produce the appearance of relative pulmonary hypertension. Most infants have a combination of intracardiac and intrapulmonary shunting, and the relative importance of each can vary with time. Profoundly hypoxemic infants may have normal $PaCO_2$ and normal or high pulmonary blood flow with the shunting being all intrapulmonary.[132] Infants with intracardiac shunting may have a closed or small duct with the majority of the shunt at the level of the foramen ovale. This may be due to raised pulmonary resistance or more due to right ventricular dysfunction. Clearly, these situations require different approaches because the former may well respond to pulmonary vasodilation whereas the latter will need inotropic support. Only echocardiography can provide the information necessary to fully assess these situations and to determine and evaluate appropriate management.

As already described, echocardiography can estimate ventricular filling and ventricular function and more precisely assess ventricular output, ductal flow, and pulmonary artery pressure. Pulmonary flow can be assessed by measuring right ventricular output if the duct is closed. However, if the duct is patent, then left ventricular output, which depends upon pulmonary venous return, is a better estimate. Left atrial size also reflects pulmonary flow, but LVO is most closely linked to outcome with a measurement less than 100 mL/kg/min, indicating a high risk of mortality.[132] No index of pulmonary pressure is as closely linked, but persistent right-to-left shunting is ominous.[133] The absence of a correlation between PA pressure and disease severity will surprise many, but the popular term *persistent pulmonary hypertension of the newborn* oversimplifies the condition. PPHN is a complex, multifactorial problem that varies among subjects. The main problem is one of low pulmonary blood flow due to raised (or relatively raised in premature infants) pulmonary vascular resistance. High pulmonary artery pressure does not necessarily equate to low pulmonary flow, especially in the preterm infant, when most infants with RDS will have prolonged raised pulmonary pressure despite normal or high flow.[63,64]

Echocardiographic features seen at diagnosis of PPHN would classically include right atrial and ventricular enlargement with the atrial septum bulging to the left. In the apical four-chamber view, transposition of the great vessels can appear similar. Color Doppler will demonstrate tricuspid and mitral regurgitation and right-to-left flow across the foramen ovale. Measurement of the peak TR jet velocity confirms high pulmonary pressure. The left atrium is usually small with an LA:Ao ratio of less than 0.5 to 1. There may be reduced RVO and/or LVO, but the latter is most concerning. Patent ducts will be present in 80% to 85% of babies, with bidirectional ductal flow in most of these (60%-70%). A minority have pure right-to-left flow (see Fig. 26-9).

Ductal flow is useful to monitor progress because it reflects the pressure differences between systemic and pulmonary circulations. Increasing RVO and LVO are also associated with improving saturations; increased pulmonary stroke distance is the best indicator of hemodynamic improvement. In monitoring progress, the diameter of pulmonary artery and aorta need only be measured once because they do not change in the short term. Increased output can therefore be followed by measuring stroke distance and heart rate.

Echocardiography provides accurate diagnosis of the hemodynamics of the hypoxic infant and also allows appropriate treatment according to the situation. It also offers a method to monitor response to treatment and is essential to the management of these infants.

Cardiovascular Management of the Ventilated Infant

It is clear from the preceding discussions that there is little evidence to offer a didactic approach to the cardiovascular management of ventilated infants. The long history of diagnosing and treating hypotension in neonates, although well intentioned, is based more upon hope than evidence. Echocardiography is not the complete answer. However, it offers more information and allows the formulation of a logical approach to an individual's hemodynamic situation. Few neonatologists will be brave enough to merely observe "hypotension" as has been suggested.[89] Echocardiography permits a better understanding of whether the underlying problem is of poor cardiac function, a rare case of volume depletion, or actually a variation of normal. The latter is especially likely during the first 24 hours of a premature life. In more mature infants with complex sepsis syndromes or PPHN, assessing cardiac function can demonstrate pulmonary pressures and both LVO and RVO. Occasionally a situation that appears to be a classical PPHN may be one of sepsis with high LVO and low systemic resistance. In that situation it is the systemic resistance that should be raised rather than the pulmonary resistance lowered.

Echocardiography also permits the assessment of therapeutic interventions, avoiding the reinforcement of treatments that do not have the desired effect. Once the beneficial aspects of the extra information available are understood, the underlying problems in acquiring it should be overcome.[115]

Perhaps the most exciting prospect of functional echocardiography is the possibility of defining disease processes in order that treatments can be tested with meaningful outcomes. This has been started,[101,104,107] but there is much more that could be achieved in multicenter trials with agreed randomization points for intervention. Agreed intervention points for PDA and low flow states can provide the evidence to guide treatment that is so lacking at present.

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27 Nutritional Support

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The objective of advanced respiratory care in the neonate is to enable the premature or critically ill infant to survive in the best possible health and with the best possible neurodevelopmental outcome. Expert nutritional support is recognized as a key factor in promoting the survival and good long-term health and development of infants who require intensive care, including assisted ventilation. The medical problems that contribute to the need for assisted ventilation—such as prematurity, infection, birth defects, and a host of cardiopulmonary issues—also increase the challenges of providing good nutritional support.

Infants who require assisted ventilation may have immature or abnormal gastrointestinal function. They face the threat of suboptimal oxygen delivery to the tissues involved in absorption, digestion, and metabolic processing of ingested nutrients, and they often face limitations in the tolerance and processing of parenterally delivered nutrients. They cannot safely suck and swallow liquid feedings, so a method of feeding must be used that bypasses the mouth and pharynx. They may have changes in fluid balance caused by both the underlying illness and the treatment—assisted ventilation. They are more susceptible to most of the complications of feeding, partly because the process of feeding may alter the infant's cardiorespiratory mechanics, which may already be compromised. To confound the nutritional challenges even more, infants who require assisted ventilation often have increased requirements for energy, protein, and other nutrients. As a result of the challenges of providing adequate nutrition to infants requiring assisted ventilation, poor postnatal growth is common in these infants.

Good nutritional support improves the survival prospects of premature and critically ill infants and may affect the long-term outcome of the survivors. Brain growth and neurodevelopmental outcome are influenced by the quantity and quality of nutrition provided to premature and ill infants during their critical early postnatal weeks. In humans, the period of maximum brain growth, and thus of maximum vulnerability to growth failure, spans from the third trimester of pregnancy through the first 18 months of postnatal life.[1] Much of the brain's growth occurs postnatally, especially in premature infants. Considerable evidence indicates that the human brain is vulnerable to the effects of nutritional deprivation during the first weeks of postnatal life.[2] Suboptimal nutrition and poor growth have been shown to increase the risks of subsequent motor and cognitive impairment in premature infants.[3-5] For infants who require assisted ventilation, the harmful effects of malnutrition on lung development,[6,7] respiratory muscle function,[8] and lung mechanics[9] are of great importance. Probably as a result of these effects, undernourished infants are thought to be more susceptible to bronchopulmonary dysplasia.[10] Finally, the work of Barker and Osmond[11] has demonstrated the impact of malnutrition and growth failure in infancy on cardiovascular health in adult life.

The goals of nutritional support for ventilated infants are to prevent catabolism and exhaustion of endogenous energy resources, to achieve growth in lean body mass, and to promote the healing, growth, and maturation of the lungs, brain, and other vital organs. These goals must be met without impairing respiratory gas exchange or tissue oxygen delivery. In order to frame specific recommendations for intake of water, energy, protein, and other nutrients for ventilated infants, it is necessary to address the requirements for each of these. The determination of nutrient requirements depends on the goals set forth for the rate and composition of weight gain. The most widely accepted standard for developing such goals for premature infants is the intrauterine growth of the fetus of corresponding postmenstrual age.[12,13] For ill term infants, the growth and nutrient intake of healthy breast-fed infants are used as references. The purpose of this chapter is to review what is known about the nutritional needs of the infant who requires assisted ventilation and to explore how these needs can best be met.

Nutritional Requirements

Water Requirement

Although water is not generally considered to be a nutrient, it is nonetheless a key element in nutritional management, because energy, protein, and other nutrients cannot be delivered without water. Moreover, competent management of water intake is of vital importance in the care of infants who are premature or ill enough to require assisted ventilation, given the potential adverse effects of inadequate or excessive water intake. Early in the second trimester of pregnancy, water comprises about 95% of the fetal body weight.[14,15] The relative contribution of water to body weight decreases gradually throughout the latter months of gestation, falling to about 85% of body weight at 28 weeks gestation[16] and to about 75% at term (Fig. 27-1).[14,15,17] This decline in body water (expressed as percent of body weight) results from a decrease in extracellular water that more than offsets a smaller increase in intracellular water.[14,15] These trends in body water and its extracellular

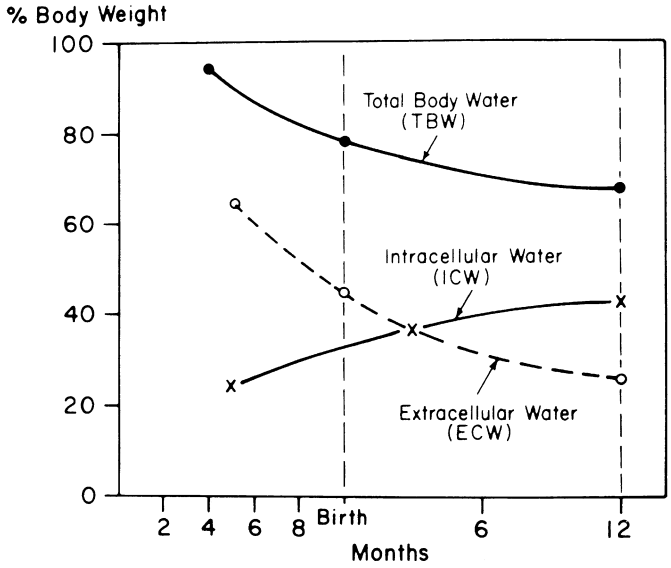

Figure 27-1 ■ Changes in body water of the fetus and infant. (Data from Friis-Hansen B: Acta Paediatr Suppl 46(suppl 110):1-68, 1957.)

and intracellular components continue after birth but are especially precipitous during the first days of life, when contraction of the extracellular water compartment results in a significant loss of body weight, typically about 10% in premature infants.[18,19] This reduction in extracellular water and postnatal weight loss are associated with improvement in renal function that occurs after birth.[20,21] Evidence suggests that this mobilization of extracellular water may be triggered, at least in part, by atrial natriuretic peptide.[22,23] Weight loss of 5% to 10% in the first days of life is to be expected as a result of the physiologic decrease in extracellular water, and no attempt should be made to prevent this weight loss. The maintenance water requirement can be accounted for by insensible water loss, renal water excretion, and stool water. In addition, water is required for growth and is produced in small amounts as a byproduct of cellular metabolism.

Insensible Water Loss

Insensible water loss (IWL) to the environment is an important factor in neonatal heat and water balance. In the case of premature infants, IWL is often the largest contributor to the water requirement. As much as 30% of the IWL is lost through the respiratory tract as moisture in expired gas.[24,25] The balance is lost through the skin. It is important to be aware of the potential influence of various factors on the rate of insensible water loss (Table 27-1).

Gestational age and body weight are both correlated inversely with insensible water loss.[26-29] The smaller, less mature infant loses more water per kilogram because of his greater surface-area-to-body-weight ratio, thinner and more permeable skin, larger body water total, and higher respiratory rate. Antenatal corticosteroids given to promote fetal maturation reduce the IWL of very premature infants during the first few days of life, presumably by enhancing epidermal barrier function.[30]

Respiratory distress may be associated with an increase in respiratory IWL. For an infant breathing spontaneously, the IWL increases with a rise in minute ventilation.[31] The same is true for the mechanically ventilated infant if the gas mixture delivered by the ventilator is not fully saturated. In addition to ventilator rate, the respiratory IWL also depends on the humidity (or water vapor pressure) gradient between the patient's upper airway and the gas mixture he is breathing, either spontaneously or through the ventilator circuit if he is being assisted through nasal prongs or an endotracheal tube. Warming and humidification are desirable to prevent injury to the respiratory mucosa and to prevent blockage of an artificial airway by viscous secretions. If the temperature and water content of the inspired and expired gas are the same, the respiratory IWL will be entirely eliminated.[32] Ambient humidity also affects cutaneous evaporative water loss, but to a lesser degree than its effect on respiratory loss.[24,25,33] Hey and Katz[24] found that a threefold rise in ambient vapor pressure was accompanied by a 55% reduction in respiratory water loss and an 18% reduction in cutaneous evaporative loss.

Increased ambient temperature above the neutral thermal zone will increase IWL as much as fourfold.[24,34,35] Similarly, elevated body temperature, whether due to fever or environmental hyperthermia, is associated with a large increase in IWL.[24,36]

Physical activity level has been shown to influence IWL.[24,36,37] The IWL in the awake, moving infant is 37% to 70% greater than in the basal, sleeping state. Crying increases the IWL to two or more times the basal state.[37]

The use of a radiant warmer increases insensible water loss by about 50%.[27,38-42] Fluorescent or halogen phototherapy has been shown to increase IWL by 20% to

TABLE 27-1 Factors That Influence Insensible Water Loss of Infants

Factor	Change in Insensible Water Loss (per kg)
Level of maturity[26-29]	Inversely proportional to gestational age and birth weight
Antenatal corticosteroids[30]	Decreased in the first few days in very premature infants
Respiratory distress (hyperpnea)[31]	Rises with increasing minute ventilation
High inspired or ambient humidity[24,25,33]	Respiratory IWL reduced more than cutaneous
Ambient temperature above the neutral thermal zone[24,34,35]	Increase proportional to temperature
Elevated body temperature[24,36]	Increase proportional to temperature
Physical activity and crying[24,36,37]	Up to 70% increase
Radiant warmer[27,38-42]	50% increase over incubator
Phototherapy[27,40,43,45]	20% to 50% increase
Plastic heat shield[26,41,47]	10%-25% reduction (in single-walled incubator)
Transparent thermal blanket[47-49] or chamber[49,50]	70% reduction in single-walled incubator[48] 30-50% reduction under radiant warmer[47,49,50]
Semipermeable membrane[51-53]	50% reduction
Topical agents[54,55]	50% reduction

IWL, Insensible water loss.

50%,[27,43,44] and the use of phototherapy and a radiant warmer together increases IWL more than either used alone.[40,45] The impact on IWL of fiberoptic phototherapy is not known but is probably negligible unless the blanket produces a warmer or moister microenvironment around the infant. Investigators using direct measurements of transepidermal and respiratory water loss have produced conflicting results regarding the effect of overhead phototherapy on IWL; one group measured an increase in transepidermal water loss with phototherapy,[44] but another did not.[46]

Several devices have been shown to decrease IWL. The use of Plexiglas (rigid acrylic) heat shields for premature infants in single-walled incubators has been shown to reduce IWL by 10% to 25%.[26,41] The effect was more clearly evident among infants who weighed less than 1250 g,[26] and is greatest if the ends of the heat shield are at least partially closed to reduce air movement near the skin. Plexiglas heat shields do not seem to be effective for infants under radiant warmers,[41,47] because Plexiglas blocks the infrared energy emitted by the radiant heaters and interferes with the feedback loop that controls the heater output. A transparent thermal blanket reduced IWL by a mean of 70% in premature infants in incubators.[48] Similar blankets or chambers of thin saran[47,49] or polyvinyl chloride[50] also reduce IWL of infants under radiant warmers. Finally, both semipermeable membranes[51-53] and topical agents[54,55] have been shown to be capable of reducing IWL of premature infants by about 50%.

Knowledge of the factors that affect IWL is essential in estimating water requirement and prescribing water intake. Changes in the infant's status that impact any of these factors require adjustment in the infant's prescription for fluid intake. Premature and critically ill infants—those who require assisted ventilation—are the infants whose IWL is most significantly influenced by changes in the clinical status or care. Of special concern is the extremely premature infant, for whom precise maintenance of water and electrolyte balance is of foremost concern and for whom the margin of error in fluid management is smallest.

Renal Water Excretion

The amount of water required for urine production depends on the renal solute load and the renal concentrating ability. The term newborn infant can produce urine as dilute as 50 mOsm per liter and can concentrate to around 800 mOsm/L.[56,57] The premature kidney is limited to a narrower range of osmolarity, although it has some capacity to increase free water clearance and urine volume in response to a fluid challenge.[58]

The renal solute load comes from two sources: *exogenous*, primarily electrolytes and metabolic products of nutrients; and *endogenous*, products of catabolism or changes in body composition. The commonly used commercial infant formulas provide a potential (exogenous) renal solute load of 18 to 28 mOsm/100 kcal (22 to 35 mOsm/kg/day at energy intake of 125 kcal/kg/day). An intravenous infusion providing 3 mmol/kg/day of sodium chloride and 2 mmol/kg/day of potassium chloride would provide a potential renal solute load of 10 mOsm/kg/day.[59,60] The addition of 2 g/kg/day of amino acids would raise the potential solute load to about 18 mOsm/kg/day. If this exogenous solute were all to be excreted in the urine, that is, 10 to 35 mOsm/kg/day, a urine volume of 60 to 80 mL/kg/day would maintain the urine concentration between 125 and 600 mOsm/L. These concentrations are within the capacity of the newborn kidney, even for premature infants.

In practice, the amount of solute excreted by the kidney is larger than the exogenous or potential solute load if the infant is in a catabolic state; in such cases, the exogenous solute intake is usually low, so that the actual solute excretion is still generally less than 35 mOsm/kg/day. On the other hand, growing infants deposit some of the exogenous solute in the body (approximately 1 mOsm per gram of weight gain[59,60]) so that the actual solute load is less than the potential. An infant receiving premature formula with potential renal solute load of 24 mOsm/100 kcal at 125 kcal/kg/day (30 mOsm/kg/day) and gaining 15 g/kg/day would excrete about 15 mOsm/kg/day.

The critically ill infant who requires assisted ventilation may have special problems with renal handling of water. Hypoxia or hypotension during the course of the illness may compromise the kidney function by causing tubular or cortical necrosis. During the anuric or oliguric phase of acute tubular necrosis, the renal water excretion is markedly reduced and its allowance in the maintenance water calculation should be reduced accordingly. In the diuretic phase, water excretion through the kidney is markedly increased.

The renal function of infants with respiratory distress syndrome (RDS) is similar to that of infants of the same gestational age without respiratory disease so long as normal blood gases and acid-base status can be maintained.[61,62] However, if infants with RDS become hypoxic and acidotic, they may have reduced renal blood flow and glomerular filtration and a lower threshold for renal bicarbonate excretion.[61-64] Most premature infants, including those with RDS, have an increase in urine volume on the second or third day of life,[65-67] which is accompanied by a rise in plasma atrial natriuretic peptide[22,23,68-72] and contraction of the extracellular water compartment.[23] These changes were often temporally associated with improvement in respiratory function in the pre-surfactant era. Infants with RDS,[73] pneumonia,[74] or pneumothorax[75,76] may have increased production of antidiuretic hormone. In the early years of assisted ventilation and continuous positive airway pressure, there were reports of impaired renal function, which was attributed to the positive pressure[77]; however, these effects most likely resulted from pulmonary overinflation. There is no evidence that renal function is affected by careful use of current methods of assisted ventilation, including high-frequency oscillation.[78]

Stool Water Loss

Stool water loss is usually estimated to be about 5 mL//kg/day.[79,80] Diarrhea increases the stool water loss by an amount that can be determined by changes in body weight. Phototherapy also increases stool water loss. Jaundiced full-term infants under phototherapy lost 19 mL/kg/day in the stool, compared with losses of 7 mL/kg/day in jaundiced control infants without phototherapy.[43]

Water for Growth

The water required for growth depends on the growth rate desired, the water content of the new tissues, and any concurrent changes in body water composition. Water for growth need not be provided until after the initial period of "physiologic" weight loss, during which time appropriate negative water balance is probably desirable. The water retained in new tissues during growth should be 0.5 to 0.8 liters per kg of weight gain[81]; the higher figure applies to the least mature infants.

Water of Oxidation

The water produced as a by-product of metabolism is a hidden source of water intake. This "water of oxidation" consists of 0.43 mL per gram of protein oxidized, 1.07 mL per gram of fat, and 0.60 mL per gram of carbohydrate.[82] Assuming a pattern of substrate utilization similar to the subjects of Reichman and colleagues,[83] formula-fed premature infants should be expected to produce about 0.14 mL of water per kilocalorie expended, or between 5 and 10 mL/kg/day. This metabolic water is roughly equal to the stool water loss plus the water retained for growth. This relationship allows a simplified approach to the estimation of water requirements, based on insensible and urine losses only.

The total water requirement can be estimated by adding the contributions of the components described above (Table 27-2).[84] These figures merely indicate average requirements. The amounts listed here are sufficient for most but not all low-birth-weight infants. These figures are intended only as an illustration of the components of water balance and as a rough guide to help in the initial prescription of water intake. Intake must be adjusted subsequently based on such data as body weight, serum sodium concentration, and urine volume.

Energy Requirement

The energy intake required for normal growth is difficult to determine and can be approached only in the setting of a balanced diet with adequate amounts of protein and other nutrients. Previous authors[83,85-93] have observed that healthy premature infants gain weight at rates similar to the fetus of corresponding postmenstrual age (13 to 23 g/kg/day) with energy intakes as low as 106 kcal/kg/day[89] and as high as 181 kcal/kg/day.[85] Within this range there appears to be no clear relation between energy intake and weight gain. It appears that an intake of 110 kcal/kg/day from high-quality infant formula or human milk is generally sufficient to support normal growth and metabolism of healthy premature infants, provided protein intake is adequate. Moreover, it seems that infants receiving high

TABLE 27-2 Estimated Water Requirement of Low-Birth-Weight Infant (mL/kg/day)

		BIRTH WEIGHT RANGE (g)					
Week	**Component**	**501-750**	**751-1000**	**1001-1250**	**1251-1500**	**1501-1750**	**1751-2000**
1*	IWL†	100	65	55	40	20	15
	Urine‡	70	70	70	70	70	70
	Stool	5	5	5	5	5	5
	Growth§	0	0	0	0	5	5
	Oxidation‖	–5	–5	–5	–5	–10	–10
	TOTAL	170	135	125	110	90	85
2	IWL	80	60	50	40	30	20
	Urine	70	70	70	70	70	70
	Stool	5	5	5	5	5	5
	Growth	0	0	5	5	10	10
	Oxidation	–5	–5	–10	–10	–10	–10
	TOTAL	150	130	120	110	105	95
3	IWL	70	50	40	35	30	25
	Urine	70	70	70	70	70	70
	Stool	5	5	5	5	5	5
	Growth	5	5	10	10	10	10
	Oxidation	–10	–10	–10	–10	–10	–10
	TOTAL	140	120	115	110	105	100
4	IWL	60	45	40	35	30	25
	Urine	70	70	70	70	70	70
	Stool	5	5	5	5	5	5
	Growth	10	10	10	10	10	10
	Oxidation	–10	–10	–10	–10	–10	–10
	TOTAL	135	120	115	110	105	100

Adapted from Bell EF, Oh W: Clin Perinatol 6:139-150, 1979.
*Days 3-7. Less water is given during the first 2 days to allow for "physiologic" negative water balance.
†Insensible water loss (IWL) for infants above 750 g adapted from Wu and Hodgman.[27] Increase by 40%-50% if phototherapy or radiant warmer used. May be less if the infant was exposed to antenatal corticosteroids.[30]
‡Sufficient urine to maintain concentration of 100 to 500 mOsm/L with solute excretion of 7 to 35 mOsm/kg/day.
§Assuming gain of 0, 7.5, or 15 g/kg/day with 67% of gain as water.
‖Water of oxidation calculated as 0.14 mL/kcal expended,[82,83] assuming energy expenditure of 35 to 70 kcal/kg/day.

energy intakes become fatter without accelerating their gain in fat-free mass.[83,85,93,94] The energy from the diet that is not lost in the stool or urine is either expended for metabolism or stored in the body for growth. The components that comprise total energy expenditure consist of minimal or resting energy expenditure (about 40 kcal/kg/day for young premature infants), energy expended for activity, cold-induced energy expenditure, diet-induced or postprandial energy expenditure (also called the specific dynamic action), and the energy expended for synthesis of new tissues. Some consider the last two categories to be synonymous, or at least overlapping. The energy expended for deposition of new tissue during growth in human infants has been estimated to be 5.5 kcal/g for protein and 1.6 kcal/g for fat.[95] Estimates of the overall energy cost of growth range from about 2.5 kcal/g[96] to 4.5 kcal/g.[97] The energy cost of activity is quite variable but accounts on average for about 3.5% of the total daily energy expenditure.[98] Energy expenditure increases with various medical care procedures,[99] presumably as a result of increased expenditure for activity and thermogenesis.

The total daily energy expenditure per kilogram of body weight is lowest in the smallest infants and increases slightly with postnatal age in both premature and term infants.[79,100-102] After the first week, it averages about 60 kcal/kg/day. The energy excreted in the stool and urine is about 10% of the intake. The energy stored for growth depends on the rate of gain and the composition of new tissues.

For the healthy growing premature infant who is enterally fed, the energy requirement is about 110 kcal/kg/day (Table 27-3). The energy required to maintain an intravenously fed infant in a nongrowing state is considerably less, about 50 kcal/kg/day (Table 27-3). Positive nitrogen balance has been reported with intravenous feedings delivering as little as 60 kcal/kg/day,[103] but consistent growth generally requires 70 kcal/kg/day or more.

Information about the energy expenditure of infants who require assisted ventilation is difficult to derive because of the technical difficulties of measuring whole-body oxygen consumption and carbon dioxide production in intubated infants. Richardson and colleagues[104] performed brief measurements of oxygen consumption (which is directly proportional to energy expenditure) in infants with RDS who required assisted ventilation. They found the oxygen consumption to be slightly higher than expected, especially during the first 24 hours of life. Billeaud et al.[105] measured oxygen consumption in mechanically ventilated premature infants with early or impending bronchopulmonary dysplasia (BPD). The oxygen consumption increased with increasing severity of lung disease, as determined by airway pressure and inspired oxygen requirement. Schulze and colleagues[106] measured the oxygen consumption of the lungs in premature infants with RDS who were mechanically ventilated. They found the pulmonary oxygen consumption to be 25% of the whole-body oxygen consumption and postulated that oxygen consumed by the lungs as a result of their extra work accounts for the elevated energy expenditure of infants with lung disease. Field and colleagues[107] found that adults with cardiorespiratory disease had a 21% reduction in oxygen consumption when mechanically ventilated. They attributed this difference to the work of breathing, which was about 10 times normal. Several other common conditions are also associated with increased energy expenditure in premature and critically ill infants. Energy expenditure is increased by 20% to 40% during therapy with aminophylline or caffeine for apnea of prematurity, at least during the first few days of treatment,[108,109] and energy expenditure is increased by 20% to 40% during episodes of bacterial sepsis.[110,111]

Several groups of investigators have found increased rates of oxygen consumption in spontaneously breathing infants with BPD.[112-117] The significance of these results has been questioned in view of the methodological difficulties presented in measuring oxygen consumption in infants who are breathing oxygen-enriched air.[118] However, the finding of increased energy expenditure in infants with BPD has been confirmed using doubly labeled water,[117] a method that is not influenced by inspired oxygen concentration. Rozé and colleagues[119] found that mechanically ventilated infants who were subsequently destined for chronic lung disease had a 30% increase in oxygen consumption after extubation. This suggests that the higher oxygen consumption and energy expenditure seen in infants with BPD results from increased work of breathing. In summary, infants ill enough to require assisted ventilation may have increased energy expenditure and energy requirement related to the increased work of breathing; however, this increase may be limited by use of appropriate ventilatory support.

An energy intake of 70 to 80 kcal/kg/day in the first week of life is sufficient to prevent starvation and promote growth in premature infants who are receiving the majority of their feeding parenterally. In subsequent weeks, it should be possible to increase the energy intake to 110 kcal/kg/day or more, allowing for the energy of digestion and synthesis and energy losses in the stool as the proportion of energy delivered enterally increases. Finally, each infant is unique, and some will require a much greater energy intake to establish growth. The ultimate tests of sufficiency of energy intake are the rate and quality of growth.

TABLE 27-3 Estimated Energy Requirement of Premature Infants

	ENERGY EXPENDITURE OR LOSS (kcal/kg/day)	
	Growing, Enterally Fed Infant*	**Nongrowing, Parenterally Fed Infant**
Resting energy expenditure	40	40
Activity	5	0
Cold stress	5	5
Postprandial or synthetic energy	10	0
Stool and urine energy loss	10	5
Energy for growth	40	0
Total energy requirement	110	50

*Adapted from Sinclair JC, Driscoll JM Jr, Heird WC, Winters RW: Pediatr Clin North Am 17:863-893, 1970.

Protein Requirement

The protein requirement of the healthy term infant in the first month of life is approximately 2.0 g/kg/day.[120] Estimates of the protein requirement of premature infants based on the rate of fetal accretion of protein are between 3.0 and 4.0 g/kg/day (Table 27-4).[12,121] These estimates are supported by experimental studies of protein turnover, nitrogen balance, and growth. Infants fed parenterally require less, approximately 3.0 to 3.5 g/kg/day of amino acids if growing well.[12,121-123] Premature infants who require assisted ventilation have been shown to benefit from intravenous amino acids starting as soon as possible after birth,[124,125] in doses up to 2.4 g/kg/day.[126] Early amino acid administration to premature infants prevents nitrogen deficit and improves protein kinetics. Whereas term infants and adults respond to increased protein intake by reducing proteolysis, premature infants respond to intravenous amino acids by increasing protein synthesis but not suppressing protein breakdown.[127,128] In a retrospective analysis of a large multicenter database, early initiation of intravenous amino acids was associated with better growth, as assessed by gain in weight, length, and head circumference from birth to 36 weeks postmenstrual age.[129] In addition to meeting the infant's needs for growth, intravenous amino acids may help to promote respiratory control center output and decrease the risk of apnea; this inference is based on studies in adult humans and experimental animals, including neonatal piglets.[130]

Lipid Requirement

Lipids are important as a source of energy for metabolism and growth. Recommendations for total lipid intake are not well established. Human milk and most commercial formulas derive 40% to 50% of their energy content from fat. The usual diet of an infant consuming human milk or infant formula contains 4 to 6 g of fat per 100 kcal and provides 5 to 7 g/kg/day of fat. Restriction of dietary fat intake is not recommended in the first 2 years of life.

The omega-3 and omega-6 polyunsaturated fatty acids play particularly important biologic roles in development as eicosanoid precursors, components of membrane phospholipids, and ligands for membrane receptors and transcription factors that regulate gene expression.[131-133] Humans cells have limited capacity for *de novo* synthesis of omega-3 and omega-6 polyunsaturated fatty acids, so these must be received from the diet. Dietary essential fatty acid deficiency in infants causes dermatitis, increased susceptibility to infection, and impaired growth.[134] The requirement for essential fatty acids can be met by providing 1% of the dietary energy in the form of linoleic and linolenic acids.[135] To provide a margin of safety, the intake recommended by the Committee on Nutrition of the American Academy of Pediatrics is 3% of the energy intake as essential fatty acids.[136]

Certain biologically important long-chain polyunsaturated fatty acids, such as docosahexaenoic acid (DHA) and arachidonic acid (AA), are found in human milk and are commonly added to commercial infant formulas. DHA and AA can be synthesized from shorter chain fatty acids in both term and premature infants.[137,138] Evidence of benefit from supplementing commercial infant formulas with DHA and AA has been equivocal.[139-141] However, it is generally accepted that supplementation of formula with both DHA and AA in appropriate amounts[133] is not harmful and may confer benefit. Most infant formulas are now supplemented with these fatty acids in an effort to achieve intakes similar to breast-fed infants.

Premature infants do not absorb fat as well as term infants. The rate of bile salt synthesis, the bile salt pool, and the intraluminal concentration of bile salts are all decreased in premature infants.[142] In addition, the activity of pancreatic lipase is lower than at term.[143] The presence of lingual lipase and its role in intragastric fat digestion help to overcome the premature infant's deficiencies of pancreatic lipase and bile salt activity.[144] Human milk fat and vegetable fats are more easily absorbed than saturated animal fats. Triglycerides of short- and medium-chain fatty acids are directly absorbed into the portal blood independent of bile salt and lipase activities. Medium-chain triglycerides (MCTs) are sometimes used to enhance fat digestion in specialized infant formulas, especially those designed for premature infants. Premature infants fed formulas containing MCT show improved absorption of fat, calcium, and magnesium,[145-149] but most studies have not found improved weight gain with MCT-containing formulas.[147,148,150] The lack of effect on weight gain may be explained by the fact that the energy content per gram of MCT is about 15% less than the energy content per gram of long-chain triglycerides.[151]

Lipid emulsions are a key component of parenteral feeding regimens for infants who require assisted ventilation. Intravenous lipid emulsions made from plant oils provide an important source of essential fatty acids and additional energy. The emulsion is given intravenously as 20% (0.2 g/mL) solution from a separate administration set that joins the main infusate (containing glucose, amino acids, electrolytes, minerals, and vitamins) shortly before the infusion needle. Lipid emulsions (20%) provide 2.0 kcal/mL. Occasionally, the lipid emulsion is added to the bag containing the main infusate prior to infusion, producing an "all-in-one" infusate. Using a regimen consisting of lipid emulsion and a solution containing glucose, amino acids, electrolytes, minerals, and vitamins given by

TABLE 27-4 Estimated Daily Requirements for Energy, Protein, and Selected Nutrients for Premature Infants

	ADVISABLE INTAKE (per kg per day)		
	0.5-1.0 kg Infant	**1.0-1.5 kg Infant**	**1.5-2.0 kg Infant**
Energy (kcal)	110	120	130
Protein (g)	4.0	3.9	3.5
Sodium (mmol)	3.3	3.0	2.6
Potassium (mmol)	2.4	2.3	2.2
Chloride (mmol)	2.8	2.7	2.5
Calcium (mg)	184	178	173
Phosphorus (mg)	126	124	120
Magnesium (mg)	6.9	6.7	6.4

Adapted from Ziegler EE: Nestle Nutr Workshop Ser Pediatr Program 59:161-176, 2007.

TABLE 27-5 Energy Sources in Peripheral Venous Nutrition

Infusate	INTAKE (per kg per day) Water (mL)	Nutrient (g)	Energy (kcal)
Dextrose (12.5 g/dL) and amino acid (2.5 g/dL) solution	135	–	–
Dextrose	–	16.9	57
Amino acids	–	3.4	13
Lipid emulsion (20%)	15	3.0	30
TOTAL	150		100

peripheral vein, it is possible to provide complete nutritional support without causing fluid overload (Table 27-5).

If lipid emulsion is infused too rapidly, serum concentrations of triglycerides and fatty acids become elevated. Small premature infants are less tolerant of infused lipid, especially those who are small for gestational age. Hypertriglyceridemia does not generally occur if the lipid infusion rate is limited to a maximum of 0.15 g/kg/hr. In infants weighing less than 1 kg, the maximum infusion rate should be limited to 0.10 g/kg/hr or less.

Rapid infusion of lipid emulsion has been found to have detrimental effects on pulmonary gas exchange and hemodynamics. These effects seem to occur only when the lipids are infused faster than they can be cleared from the plasma. Decreased arterial oxygen tension has been reported, but only when the lipid infusion rate exceeded 0.2 g/kg/hr.[152, 153] Lipid infusions in excess of 0.2 g/kg/hr have also been found to increase pulmonary artery pressure and pulmonary-to-systemic shunting[154-156]; these effects are thought to be mediated through effects on prostanoid metabolism.[154,155,157]

The fatty acids contained in lipid emulsions have the potential to displace bilirubin from its binding sites on albumin molecules. This occurs only when the molar ratio of fatty acids to albumin is greater than 6:1,[158] an unlikely event with infusion rates of 0.2 g/kg/hr or less.[159]

Review of the literature indicates that adverse effects of infused lipids are more closely related to the maximum hourly infusion rate than to the total daily dose. The risks of administering lipid emulsion are minimal when the lipids are infused at rates below 0.2 g/kg/hr. In the case of critically ill infants, it is prudent to limit the rate of lipid infusion to 0.15 g/kg/hr. With this infusion rate, a dose as high as 3.0 g/kg/day can be delivered, assuming 20 hours for lipid infusion with 4 hours of interruption for the infusion of medications. Because infants below 1 kg are especially intolerant of infused lipid, it is prudent to limit their infusion rate to 0.1 g/kg/hr (0.5 mL of 20% emulsion/kg/hr) or less. Infants who are at risk of pulmonary hypertension should also be subject to limited rates of lipid infusion. With a total fluid intake of 150 mL/kg/day, it is possible with parenteral nutrition to provide 90 kcal/kg/day with a lipid dose of 2.0 g/kg/day, and energy intake of 100 kcal/kg/day can be achieved with a lipid dose of 3.0 g/kg/day (see Table 27-5).

Studies of respiratory gas exchange and substrate utilization have demonstrated an important advantage to using lipid emulsion as an energy source in infants with compromised respiratory function.[160-162] Oxidation of carbohydrate produces more carbon dioxide (CO_2) per mole of oxygen consumed or per kilocalorie of energy expended than does oxidation of fat. For this reason, subjects receiving fat-free total parenteral nutrition produce more CO_2 than they would if receiving part of their nonprotein energy as fat. Piedboeuf et al.[161] studied 10 low-birth-weight infants who were given two isocaloric intravenous nutritional regimens, low-fat (1 g/kg/day) and high-fat (3 g/kg/day), each for 5 days, in a crossover design. During the low-fat (high-glucose) regimen, the infants had higher respiratory quotients and higher rates of carbon dioxide production and minute ventilation (Table 27-6). For healthy subjects without respiratory compromise, the additional CO_2 can be easily eliminated by increasing the spontaneous ventilation rate. However, for subjects with lung disease, the extra CO_2 produced from high-glucose parenteral nutrition may require initiation of or increase in mechanically assisted ventilation to prevent an increase in arterial CO_2 tension.

Carbohydrate Requirement

It is not possible to define an absolute requirement for carbohydrate in newborn infants. In addition to their role in preventing hypoglycemia, carbohydrates are important as metabolic fuel. Approximately half of the infant's energy needs are normally provided by carbohydrate metabolism. Moreover, glucose is the primary energy source for brain metabolism. In the premature infant, this glucose is largely derived from exogenous carbohydrate sources because of the inefficient mechanisms of gluconeogenesis; however, there is evidence that the newborn brain may use ketone bodies as an additional energy source.[163]

The usual dietary regimens provide roughly half the total energy intake as carbohydrate. Fomon and colleagues[164] showed that varying the portion of energy derived from carbohydrate from 34% to 62% produced no difference in linear or weight growth of term infants; 9% of the energy was derived from protein in both groups and the balance from fat.

The maturation of the mechanisms for carbohydrate digestion and absorption progresses in a defined sequence

TABLE 27-6 Effect of Nonprotein Energy Source on Gas Exchange and Ventilation in Parenterally Nourished Newborn Infants

	Low-Fat Regimen	High-Fat Regimen
Energy intake (kcal/kg/day)	75	81
Nonprotein energy source (%)		
Dextrose	85	55
Lipid emulsion	15	45
Oxygen consumption (mL/kg/min)	6.4	6.5
Carbon dioxide production (mL/kg/min)	6.9	6.2*
Respiratory quotient	1.08	0.96*
Energy expenditure (kcal/kg/day)	48	47
Ventilation (mL/kg/min)	160	142*

From Piedboeuf B, Chessex P, Hazan J, Pineault M, Lavoie JC. J Pediatr 118:97-102, 1991.
*Significantly lower on high-fat regimen.

in the human fetus. Sucrase, maltase, and isomaltase are usually fully active by 24 to 28 weeks' gestation, but lactase lags behind the others and is not fully active at birth until term.[165] However, there is evidence that intestinal lactase activity increases to adequate functional levels within a few days after the initiation of enteral feedings, even in infants born as early as 28 weeks' gestation.[166] Activity of pancreatic amylase remains quite low until after term.[143,165,167] Salivary amylase activity is present even in very premature infants,[168] however, and this enzyme is thought to play a role in the initial digestion of glucose polymers,[169] a carbohydrate source often used in formulas for premature infants. Glucose transport in the intestine is also limited at birth,[165] and may be the rate-limiting step in carbohydrate absorption. In spite of the late gestational rise in lactase activity and the decreased capacity for intestinal glucose transport, both term and premature infants seem to tolerate the carbohydrates in human milk and commercial formulas quite well. Normal absorption and growth have been documented with formulas containing lactose, sucrose, and glucose, alone or in combination.

Mineral Requirements

Several methods have been used to estimate the infant's requirements for electrolytes and minerals. One approach is to compare the body composition of premature and term infants at birth and thus to derive the amount of a particular substance that would have accrued had the premature infant remained *in utero*.[170] To this amount required for the formation of new tissues can be added estimates of the amount lost through the skin, urine, and stool. This method is called the *factorial approach*. Because of the uncertainty of the derivation, the estimated requirements are increased, typically by 10%, to produce recommended or advisable intakes of nutrients (see Table 27-4).[12] An indirect approach, such as the factorial approach, must be used because nutrient requirements cannot be experimentally determined without inducing a potentially harmful deficiency state.

The requirements of sodium, potassium, and chloride derived from such calculations are all between 2 and 4 mmol/kg/day.[12] The recommended intakes of these elements for premature infants are also within this range or slightly higher (Table 27-7).[136,171] Premature infants sometimes require higher sodium intakes after the first week of life because of urinary sodium loss. Serum potassium must be carefully monitored in the very premature infant because of increased risk of hyperkalemia.

The recommended intakes of calcium and phosphorus depend on the route of administration and, if given enterally, on the absorption rate. The fraction of calcium absorbed depends on the type of milk or formula, the gestational age, and the postnatal age. The adequate intake of calcium for term infants in the first 6 months of life has been determined to be 210 mg/day (70 mg/kg/day for a 3-kg infant).[172] The calcium requirement for premature infants is higher. Ziegler[12] has estimated that an enteral calcium intake of 170 to 190 mg/kg/day is necessary for small premature infants to achieve the intrauterine rate of calcium retention (see Table 27-4). The adequate intake of phosphorus for term infants has been set at 100 mg/day (33 mg/kg/day for a 3-kg infant).[172] The recommended intake of phosphorus for premature infants is 120 to 130 mg/kg/day.[12] Poor bone mineralization may occur if phosphorus intake is inadequate. Fortification of human milk is necessary to assure adequate intakes of calcium and phosphorus to premature infants who are fed human milk. For infants fed intravenously, absorption is not a consideration and lower intakes of calcium and phosphorus are adequate. Recommended intravenous intakes of calcium range from 60 to 80 mg/kg/day, and of phosphorus 45 to 60 mg/kg/day (see Table 27-7).[171,173]

The adequate intake of magnesium for enterally fed term infants has been established as 30 mg/day (10 mg/kg/day for a 3-kg infant).[172] The recommended enteral intake of magnesium for premature infants is 6 to 7 mg/kg/day (see Table 27-4),[12] with intakes as high as 15 mg/kg/day being reasonable (see Table 27-7).[171] Intravenous intake of 4 to 7 mg/kg/day is recommended for infants receiving total parenteral nutrition for prolonged periods.[171,173]

Iron at an intake of 2 to 4 mg/kg/day is recommended for both term and premature infants who are enterally fed.[136,171] During the acute care of infants requiring assisted ventilation, before enteral feeding is established, iron will most commonly be provided in the form of blood transfusions given to prevent or correct significant anemia. Infants

TABLE 27-7 Reasonable Daily Intakes of Minerals, Vitamins, and Micronutrients for Growing Premature Infants (per kg per day)

Nutrient	Enteral	Parenteral
Sodium	2-5 mmol	2-5 mmol
Potassium	2-3 mmol	2-3 mmol
Chloride	2-7 mmol	2-7 mmol
Calcium	100-220 mg	60-80 mg
Phosphorus	60-140 mg	45-60 mg
Magnesium	8-15 mg	4-7 mg
Iron	2-4 mg	0.1-0.2 mg
Zinc	1-3 mg	0.4 mg
Copper	120-150 mcg	20 mcg
Manganese	0.7-7.5 mcg	1 mcg
Selenium	1.3-4.5 mcg	1.5-4.5 mcg
Chromium	0.1-2.2 mcg	0.05-0.3 mcg
Molybdenum	0.3 mcg	0.25 mcg
Iodine	10-60 mcg	1 mcg
Vitamin A	700-1500 IU	700-1500 IU
Vitamin D	150-400 IU	40-160 IU
Vitamin E	6-12 IU	2.8 IU
Vitamin K	8-10 mcg	10 mcg
Vitamin C	18-24 mg	15-25 mg
Thiamin	180-240 mcg	200-350 mcg
Riboflavin	250-360 mcg	150-200 mcg
Niacin	3.6-4.8 mg	4.0-6.8 mg
Vitamin B_6	150-210 mcg	150-200 mcg
Vitamin B_{12}	0.3 mcg	0.3 mcg
Folic acid	25-50 mcg	56 mcg
Pantothenic acid	1.2-1.7 mg	1-2 mg
Biotin	3.6-6 mcg	5-8 mcg
Taurine	4.5-9.0 mg	1.9-3.8 mg
Carnitine	3 mg	3 mg
Inositol	32-81 mg	54 mg
Choline	14-28 mg	14-28 mg

Adapted from Tsang RC, Uauy R, Koletzko B, Zlotkin SH (eds): Nutrition of the Preterm Infant: Scientific Basis and Practical Guidelines. Cincinnati, Digital Educational Publishing, 2005, pp 415-418.

fed human milk should be given daily supplements of iron once full enteral feedings have been established but startng no later than 2 weeks of age. Formula-fed infants should receive only iron-fortified formula, beginning with the first formula feedings. There is no need to delay the start of iron supplementation until an arbitrary age.[174-176] The advisable enteral intakes of zinc and copper are 1 to 3 mg/kg/day and 0.1 to 0.2 mg/kg/day, respectively (see Table 27-7).[171] Other minerals such as selenium, manganese, iodine, chromium, and molybdenum are also required in trace amounts (see Table 27-7).[136,171]

Vitamin Requirements

Vitamin A is essential for growth and differentiation of epithelial tissues, including those in the lung. Premature infants have low stores of vitamin A at birth,[177] and infants with lung disease have lower plasma vitamin A levels than those without lung disease.[178] A large randomized clinical trial showed a reduction in the risk of death or bronchopulmonary dysplasia (defined as a requirement for supplemental oxygen at 36 weeks postmenstrual age) with vitamin A supplementation, 500 IU given intramuscularly 3 times a week for 4 weeks.[179] A systematic review of eight clinical trials of vitamin A supplementation to premature infants confirmed the beneficial effect of vitamin A in reducing the risk of death or oxygen requirement at 1 month of age by 7% (relative risk 0.93, 95% confidence interval 0.88-0.99).[180] The number needed to treat to allow survival of one more infant without bronchopulmonary dysplasia was 20. In the review, other morbidities and mortality were not significantly reduced by vitamin A. Because of concerns about absorption from the gastrointestinal tract, vitamin A supplements have generally been given by intramuscular injection. Despite its efficacy, vitamin A supplementation has not become standard practice,[181] in part because of the need for repeated intramuscular injections. Administering vitamin A and other fat-soluble vitamins in lipid emulsion provides a potential alternative to intramuscular injection.[182]

Vitamin D is essential for good bone health.[183] As with other fat-soluble vitamins, the body stores of vitamin D are low at birth, especially in premature infants.[184] Infants who require assisted ventilation have no exposure to ultraviolet light and so have minimal cutaneous synthesis of vitamin D. The recommended enteral intake of vitamin D is 400 IU per day (regardless) of body weight,[185,186] although higher doses have been recommended by some.[187] Lower intakes are required for infants who depend on parenteral nutrition support (see Table 27-7).

Vitamin E is the major natural antioxidant in the body. It protects lipid-containing cell membranes against oxidative injury and is thought to play a role in preventing neonatal oxygen toxicity.[188] The recommended enteral vitamin E intake, 6 to 12 IU/kg/day, is sufficient to compensate for variation in absorption and distribution and in the intake of other nutrients known to influence vitamin E requirement, such as iron and polyunsaturated fatty acids (PUFA). This level of intake is also low enough to avoid the possible toxicities associated with excessive intakes of vitamin E.[189]

The amount of vitamin E required to prevent lipid peroxidation in vulnerable tissues depends on the PUFA content of the tissues and diet.[188] Tissues containing higher levels of PUFA are more susceptible to lipid peroxidation. In addition to the recommended vitamin E intake of 6 to 12 IU/kg/day, it is also advisable to keep the dietary ratio of vitamin E to PUFA at or above the level of 0.6 mg of D-α-tocopherol (0.9 IU) per gram of PUFA.[188,190] Most human milk samples and current infant formulas have vitamin E–to–PUFA ratios above 0.6 mg/g.[188,191] Consequently, normal premature infants who are well enough to tolerate enteral feedings are usually not at risk for vitamin E deficiency.

Infants with fat malabsorption because of cholestatic liver disease or short bowel syndrome are at risk for developing vitamin E deficiency because of impaired absorption of fats and fat-soluble vitamins, including vitamin E. Infants who require total parenteral nutrition may also be at risk for vitamin E deficiency, particularly those who receive PUFA in the form of lipid emulsion but very little vitamin E.[192] The vitamin E contained in parenteral multivitamin preparations is in the form of *dl*-α-tocopheryl acetate, which is slowly hydrolyzed and relatively ineffective as an antioxidant when given by injection.[193,194] Nevertheless, small intravenous doses of vitamin E (2.8 IU/kg/day as α-tocopheryl acetate in a multivitamin preparation) seem to be sufficient to prevent vitamin E deficiency in infants receiving total parenteral nutrition[173,195] while avoiding potentially toxic plasma levels of vitamin E.

Individual clinical trials[196-199] and a systematic review[200] have shown that the incidence of severe retinopathy of prematurity (ROP) can be reduced in very-low-birthweight infants by administration of high-dose vitamin E supplements to premature infants. The studies showing greatest efficacy have used doses of vitamin E with potential for severe toxicity.[189] Consequently, routine administration of high-dose vitamin E supplements is not recommended for prophylaxis against ROP.[201] Perhaps the most important potential benefit of vitamin E supplementation for premature infants in the first days of life is its role in protecting against intraventricular hemorrhage.[200] The studies showing benefit have used a variety of dosing regimens. Although unproven, it has been speculated that a single enteral dose of vitamin E at birth may help to correct the relative deficiency present in the first days of life as a result of low vitamin E stores, increased vitamin E use to quench free radicals produced by oxidative reactions, and delayed supply of vitamin E from nutritional sources.[202]

Vitamin K is essential to prevent hemorrhage in the first weeks of life.[203,204] A single dose of vitamin K is routinely given at birth. Subsequent supplementation with vitamin K is necessary to prevent deficiency, especially for critically ill infants, who often receive broad-spectrum antibiotics (reducing vitamin K synthesis by gut bacteria) and may have other abnormalities of hemostasis or hepatic function.

Additional nutrients, such as water-soluble vitamins and other trace substances, are required for recovery and healthy growth of ventilated infants (see Table 27-7).

Methods of Feeding

Infants who require assisted ventilation cannot be orally fed because of the danger of pulmonary aspiration. In addition, they usually lack the strength, reflexes, and neuromuscular coordination to be orally fed from breast or bottle. Alternate methods of feeding are available for these infants. Most infants can be fed small amounts of colostrum or milk by tube into the stomach, beginning as soon as the mother's milk is available. Usually, it will also be necessary to provide parenteral nutrition support.

Parenteral Feeding

Peripheral Vein Catheters

Indwelling short plastic catheters provide safe and convenient access to the peripheral venous circulation. Veins in the extremities are preferred over scalp veins, to avoid the parental distress caused by shaving the infant's scalp hair to expose veins and to avoid the potential for intravenous infiltrations in areas of the head that may lead to adverse cosmetic results. Scalp veins should be used only after extremity sites have been exhausted and, even then, only after discussing the procedure with the infant's parents. The infusion site must be carefully observed so that extravasation can be detected as soon as possible. The most common significant complication of peripheral intravenous infusions is tissue necrosis at the site of extravasation, especially if the infusate is hypertonic or acidic or contains calcium.[205] Digital gangrene and nerve injury have also been reported as complications of peripheral vein infusions. Glucose concentrations greater than 12.5 g/dL should be avoided in peripheral veins. To prevent extravasation of fluid, the catheter should be immobilized securely by adhesive tape. If the site is near a joint, the arm or leg can be splinted with a padded board.

Central Vein Catheters

Two types of central vein catheter are used for intravenous delivery of nutrients to newborn infants. The *percutaneously inserted central catheter* (PICC) is the preferred technique for central venous access. The small-bore catheters, usually 24- or 28-gauge, are made of silicone elastomer (Silastic®) or another nonthrombogenic material and are inserted through a slightly larger introducer needle. Percutaneous central catheters, if carefully maintained, may function well for several weeks. With good care, the risk of infectious complications is very low. Percutaneous catheters provide a safe, practical technique for prolonged venous access with a lower risk of complication than is presented by larger, surgically placed catheters.

Alternatively, a large-bore catheter can be inserted through a jugular vein into the superior vena cava and tunneled subcutaneously to a skin exit site on the scalp or chest. The *surgically placed central vein catheter* is typically used for infants who have required gastrointestinal surgery for gut malformation or necrotizing enterocolitis and for whom prolonged parenteral nutrition is anticipated.

Serious complications of central venous catheters include infection and venous obstruction from thrombosis. Infection is less frequent with percutaneously inserted catheters than with surgically placed catheters. Major thrombotic complications are rare with percutaneous lines but are sometimes seen with surgical central lines in small infants. With either type of central venous catheter, the tip of the catheter should be placed in the vena cava or other large central vein rather than in the right atrium, to avoid cardiac thrombosis, infection, and perforation with cardiac tamponade.[206,207] The position of the catheter's tip should be verified radiographically from time to time because of the risk of catheter migration.[208] Because of their higher complication rate, surgically placed central lines should be avoided whenever possible in newborn infants.[209]

Umbilical Vein Catheters

During the care of an infant who is ill enough to require mechanical ventilation, umbilical vein catheters are sometimes used for monitoring central venous pressure in infants with circulatory instability or for providing temporary venous access in extremely small premature infants. Umbilical vein catheters are susceptible to the same complications as percutaneous and surgical central lines–infection, thrombosis, and cardiac perforation with tamponade.[210] The tip of the catheter should be placed in the inferior vena cava to avoid cardiac thrombosis or perforation. Other serious complications, including portal vein thrombosis,[211] have also been reported with umbilical vein catheters. Once early onset infection has been ruled out or treated and the umbilical catheter is no longer needed for venous pressure monitoring, the catheter should be replaced with a peripheral vein catheter or a percutaneous central vein catheter.

Umbilical Artery Catheters

Umbilical artery catheters are frequently used to monitor blood pressure and to facilitate blood sampling for laboratory monitoring in critically ill newborn infants. The risks of umbilical artery catheters include infection, hemorrhage, thrombosis,[212-214] and hypertension.[214-216] (See Chapter 17.) Administration of hypertonic nutritional solutions through arterial catheters increases the already significant risk of vascular injury and thrombosis. Therefore, parenteral nutrition solutions should not be delivered through umbilical artery catheters when alternative routes are available. When the umbilical artery must be used to deliver nutritional support, the concentrations of nutrients in the infused solution should not exceed those used in peripheral veins. Nutritional support solutions must never be infused into peripheral artery catheters.

In summary, the safety and longevity of percutaneously inserted central catheters make them a favorite route for delivering intravenous nutritional support. Neonatal units providing short-term care for ventilated infants should have personnel capable of inserting and maintaining peripheral venous infusions in infants. Units that provide long-term intensive care for such infants should also have personnel capable of placing and maintaining percutaneously inserted central catheters. Surgically placed central lines should be avoided whenever possible but may be needed for some infants with severe gastrointestinal dysfunction. Umbilical vein catheters may be used for short-term delivery of nutritional solutions, but longer use increases the risks of infection and thrombosis. Umbilical

artery catheters should be used to deliver nutritional solutions only when other routes of administration are not available.

Enteral Feeding

Intermittent Intragastric Feeding

Enteral feeding provides nutrients to support growth and metabolism but also, even in very small amounts, promotes intestinal development and function. Feeding stimulates secretion of gut hormones and regulatory peptides[217] and promotes intestinal growth.[218] These effects are most prominent with feeding of maternal milk,[219] which also contributes to gut health by facilitating and augmenting the innate gut immune system.[220] Enteral feeding enhances bile flow,[221] and small amounts of feeding help to prevent the cholestasis that often occurs with total parenteral nutrition.[222] Intermittent ("bolus") nasogastric or orogastric gavage feeding at 2- or 3-hour intervals is commonly used for feeding premature infants and other infants who are unable to be fed by nipple. Because of limitations in the mechanical and biochemical functioning of the gastrointestinal tract in infants who require assisted ventilation, this method generally must be combined with intravenous nutritional support to provide sufficient intake of water, energy, and nutrients.

Sick infants can usually be fed safely by gavage, even those requiring mechanical ventilation, provided there is no perforation, ileus, or malformation of the gastrointestinal tract. Small amounts of maternal colostrum or infant formula can be started within hours of birth without increasing the risk of necrotizing enterocolitis.[223] The initiation of feedings should probably be delayed in infants with significant birth asphyxia—those with very low 5-minute Apgar score—because of the risks of feeding in the presence of gut ischemia and reperfusion. Either oral or nasal feeding tubes can be used. Nasal tubes are easier to secure and offer no disadvantage for infants who are endotracheally intubated. However, nasal feeding tubes partially obstruct the infant's airway and so should probably be avoided in infants without ventilatory support who have respiratory distress or episodic apnea.

Intermittent gavage feedings can lead, under certain circumstances, to decreased arterial oxygen tension in premature and term infants, especially those with respiratory disease.[224-226] This effect, which occurs only with feedings of 2.5 mL/kg or larger, is mediated by a fall in tidal volume and functional residual capacity.[224] How significantly these changes in lung volume contribute to the risks of hypoxia and aspiration with feeding is not known, but the potential for adverse effects on respiratory function should be kept in mind when feeding sick infants who require assisted ventilation.

Nonnutritive sucking of a pacifier during gavage feedings has been tested as a way of compensating for the lack of oral stimulation in tube-fed infants. A systematic review based on published studies showed shorter hospital stay and a trend toward more rapid weight gain with nonnutritive sucking.[227] The effect on length of stay presumably indicates accelerated learning of nipple feeding as a result of the "training" effect of nonnutritive sucking.

Continuous Intragastric Feeding

An alternative method of intragastric feeding is to infuse the milk or formula continuously through an indwelling nasogastric or orogastric tube at a constant rate controlled by an infusion pump. This method offers the theoretical advantages of allowing greater volumes to be absorbed without taxing the limited gastric capacity of smaller prematures and of avoiding the volume-related post-feeding hypoxia associated with intermittent gavage.[224] Unpredictable nutrient delivery is a potential problem with continuous feeding. Human milk fat may separate from the nonfat milk and be left in the tubing or syringe.[228] This problem can be averted by positioning the infusion pump so that the opening of the syringe is pointed upward, ensuring that the fat is still delivered even if it separates. Erratic delivery of human milk fortifier is also a potential problem.[229] Analysis of the clinical trials addressing the issue of intermittent versus continuous intragastric feeding led to the conclusion that infants fed continuously took longer to reach fully enteral feedings, but there was no difference in growth or time to discharge.[230]

Transpyloric Feeding

Transpyloric feeding, done by placing the tube directly into the duodenum or jejunum, has been used successfully to feed critically ill infants. Transpyloric feeding is technically more difficult, requires x-ray confirmation of tube placement, and generally offers no advantage over intragastric feeding. A systematic review of randomized trials comparing transpyloric with intragastric feeding revealed no advantage and a trend toward higher mortality with transpyloric feeding.[231] This technique, therefore, is not recommended as a routine feeding method for ventilated infants.

Human Milk for Premature and Critically Ill Infants

Few medical interventions offer as much advantage to premature and critically ill infants as human milk feeding. The most compelling early benefit of human milk is its protective effect against necrotizing enterocolitis in premature infants.[232,233] There is a clear dose-related protective effect of human milk feeding against necrotizing enterocolitis.[233] In one study, premature infants who received only human milk were 83% less likely to develop necrotizing enterocolitis than were their formula-fed counterparts.[232] The most important long-term benefit is the favorable impact of human milk feeding on neurodevelopmental outcome, which is dose-related and unequivocal.[234] It is important for hospitals that care for ventilated infants to provide good lactation support services. These services should include parent education and information, electric breast pumps, convenient pumping and storage facilities, and the services of trained lactation specialists. Mothers of infants who require intensive care including assisted ventilation should be strongly encouraged to provide their milk for their infants, even if they had planned to feed formula at home after the infant is discharged. Most mothers will agree to do this if the benefits to their infants are explained.

Combined Enteral and Parenteral Feeding

Most critically ill infants can be fed adequately and safely by a combination of the methods described above. The

TABLE 27-8 Comparison of Feeding Methods for Ventilator-Dependent Infants

Method	Advantages	Risks and Disadvantages
Peripheral vein	Not dependent on GI function No danger of aspiration Low infection risk	Repeated infant thermal and physiologic stress Personnel effort to start and maintain infusion Risk of tissue injury with extravasation
Central vein		
Percutaneous	High concentrations of infused glucose Not dependent on GI function No danger of aspiration Low risk of necrotizing enterocolitis Avoids risks of peripheral vein No need for general anesthesia Lower risk of thrombosis than surgical line	Infection Perforation of vessel or heart
Surgical	High concentrations of infused glucose Possible when other methods fail Not dependent on GI function No danger of aspiration Low risk of necrotizing enterocolitis Avoids risks of peripheral vein	General anesthesia Vena cava thrombosis Infection Perforation of vessel or heart
Intermittent intragastric	Promotes intestinal growth Promotes gut hormone secretion Promotes bile flow Reliable nutrient delivery	Bypasses salivary and lingual enzymes
Continuous intragastric	Larger volumes may be tolerated	Bypasses salivary and lingual enzymes Feeding components may separate in tubing
Transpyloric	Does not rely on gastric emptying	More difficult tube placement Decreased fat absorption Possible increased mortality

GI, Gastrointestinal.

tolerance of each infant to a particular method of feeding cannot be predicted. Infants who require mechanical ventilation cannot be fed by nipple but can be fed adequately with orogastric or nasogastric gavage feedings, either intermittent or continuous, supplemented with peripheral or central venous nutrition (Table 27-8). The advantage of even small amounts of enteral feeding for promoting gut hormone secretion and intestinal growth warrants early enteral feeding in nearly all infants.

Practical Recommendations

Parenteral Feeding and Fluid and Electrolyte Management

Infants who are ill enough to require assisted ventilation should begin to receive intravenous fluids as soon as possible after birth but certainly within the first hour. The initial infusion should consist of 5% or 10% dextrose in water or in 0.2-*N* saline at a rate of approximately 70% of the estimated water requirement (see Table 27-2). For example, an infant weighing 1100 g at birth should receive 85 to 90 mL/kg during the first 24 hours. This relative restriction of water intake during the first day or two of life allows for a physiologic state of negative water balance that accompanies the mobilization of extracellular water.[14-19] Exactly how much postnatal weight loss is desirable is not known, but the amount of fluid given should be sufficient to prevent hypernatremia and clinical signs of dehydration. In most instances, allowance for 5% to 10% weight loss in the first week of life is appropriate.

A 10% solution of dextrose in the amount suggested previously will prevent hypoglycemia in most infants, except some who are hyperinsulinemic. Occasionally, 10% dextrose in these volumes may induce hyperglycemia in very-low-birth-weight infants. Thus, in infants weighing less than 1 kg at birth, 5% dextrose in water should be chosen as the initial infusate (or the average dextrose concentration if more than one solution is given).

If not contained in the initial infusate, sodium is added by the second day to deliver 2.5 to 3.5 mmol/kg/day, provided the serum sodium concentration is not elevated. The practice of initially withholding sodium from premature infants in the first 24 hours of life is based on the idea that exogenous sodium may inhibit the contraction of the extracellular water compartment. This practice is also supported by several clinical studies.[235,236] The sodium is usually given as sodium chloride. If metabolic acidosis is present, some or all of the maintenance sodium may be given as sodium bicarbonate or sodium acetate.[237] Potassium chloride is also added to the infusion on day 2, to give 2 to 2.5 mmol/kg/day, provided the serum potassium concentration is normal and urination is well established. On the second or third day of life, the infusion rate is usually increased to deliver maintenance volumes (see Table 27-2). Careful limitation of fluid intake to these amounts has been shown to reduce the risks of patent ductus arteriosus and necrotizing enterocolitis in premature infants.[238]

Intravenous calcium supplementation should be started if the infant has signs that are attributed to hypocalcemia (tremulousness, seizures, apnea, or cardiac arrhythmia).

Calcium supplementation should also be considered if the serum ionized calcium concentration falls below 3.5 mg/dL in an infant who is receiving little or no enteral intake. Respiratory alkalosis due to hyperventilation increases the risk of hypocalcemic tetany. The usual starting dose of parenteral calcium is 300 mg/kg/day of calcium gluconate as a 10% solution. This is equivalent to 28 mg/kg/day of elemental calcium. There are several practical precautions that should be taken during parenteral calcium therapy. First, calcium salts should not be infused along with sodium bicarbonate, because precipitation of calcium carbonate particles may occur. Second, calcium should not be administered into an artery or into a catheter with its tip placed in the heart. Third, if calcium is infused into a peripheral vein, the utmost care should be provided to avoid extravasation. The latter may cause tissue necrosis and sloughing, which in some instances can be quite severe.

Most infants who require assisted ventilation should be given parenteral amino acids, minerals, and vitamins beginning as soon as possible but certainly within 24 hours of birth. The only exception should be an infant who can safely be fed significant volumes of milk or formula soon after birth and whose feedings are likely to be advanced within several days to a volume sufficient to support growth. Intravenous amino acids should be started at a dose of 1.5 to 2.0 g/kg/day. The dose of amino acids should be increased once a day in increments of 0.5 g/kg/day until a dose of 3.0 to 3.5 g/kg/day is reached. It is customary to also add minerals and vitamins to the parenteral infusate when intravenous amino acids are begun.

Lipid emulsion should normally be given as a part of any infant's parenteral nutrition regimen. There is debate about how soon after birth lipid emulsion should be started, but the benefits probably outweigh any risks by the second or third day of life. Lipid emulsion must be started before the end of the first week to avoid essential fatty acid deficiency in infants who cannot be fed enterally. The maximum infusion rate should not exceed 3 g/kg/day (0.15 g/kg/hr for 20 hours) for infants above 1 kg and 2 g/kg/day (0.10 g/kg/hr) for infants below 1 kg. If these maximum infusion rates are observed, it is probably not necessary to monitor serum triglyceride levels. However, if the serum is found to be lipemic by visual inspection, the infusion should be stopped for 4 to 6 hours or until the lipemia clears and then resumed at a slower rate. Toxicity from lipid emulsion is more closely tied to the maximum hourly infusion rate than to the total daily dose. The doses recommended here are safe if infused at a constant rate over 20 or more hours each day, but would not be as safe if given more rapidly.

Enteral Feeding

Although extra caution is advised in the enteral feeding of infants who require assisted ventilation, intragastric gavage can be safely attempted in most cases. If a ventilated infant has a soft, nondistended abdomen and audible bowel sounds, then nasogastric or orogastric gavage feeding may be attempted. Small volumes and cautious progression of feedings are advisable, because aspiration would be particularly harmful in an infant who already requires mechanical ventilation. The presence of an uncuffed endotracheal tube would offer only partial protection from the hazard of aspiration.

The first feeding should consist of maternal colostrum or infant formula. A volume of 2 mL/kg would generally be appropriate for the first feeding of a ventilated infant. The stomach should be aspirated for residual contents 3 hours later. If the stomach is empty or nearly so, the feeding can be repeated. This process is repeated every 3 hours. The feedings may be increased once daily by an increment not to exceed 20 mL/kg/day. The gastric residual volume is recorded every 3 hours. If it is more than 10% of the volume of the previous feeding (or 1 mL, whichever is larger) is present, the infant should be examined. If significant residuals are found repeatedly, feedings should be stopped and the patient carefully evaluated for signs of systemic infection, necrotizing enterocolitis, and intestinal obstruction.

If enteral feeding is successful, the rate of intravenous feeding should be reduced to keep the total fluid intake the same or to allow a slight increase appropriate for advancing postnatal age (see Table 27-2). After the first week or so, fluid intake can usually be increased to 1.5 times the estimated requirement to allow greater energy and nutrient intake.

When an infant no longer requires assisted ventilation or continuous positive airway pressure, has achieved stable cardiorespiratory status, and has demonstrated adequate sucking and swallowing of secretions, nipple feedings may be introduced. The transition to oral feedings typically requires more time for infants who required assisted ventilation and those who were most premature at birth.[239]

With the methods described above, it is possible to provide adequate nutrition to all infants requiring assisted ventilation, thereby allowing each infant the best possible chance for recovery and normal growth and development.

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28 Respiratory Conditions and Brain Injury in Ventilated Infants

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Neonatal respiratory conditions, both acute (i.e., respiratory distress syndrome [RDS]) and chronic (i.e., bronchopulmonary dysplasia [BPD]), are strongly linked to hemorrhagic-ischemic cerebral injury and to long-term neurodevelopmental deficits in premature infants. Several mechanisms are thought to contribute to this association—in particular, perturbations in cerebral blood flow (CBF), which in turn may be directly related to the primary respiratory disease process and/or the interventions used to treat the respiratory symptoms.[1,2,3] Each of these factors independently increases the risk of developing hemorrhagic-ischemic cerebral injury. This chapter discusses the variables that may link respiratory disease and its treatment to hemorrhagic-ischemic cerebral injury in neonates, including the importance of CBF. Potential mechanisms whereby interventions and comorbidities may adversely affect neurodevelopmental outcome are highlighted.

Cerebral Blood Flow in the Neonate

CBF is tightly coupled to cerebral metabolic demands in the normal brain.[1,3,4] In the newborn infant, CBF is low, which corresponds to low neuronal activity in this patient population.[1] Various methods of evaluation, including positron emission tomography,[5] Xenon clearance technique,[6] ultrasound flowmetry,[7] and near-infrared spectroscopy (NIRS),[8] indicate a wide range of CBF values of between 10 to 20 mL/100 g/min. These values are approximately one third of the value for a healthy adult brain.[1,9] A low CBF value in this patient population does not imply poor outcome.[5,10] Indeed, the lower threshold required to maintain neuronal viability remains unknown.[9]

In general, CBF is controlled by a pressure gradient across the cerebral vascular bed, the cerebral perfusion pressure (CPP) and the total resistance to blood flow in the cerebral vasculature or cerebrovascular resistance (CVR). These are related as follows: CBF = CPP/CVR.[1,9,11] Total and regional CBF, coupled with cerebral oxygen consumption, increases with postconceptual and postnatal age corresponding to increases in cerebral metabolic rates and energy demands.[3,4,7,12] This increase is most prominent in the first day of life and likely represents a normal adaptive response of the cerebral circulation to postnatal life.[7,10] Regional differences in CBF also reflect varying metabolic demands.[4] Thus blood flow to parasagittal and periventricular white matter is lower relative to that of other regions such as the cerebellum and basal ganglia.[3]

Cerebral Autoregulation and Pressure-Passive Circulation

Cerebral autoregulation is the intrinsic ability of the cerebral blood vessels to maintain relatively constant CBF over a range of systemic blood pressures. As CPP decreases, CVR also decreases by way of alterations in the diameter of the precapillary arterioles, thus maintaining CBF.[1,11,13,14] This adaptive ability has a limited capacity and will result in a decrease of CBF when the blood pressure falls below a certain threshold, and conversely, will increase when blood pressure reaches an upper threshold, that is, a loss of autoregulation or a pressure-passive state (Fig. 28-1).[11]

Cerebral autoregulation appears to be intact in fetal and neonatal animal models (lambs, piglets, puppies, rat pups).[3,11,13] It also appears to be intact in the stable human preterm infant.[11,15,16] Thus in a study of extremely preterm babies with median gestational age of 24 weeks, CBF determined by the near-infrared method was found to be low (range of 4.4 to 11 mL/100 g/min), with no relationship of CBF to blood pressure, suggesting intact autoregulation.[10] In another study of preterm infants aged 1.5 to 40 hours, with a mean gestational age of 26 weeks, normotensive infants (mean arterial pressure 37 ± 2 mm Hg) were shown to have intact autoregulation although there was loss of autoregulation in those who became hypotensive (mean arterial pressure 25 ± 1 mm Hg). This study also identified a mean arterial blood pressure threshold of ~30 mm Hg, below which the CBF became pressure passive.[17] However, a definition of this lower threshold remains elusive. One study showed no significant difference in mean CBF between a group of preterm infants with a mean arterial blood pressure (MABP) of less than 30 mm Hg (CBF 13.9 ± 6.9 mL/100 g/min with median MABP of 27.2 mm Hg) and another group with a MABP greater than 30 mm Hg (CBF 12.3 ± 6.4 mL/100 g/min with median MABP of 35.3 mm Hg).[18]

To summarize, although cerebral autoregulation has been documented in the premature infant, it appears to function within a limited blood pressure range, and is likely to be absent in the sick hypotensive preterm infant.[11,15,19] This state places the developing brain at great risk for injury during times of hypotension and/or elevated blood pressures. A pressure-passive state also increases vulnerability to injury in a variety of situations that involve fluctuations of systemic blood pressures, such as may occur during routine care (e.g., suctioning)[20,21] or with respiratory distress syndrome, mechanical ventilation,

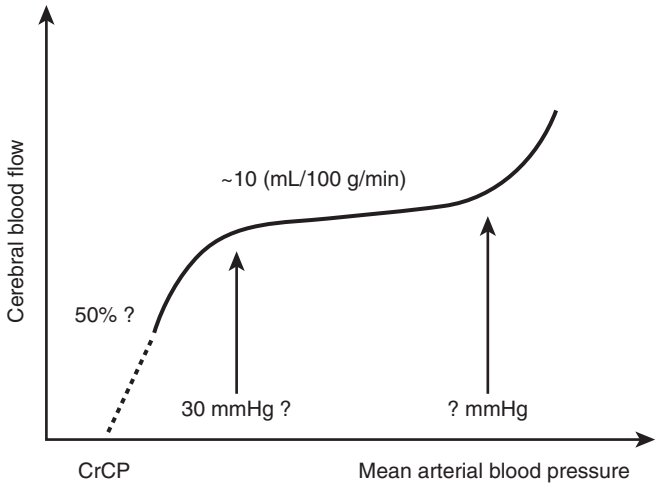

Figure 28-1 ■ Schematic depiction of the relationship between cerebral blood flow and mean arterial blood pressure.

pneumothorax, rapid volume expansion, patent ductus arteriosus, and seizures (see below).[22]

Influence of Oxygen Concentration and Carbon Dioxide on CBF

The cerebral circulation of the healthy newborn infant, and even in the very preterm infant, responds to physiologic stimuli in much the same way as in the adult. Cerebral blood vessels are sensitive to changes in arterial carbon dioxide tension ($PaCO_2$), arterial oxygen concentration (CaO_2), and pH.[1] In pathologic states, a pressure-passive state occurs and cerebral blood vessels may not react to chemical or metabolic stimuli. These infants are at increased risk for developing hemorrhagic and/or ischemic cerebral injury.

Oxygen and Hemoglobin

CBF increases when arterial oxygen tension decreases markedly in the human infant and in neonatal animals.[1,3,11] In experimental models, CBF is regulated by the CaO_2, which in turn is determined by hemoglobin concentration, oxygen affinity of hemoglobin, and PaO_2.[1,15,16,23] In preterm infants studied in the first 3 days of life, it has been shown that CBF increases by approximately 12% for every 1 millimolar (mM) decrease in hemoglobin concentration.[15] There is also a direct relationship of CBF with the relative proportion of fetal hemoglobin. This is likely due to the stronger affinity of fetal hemoglobin for oxygen. Oxygen delivery to the brain may also be affected by blood viscosity, although viscosity is not typically altered by a hematocrit value below ~60%.[3]

Cerebrovascular dilation occurs rapidly in response to hypoxia, usually within 30 to 60 seconds.[1] Hypoxia increases smooth muscle membrane potential, that is, hyperpolarization caused by the opening of calcium-activated potassium channels or the ATP-sensitive potassium channels in the cell membrane.[11,23] In addition, at lower blood pressures, the vasodilator response to hypoxia may be impaired.[11,23] Conversely, hyperoxia induces a fall in CBF in preterm infants through cerebral vasoconstriction.[1,24] Median reduction was found to be 0.06 cm/sec for every 1-kPa (~7.5 mm Hg) increase in oxygen tension. In addition, when 80% oxygen was given during resuscitation at birth, preterm infants were subsequently shown to have approximately a 25% reduction in cerebral blood flow velocity values than those infants given room air during stabilization.[25]

Carbon Dioxide

The fetal and neonatal brain, even in the preterm infant, remains sensitive to changes in $PaCO_2$, where hypocarbia decreases CBF through vasoconstriction of cerebral arteries whereas hypercarbia has a relaxant effect.[1,4,11,26,27] The primary mediator linking arterial carbon dioxide tension and cerebral vasoreactivity may be pH.[4] In one study performed on isolated dog cerebral arteries, hypercarbia-induced cerebral arterial relaxation was shown to be mediated mainly with a fall of extracellular pH.[28] Because CO_2 crosses the blood-brain barrier readily, abrupt changes in carbon dioxide tension also cause a rapid change in vascular reactivity within 1 to 2 minutes. This acute effect is then actively regulated by perivascular pH causing the vessel diameter to normalize gradually during the next 24 hours.[1]

In the healthy adult, CBF changes by a mean of approximately 30% for every 1-kPa change in PCO_2. In spontaneously breathing preterm infants studied at 2 to 3 hours after birth, CBF–carbon dioxide reactivity was shown to be approximately 30% per 1-kPa change in $PaCO_2$. In mechanically ventilated preterm infants, this reactivity was much less, that is, 11% to 12% per 1-kPa change in $PaCO_2$ when studied shortly after birth, although it returned to near-adult levels by the second day of life. In the infants in whom severe intracranial hemorrhage subsequently developed, there was a loss of cerebral blood flow reactivity to changes in $PaCO_2$, implying an impairment of CBF regulation before hemorrhage.[15]

Brain Injury in the Preterm Infant

The most frequent injuries noted in the premature brain are periventricular-intraventricular hemorrhage (PV-IVH) including periventricular hemorrhagic infarction (PVI) and periventricular leukomalacia (PVL). The lesions of PVL also include diffuse white matter injury (WMI). These lesions are more likely to occur in the smallest infants with respiratory distress syndrome requiring mechanical ventilation.[27]

Periventricular-Intraventricular Hemorrhage

The overall incidence of PV-IVH has declined over the last few decades, although severe hemorrhage continues to be a significant morbidity in the increasing population of very-low-birth-weight (VLBW) survivors.[2,29,30] The incidence and severity of IVH are inversely proportional to gestational age. Thus approximately 25% of infants between 501 and 750 g and 14% between 751 and 1000 g still develop the most severe forms of hemorrhage, with the incidence remaining essentially unchanged since the mid-1990s.[2,29,30] It is also critical to note, however, that a normal sonogram in the neonatal period does not preclude neurocognitive deficits later in life, illustrating the limitation of ultrasonography in predicting outcome.[31,32]

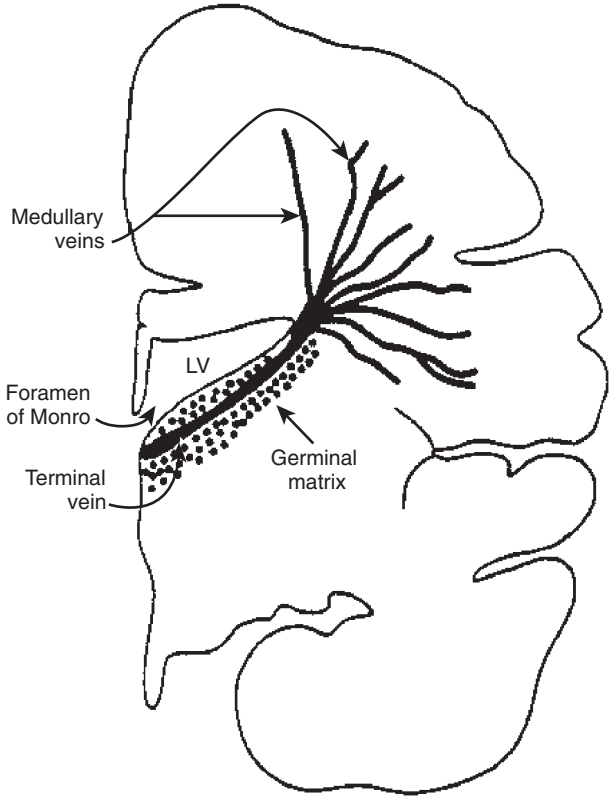

Figure 28-2 ■ Schematic depiction of medullary veins draining into the terminal vein. The vein then makes a U-turn at the head of the caudate nucleus. At this site the potential for increasing venous distension is increased.

Magnetic resonance imaging (MRI) performed closer to term-corrected gestational age is more likely to delineate white matter involvement and thus long-term neurodevelopmental deficits.[33]

The primary lesion in PV-IVH is bleeding from the periventricular subependymal germinal matrix. This matrix is a transitional gelatinous region that provides support for a large, immature network of blood vessels and is located between the caudate nucleus and thalamus at the level of or slightly posterior to the foramen of Monro.[2] The blood vessels that populate this matrix are primarily supplied by Heubner's artery, a branch of the anterior cerebral artery. Blood supply for the upper and middle regions of the matrix comes from the terminal branches of the lateral striate arteries, which originate from the middle cerebral artery. The anterior choroidal artery, which is derived from either the internal carotid or the middle cerebral artery, also contributes to this matrix. Venous drainage includes the terminal, choroidal, and thalamostriate veins that lead to the internal cerebral vein. The blood flow then makes a U-turn in the subependymal region at the level of the foramen of Monro.

This unique venous anatomy perhaps suggests that elevated venous pressure secondary to obstruction of the venous drainage may lead to venous distension and rupture (Fig. 28-2).[2] Moreover, hypotension leading to decreased CBF probably also plays a role in the genesis of PV-IVH in some infants. Presumably, the mechanism entails the rupture of blood vessels upon reperfusion. Precise description of the vasculature of the germinal matrix has been elusive because the small capillaries, venules, and arterioles that populate the matrix are hard to distinguish from one another histologically because of their relatively simple endothelial wall structure.[34]

The vascular source of PV-IVH has not been definitively established. Some investigators have theorized that the etiology is venous,[20,35] whereas others have categorized the bleeding as coming from capillary or arterial vessels.[34] Most likely, PV-IVH is contributed by both arterial and venous perturbations.[2]

The germinal matrix is an active site of cellular proliferation and is a source of neuronal precursors early in gestation and also the source of glial elements that become oligodendroglia and astrocytes in the third trimester.[22] It begins to involute after 34 weeks, and by term gestation, this region is essentially absent. Destruction of the germinal matrix may result in impairment of myelination, brain growth, and subsequent cortical development.[3]

The factors contributing to increased risk of PV-IVH are complex and include a combination of vascular, intravascular, and extravascular influences (Boxes 28-1 and 28-2).[2,22] Intravascular factors, especially those that involve

Box 28-1 POTENTIAL FACTORS THAT INCREASE RISK FOR BRAIN INJURY IN THE PRETERM INFANT

Cerebral factors	Vulnerable cerebral vascular beds
	Pressure passive circulation
Respiratory factors	Respiratory distress syndrome
	Pneumothorax
	High mean airway pressure
	Hypocarbia, hypercarbia
	Hypoxia, hyperoxia
Vascular factors	Hypotension, hypertension
	Blood pressure fluctuations
Perinatal factors	Chorioamnionitis
Metabolic factors	Hypernatremia

Box 28-2 POTENTIAL STRATEGIES THAT DECREASE THE RISK OF BRAIN INJURY

Antenatal interventions	Prevention of premature delivery
	Antenatal corticosteroids
	Maternal transfer to perinatal center
Intrapartum interventions	Mode of delivery
Postnatal interventions	Avoidance of hemodynamic fluctuations, e.g., sedation
	Synchronized mechanical ventilation
	? Administration of surfactant
	Minimizing complications of RDS, e.g., pneumothorax
	Minimize mean airway pressure
	Minimize the hemodynamic effects of PDA
	Avoidance of extremes of $Paco_2$
	Avoidance of metabolic disturbances, e.g., metabolic acidosis
	Minimize postnatal steroid use
	Use of caffeine in apnea of prematurity

PDA, Patent ductus arteriosus; *RDS,* respiratory distress syndrome.

perturbations in CBF and volume, play a critical role in the development of hemorrhage. A pressure-passive circulation in the sick preterm brain leads to direct changes of CBF with changes in systemic blood pressure. Acute changes in blood pressure and cerebral perfusion likely lead to disruption of the vulnerable blood vessels in the germinal matrix. Fluctuating CBF velocity in the VLBW infant also predisposes the infant to hemorrhage.[20,22,36] Another intravascular component that has been implicated as playing a role in IVH is inflammation, with chorioamnionitis perhaps contributing to increased risk of early IVH.[2,37,38] Conversely antenatal steroids decrease the risk. The protective effect of steroids may be related to enhanced support for the blood vessels within the germinal matrix.[2] Fluctuations of intrathoracic pressure, which may occur with mechanical ventilation or the development of pulmonary air leaks, also contribute to PV-IVH. Intrathoracic pressure is directly transmitted to cerebral vessels and these fluctuations are applied to vessels already maximally dilated with little autoregulation.[39]

In most cases the diagnosis of PV-IVH is made with screening ultrasound. The most vulnerable period for PV-IVH is in the first 3 postnatal days, with greater than 50% occurring in the first 24 hours of life.[38] Risk factors associated with the development of IVH have included low birth weight and gestational age, maternal smoking, breech presentation, premature rupture of membranes, postnatal resuscitation and intubation, early onset of sepsis, RDS, pulmonary air leaks, metabolic acidosis, and rapid bicarbonate infusions.[40] Extremes of $PaCO_2$ in the first 4 days of life are also associated with severe IVH (see below).[41] By contrast, factors associated with decreased risk include antenatal steroid exposure, higher initial hematocrit, and relatively low $PaCO_2$ in the first 24 hours of life.[40]

Periventricular Hemorrhagic Infarction (Grade 4 Intraventricular Hemorrhage)

One of the complications of PV-IVH is periventricular hemorrhagic infarction (PVI), also termed *grade 4 IVH*. PVI is a venous infarction that is associated with severe and usually asymmetric IVH and occurs in about 15% of infants with IVH. On brain imaging, there is a large, fan-shaped region of hemorrhagic necrosis in the periventricular white matter, invariably on the side with the larger amount of intraventricular blood (Fig. 28-3). A variety of studies have shown that this lesion is not merely an extension of PV-IVH. Instead, the likely mechanism is the obstruction of the medullary and terminal veins by the intraventricular and germinal matrix blood clot leading to venous congestion in the periventricular white matter with subsequent hemorrhage and ischemia. It also occurs more frequently with decreasing weight and earlier gestational age.[14,22,42] PVI is associated with a high rate of mortality (38%-60%), with survivors being at very high risk of cerebral palsy (66% in one recent study) and other neurologic abnormalities.[42]

Periventricular Leukomalacia and Diffuse White Matter Injury

Bilateral white matter injury (WMI) may occur adjacent to the lateral ventricles in the absence of any hemorrhage—a condition referred to as *periventricular leukomalacia (PVL)*

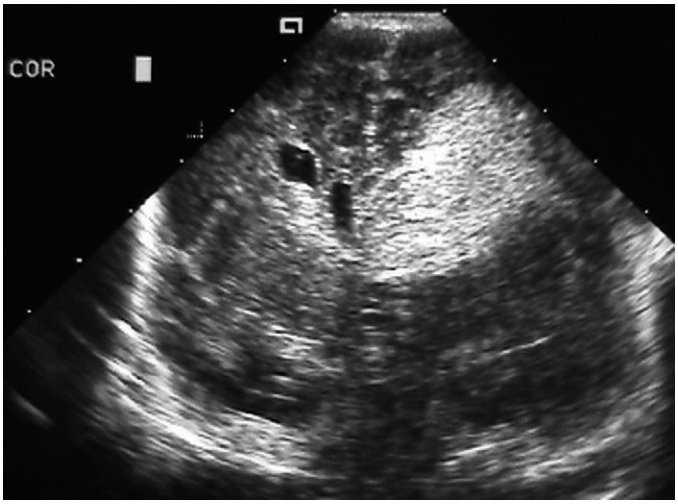

Figure 28-3 ■ Coronal ultrasound scan—note the increased echodense area in the left frontal white matter conforming to the distribution of the medullary veins.

(Fig. 28-4). Both focal and diffuse involvement of the white matter may occur. The sonographic evolution of focal injury includes cyst formation and ventriculomegaly. Diffuse WMI occurs most commonly in premature infants who require prolonged ventilator support and often manifests with ventriculomegaly in the absence of cyst formation. The pathogenesis of WMI is complex and likely involves vascular factors, as well as the intrinsic vulnerability of oligodendrocytes to noxious substances. The vascular factors include at least three potential factors. First, the white matter is a border zone region,[43] which increases the likelihood for injury during periods of systemic hypotension. Second, the risk for injury to these regions is increased in the face of a pressure passive circulation as discussed above. Third, there is a limited vasodilatory response to $PaCO_2$ of those vessels supplying the white matter.

The intrinsic vulnerability of the early differentiating oligodendrocyte has been established in studies that show that these cells are vulnerable to injury secondary to the

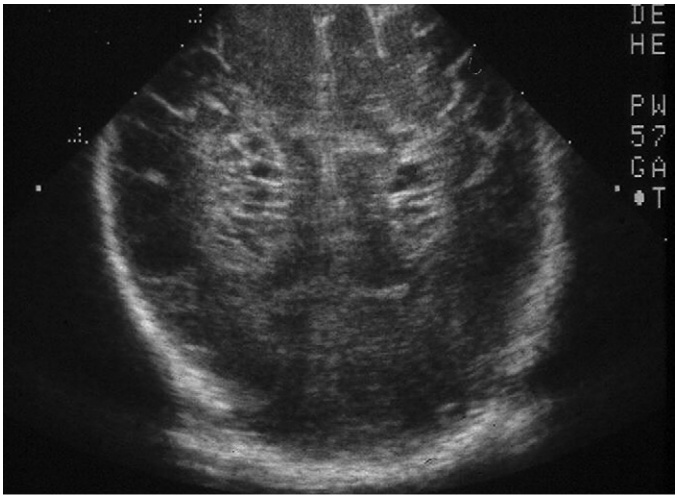

Figure 28-4 ■ Cranial ultrasound scan—coronal posterior view. Note the bilateral cystic areas within the white matter.

release of numerous factors including free radicals, excitotoxins, and cytokines, and also a lack of growth factors.[44] Indeed the importance of intrinsic vulnerability is suggested from a report of 14 of 632 infants (2.3%) weighing less than 1750 g at birth who developed bilateral cystic PVL.[45] Overt hypotension was found in only four of the babies with PVL, mostly in the immediate postnatal period. In the other 10 cases, PVL was seen in infants with mild-to-moderate lung disease without overt hypotension and was detected only on routine ultrasound screening. Two conditions were found to be significantly associated with development of PVL—chorioamnionitis and prolonged rupture of membranes. Other conditions that have been associated with the development of PVL include hypocarbia, meningitis, and recurrent severe apnea and bradycardia.

Linking Respiratory Events to Hemorrhagic-Ischemic Cerebral Injury

Respiratory Distress Syndrome and IVH

A strong association has been reported between fluctuations in cerebral blood flow velocity (CBFV) and subsequent PV-IVH in preterm infants with RDS. Thus in a study of preterm infants weighing less than 1500 g and requiring mechanical ventilation for RDS, 21 of 23 infants (91%), with a fluctuating CBFV pattern measured at 12 hours of life subsequently developed IVH. Typically the hemorrhage occurred within the following 24-hour period, as compared with 7 of 27 infants (26%) with stable CBFV patterns.[36] In order to test the hypothesis that there was a relationship between the fluctuations and PV-IVH, when the CBFV fluctuations were eliminated by muscle paralysis, the incidence of subsequent hemorrhage was significantly reduced. Thus in a randomized controlled study, all 10 controls subsequently developed IVH as compared with only 5 of 14 infants treated with muscle paralysis, and in 4 of these 5 cases, the hemorrhage developed only after cessation of the paralysis.[46]

The rationale for the "protective effect" of muscle paralysis is based, in part, on the relationship between simultaneous changes in respiratory muscle activity and fluctuations in arterial blood pressure (BP) (Fig. 28-5).[47] As these infants work hard to maintain adequate ventilation, wide swings in arterial as well as venous pressures occur, similar to the pulsus paradoxus seen in common cardiorespiratory disorders in older patients. Fluctuations in systemic arterial BP translate into similar fluctuations in CBFV, which can lead to subsequent IVH in a susceptible premature infant.[36]

The advent of newer ventilators that work in tandem with the infant's own respiratory efforts, coupled with the antenatal use of steroids, has made this association less prominent. However, in a susceptible infant, close attention to fluctuations in blood pressure should be made and, when present, corrected.

Fluctuations in venous pressure have been noted simultaneously with the arterial pressure changes in preterm infants who developed severe PV-IVH. These fluctuations

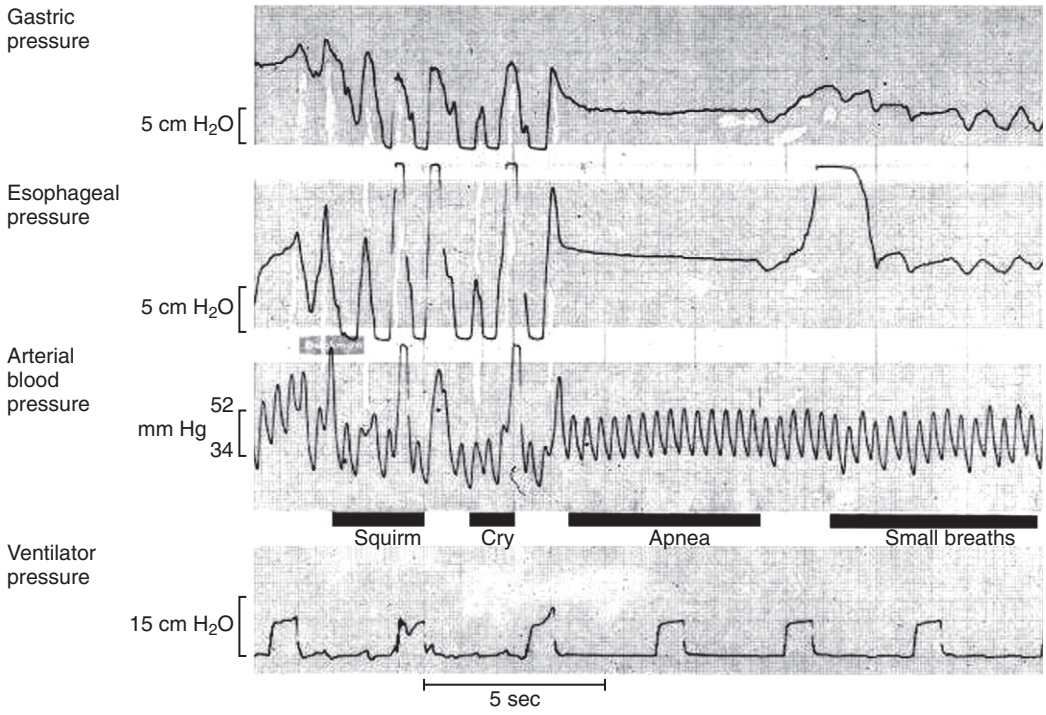

Figure 28-5 ■ Tracing obtained from an infant depicting the ternporal association between blood pressure fluctuations and gastric, esophageal, and respiratory pressure changes. Note the temporal association between blood pressure fluctuations and respiratory effort. Note the increased fluctuations with increased respiratory effort.

can be exacerbated by higher mean airway pressures such as may be observed with high-frequency oscillatory ventilation (HFOV) (see below), pulmonary interstitial emphysema, or pneumothorax. The potential importance of venous fluctuations in the genesis of hemorrhage is intertwined with the venous drainage of the deep white matter (see above). Thus the medullary veins that drain the deep white matter meet at the level of the caudate nucleus, where they take a peculiar U-shaped turn ending at the terminal vein in the region of the germinal matrix. Increases in venous pressure at this U-shaped junction raise the likelihood of venous distension and resultant obstruction of the terminal and medullary veins resulting in a venous infarction (see Fig. 28-2). From the preceding sections, it should be apparent that preterm infants with RDS experience intravascular perturbations in both the arterial and venous vascular beds, often manifesting simultaneously and thereby increasing the risk for hemorrhage.

Pneumothorax

An association between pneumothorax and subsequent PV-IVH has been described.[48,49,50] The potential mechanisms that link these two conditions are likely multifactorial. Hill et al.[49] described increased CBFV as measured by the Doppler technique, as well as increased mean blood pressure, at the time of occurrence of the pneumothorax, with return to baseline after resolution of the air leak. On the other hand, Mehrabani et al.[50] described a strong link between pneumothorax, hypotension, and increased risk of grades 3 or 4 IVH. Additional factors linking the two states include impediment of venous return, decrease in cardiac output, increase in $PaCO_2$, and hemodynamic changes that accompany evacuation of pleural air.[27]

Role of the Patent Ductus Arteriosus

Vascular perturbations may also occur as a consequence of a patent ductus arteriosus (PDA) commonly noted during the recovery phase of RDS. With a PDA there is shunting of blood from the aorta across the ductus to the lungs at the expense, or "steal," of blood from the systemic, including cerebral, circulation.[51,52] Indeed, in a prospective evaluation of 124 preterm infants weighing less than 1250 g, the development of symptomatic PDA occurred earlier and more frequently in infants with severe IVH compared with those with minimal or no IVH.[53]

Linking Changes in $PaCO_2$ to Hemorrhagic Ischemic Injury

Hypocarbia and White Matter Injury

The use of hyperventilation to reduce $PaCO_2$ to augment pulmonary blood flow may result in hypocarbia that could lead to decreased CBF.[27] Several studies have reported the association of hypocarbia and PVL as well as with subsequent neurodevelopmental defects.[27,54] In one study, exposure of preterm infants to $PaCO_2$ less than 20 mm Hg at least once during the first 3 days of life was associated with increased risk of periventricular cysts, cerebral palsy, or both.[55] In another study, time-averaged $PaCO_2$ on the third day of life was lower in preterm infants that developed PVL than in those who did not develop PVL.[56] Importantly, the ventilator settings were not significantly different between the group that developed PVL and the group that did not. Wiswell et al.[57,58] and Bhuta et al.[59]demonstrated that infants treated with high-frequency jet ventilation using a "low-volume strategy" in the first 3 days of life with marked hypocarbia had an increased risk of developing cystic PVL. However, this has not been a consistent finding. Thus, in a study by Keszler et al.,[60] when a "high-volume strategy" of high-frequency jet ventilation was used, there was a trend toward a reduction in risk of PVL. A third study in which there was significant difference in postrandomization, $PaCO_2$ showed no significant difference in the rate of IVH.[61] Other studies also have failed to demonstrate an association between high-frequency oscillatory ventilation and increased brain injury or neurodevelopmental outcome.[62-64] Interestingly, it has been shown that hypocarbia induces apoptosis in the hippocampus of hypotensive newborn rabbits.[65] Finally, it remains unclear whether hypocarbia leads to PVL or is merely a marker of increased risk.

Hypercarbia and Intraventricular Hemorrhage

Permissive hypercarbia has been advocated as a ventilatory strategy to minimize barotrauma or volutrauma to the lungs of preterm infants and thus prevent the evolution to chronic lung disease.[66,67] Although hypercarbia is associated with an increase in CBF, it impairs cerebral autoregulation in ventilated VLBW infants.[68] Regarding the former, in newborn piglet studies, normoxemic hypercarbia was associated with increased total brain blood flow, with regionally increased blood flow to the brainstem, cerebellum, and thalamus relative to the cerebrum, and increased percentage of cardiac output distributed to the brain.[69] Regarding the relationship between hypercarbia and autoregulation, in a study undertaken in the first week of life in VLBW infants of gestational age 26.9 ± 2.3 weeks, increasing $PaCO_2$ resulted in increasing impairment of cerebral autoregulation.[68] Hypercarbia, defined by the maximum $PaCO_2$ recorded during the first 3 days of life, was also associated with severe IVH in a retrospective cohort study of 574 VLBW infants born between 1999 and mid-2004.[70] As maximum $PaCO_2$ increased from 40 to 100 mm Hg, the probability of severe IVH increased from 8% to 21%. Because none of the infants had $PaCO_2$ of less than 35 mm Hg, the impact of hypocarbia on risk of severe IVH could not be determined in this study. However, a recent single-center retrospective review of 849 infants weighing less than 1250 g suggests that extremes in $PaCO_2$, both hypocarbia and hypercarbia, as well as fluctuations in $PaCO_2$ during the first 4 days of life, increased the risk of severe IVH.[41] In this analysis, infants who developed severe IVH had higher maximum $PaCO_2$ (median: 72 versus 59 mm Hg, $P < 0.001$), lower minimal $PaCO_2$ (median: 32 versus 39 mm Hg, $P < 0.001$), and a greater range between maximum and minimal $PaCO_2$ values (median: 39 versus 21 mm Hg, $P < 0.001$). Taken together, these studies indicate that extremes in $PaCO_2$ and PaO_2 should be avoided during the period in which infants are at high risk of IVH.

Ventilation and Potential Brain Injury

Conventional Mechanical Ventilation

Mechanical ventilation can directly or indirectly affect CBF via modulating cardiac output by impeding venous return or via changes in the acid-base balance (see above). Impedance of venous return may result from elevated mean airway pressure, which can result in increased central venous pressure and, therefore, increased intracranial venous pressure. It can also decrease cardiac output.[71-75] This puts the premature brain at risk of hypoperfusion, especially in the vulnerable regions such as the periventricular white matter.

Prolonged exposure to these fluctuations of cerebral blood flow with prolonged mechanical ventilation presumably results in repeated insults throughout the course of intensive care. Walsh et al.[76] demonstrated that ELBW infants who are ventilated longer, likely representing the sickest of the cohort, have increased incidence of cerebral palsy (Fig. 28-6). All surviving infants who were ventilated for 120 or more days had neurologic impairment.

High-Frequency Oscillatory Ventilation

In a meta-analysis of 15 studies involving a total of 3585 preterm infants, high-frequency oscillatory ventilation (HFOV) did not affect neonatal mortality compared with conventional ventilation.[64] Although HFOV has been associated with short-term neurologic morbidity in some studies, this has not been a consistent finding.[61,62] Thus HFOV compared with conventional ventilation did not significantly increase the risk of severe IVH (summary relative risk [RR], 1.11; 95% confidence interval [CI]), 0.95-1.30) or PVL (RR, 1.10; 95% CI, 0.85-1.43). However, in two trials that used a "low-volume strategy," HFOV was associated with an increased risk of adverse neurologic outcomes. At present longer-term neurologic morbidities have not been shown to be increased with the use of HFOV.[63,64] Physiologically, overinflating the lung leads to higher mean airway pressure, which is associated with an increased risk of venous distension, particularly to the medullary veins in the periventricular white matter (see above). There is also lower cerebral perfusion pressure during HFOV with increasing mean airway pressures related to the increased intracranial pressure and cerebrovascular resistance with increasing intrathoracic pressure.[77] However, when the lungs are poorly inflated, complications may result secondary to poor ventilation and low oxygenation. Thus there appears to be an optimal mean airway pressure that needs to be achieved for each infant needing ventilation. How to define this value for the individual infant remains unclear.

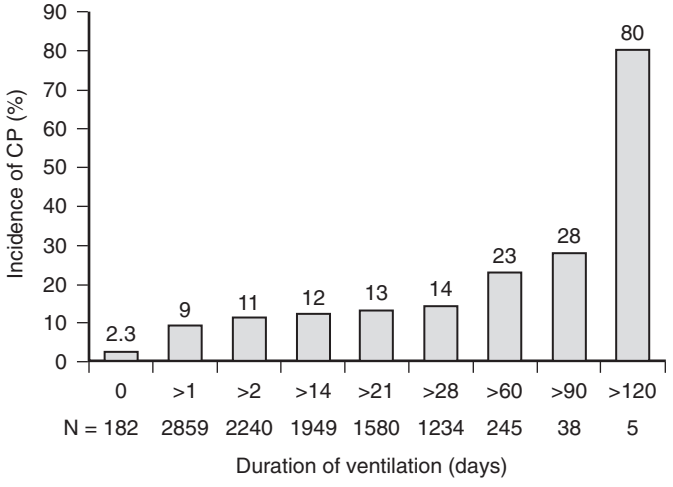

Figure 28-6 ■ Progressive increase in incidence of cerebral palsy with increasing duration of mechanical ventilation in extremely-low-birthweight (ELBW) infants. *CP*, Cerebral palsy.

Medications Used to Treat Respiratory Conditions

Surfactant

In the pre-surfactant era, VLBW infants, especially those that developed pneumothorax, had increased risk of PV-IVH. Because surfactant reduced the severity of RDS and the rate of pneumothorax, it was postulated that it would also lead to a decrease in the rates of IVH. However, this has not borne out to be true in the many surfactant trials, despite the type of intervention-prophylactic versus rescue, or the type of surfactant used—synthetic versus natural.[78] This lack of effect has been attributed to the impact of surfactant administration on fluctuations of CBF in sick preterm infants who have pressure passive circulations and the rapid changes of $PaCO_2$ and PaO_2 that may subsequently lead to brain injury.[79,80] There are multiple studies on the effect of surfactant administration on CBF. The results have been equivocal, with both human and animal data demonstrating conflicting results. Thus increases,[80,81] decreases,[82,83] or no significant change[84] in CBFV have been described after surfactant administration. Some investigators have also attributed the association to the method of instillation or mode of administration. One study showed minimal change in CBFV after slow administration of Exosurf as opposed to significant, although transient, rise in CBFV in the group with rapidly administered surfactant.[81] Alternative methods of surfactant delivery have been proposed. Nebulization of surfactant was studied in a rabbit model, with less prominent blood pressure and CBF changes than with standard intratracheal surfactant instillation.[85]

Inhaled Nitric Oxide

The impact of inhaled nitric oxide (iNO) in mechanically ventilated preterm infants has been assessed in several randomized controlled trials. In an initial evaluation, 207 premature infants were randomized to receive either iNO or placebo, and in addition, to either HFOV or intermittent mandatory ventilation.[86] The iNO was administered for 6 days, that is, initially at a dose of 10 ppm by continuous inhalation for 1 day, followed by 5 ppm for the remainder of the therapy. Treatment with iNO significantly reduced the risk of death or chronic lung disease—the primary efficacy endpoint as compared with placebo (49% versus

64%, RR, 0.76; 95% CI, 0.60-0.97; $P = 0.03$), whereas the type of ventilation (HFOV versus intermittent mandatory) did not affect outcome. In this study, the risk of severe IVH or PVL was significantly lower with iNO than with placebo (12% versus 24%; RR, 0.53; 95% CI, 0.28-0.98; $P = 0.04$). In a subsequent multicenter study,[87] 420 premature infants with a birth weight of 401 to 1500 g and severe respiratory failure at 4 hours after treatment with surfactant were randomly assigned to receive iNO (5 to 10 ppm) or placebo. iNO was continued for 10 to 14 hours in infants who responded to treatment based on changes in PaO_2, but was discontinued in those who did not respond to the 10 ppm dose after 30 minutes of inhalation. Overall, the rate of death or bronchopulmonary dysplasia (BPD), the primary study endpoint, was comparable in the iNO and placebo groups (80% versus 82%). However, a posthoc analysis suggested that iNO reduced risk of this composite endpoint in the subgroup with a birth weight greater than 1000 g (50% versus 69%, $P = 0.03$), but increased risk in the 1000 g or less subgroup (62% versus 48%, $P = 0.01$). The risk of severe IVH or PVL did not differ significantly between groups in the overall cohort (39% versus 32%, $P = 0.11$) or in the greater than 1000 g subgroup. However, IVH/PVL was higher with iNO than placebo in the 1000 g or less subgroup ($n = 316$; 43% versus 33%, $P = 0.03$).

The effect of early, prolonged iNO treatment was evaluated in another multicenter randomized controlled study.[88] A total of 793 preterm infants weighing 500 to 1250 g and requiring ventilation for respiratory failure were randomly assigned to iNO (5 ppm) or placebo within 48 hours of birth. Treatment was continued for 21 days or until extubation. The baseline characteristics of this study cohort indicated that they were not as sick as those infants enrolled in the two iNO studies described above. Cranial ultrasound was performed before enrollment, then repeated at 7 to 14 days of age, and again at more than 30 days of age. As in the previous study, treatment with iNO did not significantly affect the rate of death or BPD compared with placebo (72% versus 75%, $P = 0.24$). IVH was again evaluated as a secondary outcome both as a single endpoint and as part of composite endpoints. Treatment with iNO reduced the risk of severe IVH, PVL, or ventriculomegaly (18% versus 24%, $P = 0.03$) and risk of PVL alone (5.2% versus 9.0%, $P = 0.048$).

Comparisons across these studies are not appropriate given the differences in the study populations and treatment paradigms. Thus the issue of whether iNO protects against IVH or PVL will have to await results from future clinical studies that are appropriately powered to address this outcome. In terms of longer-term neurodevelopmental outcomes, information about iNO is only available from the single-center study. A total of 138 children (82% of survivors) were assessed at 2 years of age.[89] Treatment with iNO was associated with a lower risk of abnormal neurodevelopmental outcome—either disability or delay—compared with placebo (24% versus 46%, RR, 0.53; 95% CI, 0.33-0.87, $P = 0.01$).

Antenatal Steroids

Administration of one course of antenatal corticosteroids for lung maturity has had the unanticipated benefit of significant reduction in severe IVH.[2,90] A review involving 13 randomized controlled trials of any steroid course administered to pregnant women in preterm labor showed a significant reduction in IVH, with RR of 0.43 to 0.69. In the same review, two studies showed that antenatal steroid exposure was associated with less developmental delay in childhood (RR, 0.24-1.00) and five studies showed a trend towards fewer children having cerebral palsy.[90] Despite concern for delay in myelination and decreased brain growth in animal studies with maternal corticosteroid administration, there has been no evidence to show this effect with a single-course antenatal administration in humans.[91]

Although there has been no randomized controlled trial directly comparing dexamethasone and betamethasone, there are some animal and human data suggesting that dexamethasone may be associated with increased risk of poor neurologic outcomes versus betamethasone.[91-93] Antenatal betamethasone exposure was associated with increased likelihood of unimpaired neurodevelopmental status, a reduced risk of hearing impairment at corrected ages of 18 to 22 months,[93] and decreased risk of PVL[94] compared with dexamethasone or no steroid exposure. Repeat courses of antenatal steroids remains controversial, given that several animal studies have shown detrimental effects on the fetal brain.[91]

Postnatal Steroids

The use of postnatal systemic glucocorticoids, particularly dexamethasone, to prevent or treat chronic lung disease in the preterm infant has been shown to be associated with increased risk of cerebral palsy and neurodevelopmental impairment.[95] The American Academy of Pediatrics and the Canadian Paediatric Society published a statement in 2002 that restricted the use of postnatal steroids to randomized controlled trials or exceptional clinical situations.[96] However, it continues to be in used in various clinical settings such as was found in a retrospective analysis of 3 large network registries in 2006, where about 8% of VLBW infants continue to be treated with postnatal corticosteroids.[97] There have been attempts to use lower doses and shorter courses of dexamethasone; however, there is no evidence that use of lower doses or shorter courses will have any different affect on neurodevelopmental outcomes.[98]

Methylxanthines

Methylxanthines have been used in neonatology as respiratory stimulants since the 1970s, with caffeine being one of the top 10 medications most frequently prescribed in neonatal intensive care.[99] Caffeine has been found to decrease the frequency of apnea of prematurity as well as decrease the need for mechanical ventilation. The mechanism of action remains unclear, but it is likely related to an increase in chemoreceptor responsiveness, enhanced respiratory musculature performance, and generalized central nervous system excitation.[100] The most likely pathway is as antagonist of adenosine receptors at the cell membrane. There were concerns regarding the central nervous system effects of caffeine because adenosine is protective of the brain during experimental hypoxia and ischemia.[101] The Caffeine for Apnea of Prematurity Trial Group has recently reported on the short- and long-term effects of caffeine. In

this randomized, placebo-controlled trial of VLBW infants followed postnatally up to 18 to 21 months, it was found that there was a decreased rate of BPD (36% versus 34%; odds ratio [OR], 0.52-0.76), and a decreased rate of death or survival with a neurodevelopmental disability in the caffeine-treated group (40% versus 46%, OR, 0.64-0.93). The study also demonstrated less cerebral palsy (4.4% versus 7.3%), fewer cognitively affected infants (33.8% versus 38.3%), and even decreased incidence of severe retinopathy of prematurity in the treatment group. One postulate for the protective benefit is that earlier discontinuation of positive airway pressure in the group assigned to caffeine, as compared to placebo, may account for the difference in outcomes.[99,102] Longer-term follow-up studies are currently being awaited.

Brain Injury in the Term Infant

Major brain injury in term infants in contrast to the premature infant is a relatively uncommon event. As infants approach term gestation, the germinal matrix becomes progressively less prominent with the larger vessels acquiring a collagenous adventitial sheath and presumably decreasing the likelihood to rupture.[3] Moreover, the white matter vasculature has developed such that this region is less vulnerable to periods of relative hypoperfusion. However, the term neonate with respiratory failure requiring assisted ventilation secondary to conditions such as persistent pulmonary hypertension (PPHN) or meconium aspiration syndrome is at increased risk for neurologic sequelae, as a consequence of perturbations in arterial or venous pressure, hypoxemia or hypocarbia. Thus infants with PPHN treated with hyperventilation and respiratory paralysis have demonstrated prominent hearing loss in approximately 50% in one study.[103] Subsequent management strategies that avoided induced alkalosis or respiratory paralysis showed no sensorineural hearing loss. However, approximately one third of the infants exhibited an abnormal neurologic outcome.[104] It has been theorized that these neurologic complications are in part modulated by hypocarbia with a resultant decrease in CBF. The central nervous system (CNS) morbidities associated with extracorporeal membrane oxygenation (ECMO), which include brain hemorrhage associated with the anticoagulation necessary to perform bypass, are discussed in Chapter 16.

Conclusions

The developing brain of the fetus and newborn is extremely vulnerable to hemorrhagic and/or white matter injury as a consequence of multiple causes. There is an intimate relationship between cardiorespiratory disease and an increased risk for brain injury in the premature infant. The mechanisms leading to this association include vulnerable capillary beds, the immature differentiating oligodendrocyte, perturbations in CBF, and a pressure-passive cerebral circulation. Multiple factors including pneumothorax and PDA, physiologic variables such as acid-base disturbances in the form of extremes of $PaCO_2$, ventilatory support and commonly used respiratory medications, in combination or singularly may increase the risk for brain injury. Thus in the management of a sick newborn infant with respiratory distress, the potential risk/benefit ratio of any intervention as it relates to hemorrhagic ischemic injury should be considered in each case to minimize such injury and thus improve long-term neurodevelopmental outcome.

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29 Intraoperative Management of the Neonate

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Disease states, anesthesia, and surgery all affect the transition from intrauterine to extrauterine life. Safe, perioperative care of the newborn requires a multidisciplinary team, including experienced neonatologists, pediatric surgeons, and pediatric anesthesiologists. Over the years, many factors have contributed to improved survival in neonatal surgery: increased understanding of neonatal physiology, advances in airway management, neonatal monitoring, parenteral nutrition, antibiotics, and the establishment of neonatal intensive care units.[1]

Neonatal anesthesia care is one of the most challenging tasks an anesthesiologist can face. The Pediatric Perioperative Cardiac Arrest (POCA) Registry examined data submitted by participating hospitals and found that infants less than 1 year of age accounted for 55% of the anesthesia-related cardiac arrests for the period of 1994 to 1997 and 38% for 1998 to 2004.[2,3] Other studies have shown that mortality is inversely proportional to age with the highest risk patient population being less than 1 month of age.[4-6] The extensive use of surfactant and antenatal steroids have contributed to improved viability of very-low-birth-weight (VLBW) and extremely low-birth-weight (ELBW) infants leading to the increasing need for neonatal anesthesia when these infants face surgical interventions.[7] These infants often require surgical procedures during the neonatal period despite the comorbidities of complex medical and congenital disorders. The provision of safe intraoperative care creates an obligation for the anesthesiologist to understand the pathologic implications of the surgical problem as well as the unique anesthetic implications of the neonatal anatomy and physiology so that appropriate evaluation, planning, and intervention can be performed.

Intraoperative Concerns Related to Anatomy and Physiology

Airway Management

Several differences between the newborn and adult airway can result in difficulty when trying to maintain a patent airway or exposing the glottic opening during laryngoscopy.[8-10] The neonate head is relatively large and the neck is short. The tongue is large in proportion to the size of the mouth and blocks the pharynx during induction or recovery from anesthesia. Frequently, anterior pressure on the angle of the mandible, or the use of oropharyngeal airway devices are required for adequate airway exposure. The larynx is cephalad and appears more anterior because the cricoid cartilage is located more superior at the level of C4 in the full-term infant and C3 in the premature infant. The combination of a large occiput, large tongue, short neck, and anterior larynx require the placement of a roll under the neck to improve both airway patency and visualization for laryngoscopy. The epiglottis is long, omega-shaped, and sits at a 45-degree angle above the glottis and may be more easily elevated using a straight blade laryngoscope (Miller 00, 0, or 1) instead of a curved blade to visualize the vocal cords. The vocal cords are bow-shaped and angulated in the neonate, whereas in the adults they are linear and their plane is perpendicular to the long axis of the trachea.[6] This may require the tip of the endotracheal tube to be rotated while being advanced through the glottic opening. Pressure on the anterior larynx by an assistant or the anesthesiologist improves visualization of the neonatal glottis. The narrowest part of the neonatal airway is not the vocal cords but the cricoid ring. Therefore, even though an endotracheal tube passes easily through the vocal cords, it may still fit tightly within the cricoid ring, resulting in edema, trauma, and the risk of short- and/or long-term increases in airflow resistance[11] because of the subsequent development of stenosis at this point.

Endotracheal tube (ETT) sizes vary from 3.5 mm for the full-term neonate to 2.5 mm for the ELBW infant. Securing the ETT at the lip follows this general guideline: 1-2-3 (weight in kilograms) correlates with 7-8-9 (cm at the lip), with 1 cm added for nasal intubation. Many pediatric anesthesiologists stop advancing the tube and record the distance at the lip when the distal guide marker is at the vocal cord. The neonatal tracheal length is approximately 4 to 5 cm; therefore precise placement and secure fixation is important to avoid accidental extubation or endobronchial intubation. The likelihood of accidental extubation is associated with younger gestational age, higher level of consciousness, higher volume of secretions, and inadequate securing of the tube.[12] After the tube is secured, the "leak" is determined. This is done by closing the pop-off valve, exerting manual positive pressure on the ambu bag, and recording the pressure at which a leak is heard. A leak at no greater than 20 to 25 cm H_2O of positive pressure is acceptable. If no leak is heard at this pressure, the ETT should be down-sized.

Implications of Respiratory Physiology

In the human fetus, breathing activity can be identified between the 10th and 12th week of gestation.[13,14] The respiratory rate ranges from 30 to 70 breaths per minute and the fetus breathes the majority (55% to 99%) of the day.[15] By 28 weeks' gestation, peripheral chemoreceptors are active but their function remains immature until several weeks after birth. The ventilatory stimulation to hypercapnia is impaired but improves with increasing postnatal age.[16,17] In term infants, hypoxia results in brief hyperpnea followed by respiratory depression.[18] Small preterm infants have only a sustained decrease in ventilation in response to hypoxia,[19] with no initial increase in ventilation. Hypoxia, which normally increases the respiratory drive in response to hypercapnia, depresses the neonatal response to carbon dioxide.[20,21] Another manifestation of the immature respiratory center is periodic breathing, defined as apnea lasting up to 10 seconds that is not associated with cyanosis or bradycardia. Periodic breathing represents 2% to 6% of breathing time in healthy term neonates and up to 25% in preterm neonates.[22] Apnea lasting more than 20 seconds, or associated with cyanosis or bradycardia, can be life threatening. Factors such as hypothermia, anemia, sepsis, and prematurity predispose to apnea. The incidence of periodic breathing in preterm infants is twice that of term neonates (see Chapter 3).[23]

Anesthesia accentuates periodic breathing and apnea. The neonate is at risk for anesthesia-induced augmentation of apnea until approximately 60 weeks postconceptual age.[24] The diaphragm, the primary respiratory muscle in the neonate, has relatively few type 1 fibers (slow twitching, highly oxidative, and fatigue resistant) compared to the adult. Considering that intercostal muscles follow a similar pattern of immaturity, the neonate has difficulty sustaining increases in ventilatory demands.[25,26] Breathing efficiency is also affected by a relatively higher chest wall compliance and lower lung compliance compared to adults. This creates a paradoxical chest wall motion that limits inspiratory airflow.[27] This combination of factors leads to an increased risk of life-threatening hypoventilation, apnea, and hypoxemia during spontaneous ventilation both during anesthesia and in the postoperative period.[28,29] To counteract these factors, many anesthesiologists use intravenous respiratory stimulants such as caffeine (10 mg/kg) after anesthesia induction of preterm infants and/or those with a history of apnea. Multiple studies have shown that the avoidance of general anesthetic agents and the exclusive use of neuraxial blocks does not eliminate the risk of postoperative apnea.[30-32.] Careful monitoring of vital signs postoperatively is mandatory.

General anesthesia and operations also affect lung mechanics. The induction of anesthesia and mechanical ventilation results in the loss of functional residual capacity (FRC) and lung volume below closing capacity, leading to right-to-left intrapulmonary shunting and rapid hypoxemia.[33,34] This effect is exaggerated if the neonate is surfactant deficient. According to Laplace's relationship, surface tension is greatest in small alveoli because of their small radii. In the absence of surfactant, small alveoli and bronchioli collapse and large alveoli distend. Surfactant reduces surface tension when surface area is reduced at end-expiration and allows (by dispersion) an increase in surface tension with lung expansion. This facilitates elastic recoil at end-inspiration, thus providing both distensibility and end-expiratory volume stability.[35,36] Type 2 pneumocytes begin producing surfactant around 24 weeks' gestation, but the production and secretion into the airway is not adequate until approximately 35 weeks, which explains the lower incidence of respiratory distress syndrome (RDS) in neonates born later in gestation. An inadequate amount of surfactant places preterm neonates and neonates born to diabetic mothers at increased risk of decreased lung compliance and alveolar collapse at end-expiration, contributing to the development of RDS (see Chapter 22).

Compared to adults, neonates have higher oxygen consumption. Consequently, hypoxia occurs faster in neonates with apnea or airway obstruction. The tidal volume, when normalized to body weight, is similar to that of an adult, but the respiratory rate is significantly higher, such that neonatal alveolar ventilation is twice that of an adult. The higher ratio of alveolar ventilation to FRC in neonates versus adults contributes to among other things, the rapid uptake and clearance of volatile anesthetics in neonates.

Cardiovascular Physiology

The fetal circulation is characterized by high pulmonary vascular resistance, decreased pulmonary blood flow (only 10% OF right ventricular output), decreased systemic vascular resistance (presence of placenta), and right-to-left flow through the patent ductus arteriosus (PDA) and the foramen ovale.[37,38] Aeration of the lungs at birth causes an acute decrease in pulmonary vascular resistance with a 10-fold rise in pulmonary blood flow within a few hours, resulting in increased pulmonary venous return and left atrial pressure. The cessation of placental blood flow increases the systemic vascular resistance and decreases the pressure in the inferior vena cava and the right atrium. The net result is functional closure of the foramen ovale. Reduction of pulmonary vascular resistance is caused mainly by the decrease of hypoxic pulmonary vasoconstriction and the endogenous production and release of nitric oxide (NO).[39,40] Functional closure of the PDA also occurs shortly after birth. The main stimulus for PDA constriction is the rise of arterial oxygen tension and subsequent inhibition of prostaglandin production.

This transition from fetal to neonatal circulation is fragile. Factors that increase pulmonary vascular resistance (such as pain, hypoxemia, hypercapnia, acidosis, over- or under- pulmonary inflation) can precipitate a return to fetal circulation manifested by pulmonary hypertension, reduced pulmonary blood flow, and right-to-left shunting through the foramen ovale and ductus arteriosus, creating a vicious, self-perpetuating cycle of worsening hypoxemia and acidosis.[41,42] This potential to revert to fetal circulation necessitates monitoring of pre- and postductal oxygen saturations in certain high-risk surgical interventions in the first few days after birth (e.g., repair of diaphragmatic hernia) and delaying surgical interventions for several days in semielective situations (e.g., high intestinal obstruction) until pulmonary vascular resistance has fallen.

The shift from right (fetal circulation) to left (extrauterine circulation) heart dominance that occurs during

the first few months of life is, in large part, the result of increased left-sided heart pressures. During this transition, it is crucial to avoid the inadvertent, intravenous injection of air bubbles, because the ductus and foramen ovale may be patent intermittently. The left ventricle progressively increases in size in response to the increase in hemodynamic workload whereas the right ventricle size and workload decrease. The neonatal myocardium is also different from the adult. The neonate requires a higher cardiac output per kilogram but the myocardium is relatively less compliant.[43] Therefore, increases in cardiac output are achieved by increases in heart rate, not stroke volume. Therapeutically, this means that, unlike adults, volume loading a normovolemic neonate will not increase cardiac output. Conversely, bradyarrythmias must be treated aggressively. Inhalational anesthetics reduce myocardium contractility[44,45] and are cardiovascular depressants.[46,47] A neonate's increased sensitivity to anesthetics may be the result of an immature sympathetic nervous system and a relative predominance of the parasympathetic nervous system.[48-50]

Hematology

Neonatal blood volume is high, varying from 80 to 100 mL/kg, depending on the amount of placental blood transfused into the infant during delivery.[50] Heart rate, and to a lesser extent, systolic blood pressure are direct reflections of the circulating blood volume. The neonate's inability to tolerate blood loss is related to the limited cardiac reserve, immature baroreceptor reflexes, and less efficient control of vascular capacitance. Importantly, intraoperative volume status and fluid loss are frequently underestimated. Data from the POCA Registry show that of the clearly identifiable cardiovascular causes of perioperative cardiac arrest, the consequences of hemorrhage (hypovolemia and inadequate fluid replacement) or its treatment (transfusion-related hyperkalemia) top the list.[3,51]

The hemoglobin concentration (18-20 g/dL in full-term and lower in preterm infants) will decrease to 10 to 12 g/dL over the first 8 to 10 weeks of life because of reductions in red blood cell production and survival. Sepsis and frequent blood sampling for laboratory investigations may aggravate anemia. At birth, 70% to 80% of hemoglobin is fetal hemoglobin (HbF), which has higher affinity for oxygen than its adult counterpart (HbA). The P_{50} of HbF is 19 mm Hg versus 26 mm Hg for HbA, indicating a shift of the oxyhemoglobin dissociation curve to the left and a higher affinity of oxygen for HbF versus HbA.[52] This higher affinity for O_2 is compensated in part by the higher concentration of Hb and higher cardiac output. When the physiologic anemia of infancy resolves, HbF will have been almost entirely replaced by HbA. During neonatal surgery, it is important to compensate for the presence of HbF and improve oxygen delivery to the tissues by maintaining the hemoglobin above 13 g/dL in the newborn with congenital heart disease, major respiratory diseases, metabolic derangements, or sepsis. Cross-matched blood should be available for any major surgery, because blood loss of more than 15% (about 35-40 mL in a 3-kg infant) is not well tolerated. Neonates routinely receive vitamin K to prevent coagulopathy. Assessing clotting factors and a platelet count are important determinations to make before surgery when the history of perinatal events includes hypoxia or septicemia that can result in coagulopathy.

Fluids and Electrolytes

Total body water is greater in neonates (75% of body weight versus 60% in adults) with the major increase being in the extracellular fluid volume compartment (40% versus 20% in adults).[53] Renal function is characterized by a high renal vascular resistance, low glomerular filtration rate, limited tubular reabsorption of sodium, bicarbonate, glucose, phosphates, and limited tubular excretion of hydrogen (especially in the preterm infant).[54] In addition, neonates have difficulty handling overhydration, electrolyte loads, and metabolic acidosis. Dehydration occurs rapidly by preoperative fasting, insensible losses, and intraoperative third-space translocation of fluids. The glomerular filtration rate (GFR) increases two-fold to three-fold over the first 3 months, with maturity of GFR and renal concentrating ability being achieved by 12 to 24 months of life.

Decreased glycogen stores at birth (particularly in preterm, small for gestational age [SGA], and large for gestational age [LGA] infants) and limited tubular reabsorption of glucose, predispose the neonate to hypoglycemia after only brief periods of starvation. Other etiologies of hypoglycemia include sepsis, cold stress, perinatal hypoxemia, excess insulin in the infants of diabetic mothers, polycythemia, pancreatic tumor, and Beckwith-Wiedemann syndrome.[55,56] Therefore, intraoperative serial glucose measurements are necessary to detect hypoglycemia and guide its therapy. The neonate's serum glucose should be maintained between 40 and 125 mg/dL with a 200 mg/kg bolus of glucose (2 mL $D_{10}W$/kg) to correct hypoglycemia and 4 to 6 mg/kg/min of glucose for maintenance.[57]

Fluid and electrolyte losses are replaced intraoperatively by an estimate of the insensible and third-space losses, monitoring of urine output, cardiovascular and respiratory status, and laboratory measurement. The incidence of hypocalcemia is inversely proportional to the gestational age. Hypocalcemia must be anticipated in infants who are SGA, LGA, or have a history of perinatal asphyxia, absence of oral feed during first day of life, blood transfusion, administration of serum bicarbonate, DiGeorge syndrome, or any other severe neonatal disease. Hypocalcemia is determined by measurements of ionized calcium and treated with calcium chloride (10-20 mg/kg) or calcium gluconate (100-200 mg/kg), preferably via a central line to avoid the tissue injury caused by infiltration of calcium in the subcutaneous tissue. Infusions of intravenous (IV) calcium must be given slowly to avoid significant bradycardia.

Temperature Regulation

Neonates are prone to heat loss because of their large body surface area-to-mass ratio and limited subcutaneous fat. They lose heat by radiation, conduction, convection, and evaporation. Unlike the adult, the neonate generates heat by nonshivering thermogenesis, mainly in brown fat located in the mediastinum, between the scapulae, and around the kidneys and adrenal glands. In response to cold, norepinephrine is released by sympathetic nerve

endings promoting hydrolysis of triglycerides to fatty acids and glycerol. This process produces heat but dramatically increases oxygen consumption. Exposure to cold and a subsequent drop in core temperature in the nonanesthetized infant leads to thermoregulatory peripheral vasoconstriction. This creates a core-to-periphery temperature gradient that progressively disappears if heat production does not keep up with heat losses. The resulting hypothermia leads to increased oxygen and glucose consumption, inadequate oxygen delivery, hypoventilation, apnea, acidosis, and if untreated, cardiovascular collapse.[58]

Intraoperatively, neonates may have a rapid temperature drop as a result of the inhibition of nonshivering thermogenesis by inhalation anesthetics[59] and decreased response of thermoregulatory vasoconstriction to hypothermia.[60,61] This allows rapid redistribution of heat from the core to the periphery with subsequent loss to the environment. Besides low ambient temperature in the operating room (OR), other perioperative factors that lead to hypothermia include skin preparation with cold solutions, infusion of cold solutions, and the use of dry anesthetic gases in high-flow circuits. Monitoring body temperature to prevent and treat hypo- and hyperthermia should be part of any intraoperative management. Core temperature is of most clinical interest[62] and is measured at different sites including the tympanic membrane, nasopharynx, esophagus, rectum, and bladder. Prevention of hypothermia[63,64] necessitates keeping operating room temperatures between 27° and 29° C, avoiding unnecessary exposure of the baby, and the use of radiant heaters, reflecting blankets, skin-warming devices, warming mattresses, humidified and heated gases, and warm intravenous fluid. If intraoperative irrigation of the surgical wound is necessary, the fluid should likewise be warmed before use.

Neonate Pain Perception

One should assume that any patient undergoing surgery is in need of pain control. For the proper care of the surgical neonate, the following concepts must be recognized and taken into account.[65] Nociception consists of transduction, transmission, modulation, and perception of painful inflammatory, mechanical, or thermal stimuli. As early as 23 weeks' gestation, many of the pathways essential for nociception are present. Neonates are consequently capable of experiencing pain and appear more vulnerable to the adverse consequences of untreated pain because of their immature nervous system. The neonate nociceptive system has more diffuse input, larger receptive fields, lower thresholds on the dorsal horn of the spinal cord, hyperreflexivity, and poorly developed central and interneuronal inhibitory mechanisms.[66] Poor pain control may lead to physiologic consequences such as increased systemic stress responses, increased risk of intraventricular hemorrhage, and pulmonary hypertension with reversion to fetal circulation. Poor pain control could indeed contribute to increased surgical morbidity and mortality.[67,68] Prolonged or repeated nociception affects functional and structural organization of the dorsal horn of the spinal cord with risk of hyperalgesia (increased response to noxious stimulus) and allodynia (sensation of pain from nonnoxious stimulus) because of central sensitization. Long-term behavioral changes are a potential side-effect of inadequate pain treatment. One remarkable example is the excessive pain response to immunization seen in male infants that had previous neonatal circumcision without anesthesia.[69,70]

Analgesia is provided by the use of general anesthetics (volatile agents, IV agents) and/or regional anesthesia or local anesthetic infiltration. Optimal postoperative pain management requires competent pain assessment[71] using physiologic parameters (such as heart rate, blood pressure, respiratory rate, and oxygen saturation) and behavioral tools (crying, facial expression, leg position), keeping in mind that many parameters will be absent in neonates who are neurologically impaired or pharmacologically paralyzed. Some of the most common postoperative neonatal pain assessment tools are CRIES (*C*rying, *R*equires oxygen, *I*ncrease heart rate and blood pressure, *E*xpression, and *S*leeplessness), PIPP (premature infant pain profile), and NIPS (neonate infant pain scale). Each institution must adopt and develop competency in a uniform set of tools.

Intraoperative Concerns Related to Diseases

Airway Anomalies

The neonatal airway may be affected by a variety of syndromes and malformations of the head, neck and the cervical spine. Box 29-1 lists diverse anatomic abnormalities of the airway (see also Chapter 25).

Difficulties managing the airway can arise from a variety of causes;[72] limited mouth opening, the presence of large soft tissues in the mouth, a small mandible, abnormal larynx or trachea, and difficulty ventilating caused by the presence of an anterior mediastinal mass. Control of the airway is possible by (1) supraglottic devices, such as a laryngeal mask airway (LMA), or laryngeal tube; (2) alternatives to direct laryngoscopy such as lighted stylets, Bullard scope, flexible fiberoptic scope, GlideScope®, and retrograde intubation; and (3) surgical airway, such as tracheostomy.

Managing a difficult airway requires an appropriate assessment of the neonate and developing a care plan that includes alternatives. Specific plans and alternatives are discussed with the entire OR team. Difficult intubation situations are usually predictable in neonates. Several difficult airway algorithms have been developed, but the cardinal rule of management is that spontaneous ventilation should be preserved until the airway is secured unless the success of positive-pressure mask ventilation has been demonstrated. Direct laryngoscopy can be attempted with minimal sedation or after establishing a deep level of anesthesia. The American Society of Anesthesiologists Difficult Airway Algorithm is an established guideline that is adaptable to neonatal situations (Fig. 29-1).

Prematurity

Improvements in prenatal and neonatal care have increased the survival of premature infants. The current survival statistics for premature infants vary from 19% in infants less than 24 weeks' gestation to 90% for those older than

Box 29-1 ANATOMIC ABNORMALITIES OF THE AIRWAY

Encephalocele

Nasopharyngeal Obstruction
- Choanal atresia

Oropharyngeal Obstruction: Macroglossia
- Beckwith-Wiedemann syndrome
- Metabolic disorders
- Down syndrome

Craniofacial Deformities
- Pierre Robin syndrome
- Treacher Collins syndrome
- Hallermann-Streiff syndrome
- Moebius sequence

Laryngeal Anomalies
- Laryngeal atresia
- Laryngeal web
- Congenital vocal cord paralysis
- Laryngomalacia
- Congenital or acquired subglottic stenosis
- Laryngeal cleft
- Subglottic hemangioma

Tracheal Anomalies
- Internal tracheal compression
- Tracheomalacia
- Tracheal stenosis
- Necrotizing tracheobronchitis

External Tracheal Compression
- Cystic hygroma
- Vascular rings

Cervical Spine Anomalies
- Goldenhar syndrome
- Klippel-Feil sequence
- Down syndrome

27 weeks' gestation.[73] The major morbidities of prematurity in ELBW infants (birth weights less than 1000 g) include chronic lung disease, patent ductus arteriosus, necrotizing enterocolitis, sepsis, retinopathy of prematurity, grades 3 or 4 intraventricular hemorrhage, and periventricular leukomalacia.[74] The anesthesiologist also needs to be aware of the risk of hypothermia, hypoglycemia, the danger of hyperoxia, and the possibility of postoperative apnea.

Respiratory Distress Syndrome and Bronchopulmonary Dysplasia

Respiratory distress syndrome (RDS) results from a deficiency in pulmonary surfactant, leading to decreased lung compliance, alveolar instability, progressive atelectasis, and intrapulmonary shunting. The incidence of RDS correlates inversely with gestational age and is increased by male gender, white race, perinatal asphyxia, sepsis, and maternal diabetes mellitus. The incidence of RDS decreases with antenatal steroid administration and prolonged rupture of fetal membranes. Clinically, the newborn presents shortly after birth with hypoxemia, cyanosis, respiratory distress, and progressive respiratory failure. Shunting through the PDA or patent foramen ovale (PFO) may worsen the hypoxemia. Respiratory acidosis develops from respiratory insufficiency, and metabolic acidosis may appear subsequent to circulatory failure. The level of respiratory support, from warm humidified oxygen or continuous positive airway pressure (CPAP) to intubation and ventilation, depends on the respiratory drive and severity of the RDS.

Briefly, the fraction of inspired oxygen (FIO_2) is adjusted to maintain partial arterial oxygen tension (PaO_2) between 50 and 80 mm Hg (functional oxygen saturation [SpO_2] less than 96%). Endotracheal intubation is the safest method of airway control. The goals of ventilation are to provide gas exchange while minimizing volutrauma and barotrauma. The analysis of neonatal data comparing pressure-limited ventilation versus volume-targeted ventilation suggests that volume target ventilation reduces duration of ventilation, pneumothorax, and the rate of severe intraventricular hemorrhage (IVH) (grades 3 or 4).[75] The complications of RDS treatment such as pneumothorax, oxygen toxicity, pulmonary interstitial emphysema, subglottic stenosis, and chronic lung disease, needs to be taken into account perioperatively and discussed with the family.

Bronchopulmonary dysplasia (BPD) is defined as the continued need for respiratory support with supplemental oxygen or mechanical ventilation beyond 36 weeks postconception. In addition to RDS, a variety of factors are associated with BPD, including oxygen toxicity, inflammatory mediators, and mechanical ventilation. Other clinical features include inspiratory rales and evidence of increased work of breathing. Hypoxemia is a manifestation of nonhomogenous lung ventilation, intrapulmonary shunt, pulmonary hypertension, and bronchospasm (see Chapter 23). Preoperative evaluation is focused on the clinical condition, especially the degree of respiratory support and medications needed to maintain oxygenation and ventilation. The risks of respiratory complications under anesthesia (such as pneumothorax, bronchospasm, pulmonary hypertension, hypoxia, emergence, and extubation) present significant management challenges.

Persistent Pulmonary Hypertension of the Newborn

Persistent pulmonary hypertension of the newborn (PPHN) is an abnormal persistence of high pulmonary vascular resistance after birth, which disrupts the normal transition to postnatal life. This causes persistent shunting of blood away from the lungs via the ductus arteriosus and/or the PFO. The incidence of PPHN is 1 to 2 infants per 1000 live births, and data suggest an increased risk with cesarean section delivery, late preterm or postterm birth, perinatal asphyxia, LGA, and maternal factors such as race (black or Asian), obesity, diabetes, and asthma.[76-79] Newborns with PPHN have severe systemic hypoxemia within hours after birth, unrelieved by breathing high FIO_2. The presence of higher preductal versus postductal SpO_2 is evidence of right-to-left shunt at the level of the PDA and can be confirmed by echocardiography (see Chapter 26).

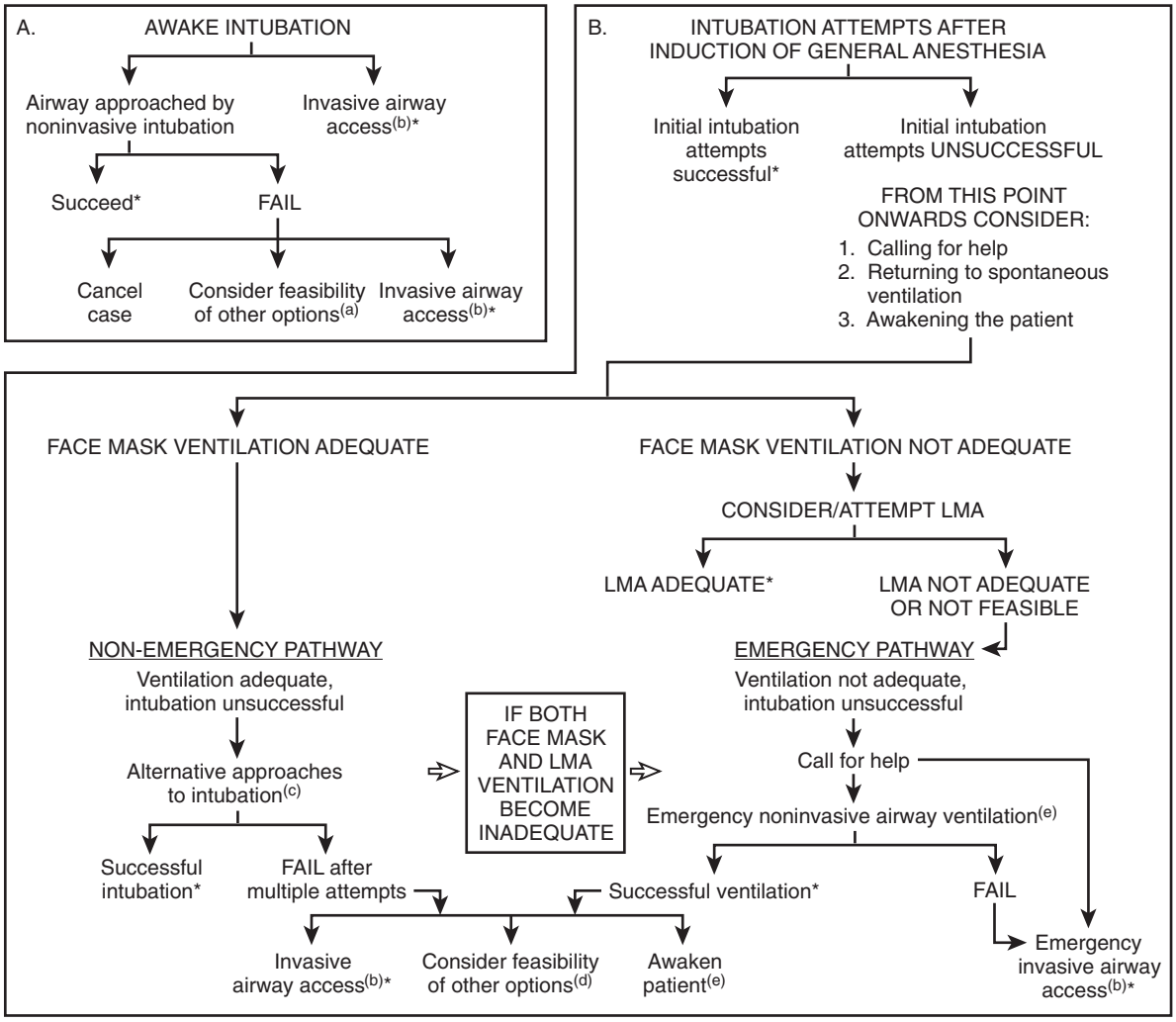
AMERICAN SOCIETY OF ANESTHESIOLOGISTS

DIFFICULT AIRWAY ALGORITHM

1. Assess the likelihood and clinical impact of basic management problems:
   - A. Difficult ventilation
   - B. Difficult intubation
   - C. Difficulty with patient cooperation or consent
   - D. Difficult tracheostomy
2. Actively pursue opportunities to deliver supplemental oxygen throughout the process of difficult airway management
3. Consider the relative merits and feasibility of basic management choices:

A.	Awake intubation	vs.	Intubation attempts after induction of general anesthesia
B.	Noninvasive technique for initial approach to intubation	vs.	Invasive technique for initial approach to intubation
C.	Preservation of spontaneous ventilation	vs.	Ablation of spontaneous ventilation

4. Develop primary and alternative strategies:



*Confirm ventilation, tracheal intubation, or LMA placement with exhaled CO_2

a. Other options include (but are not limited to): surgery utilizing face mask or LMA anesthesia, local anesthesia infiltration or regional nerve blockade. Pursuit of these options usually implies that mask ventilation will not be problematic. Therefore, these options may be of limited value if this step in the algorithm has been reached via the Emergency Pathway.

b. Invasive airway access includes surgical or percutaneous tracheostomy or cricothyrotomy.

c. Alternative non-invasive approaches to difficult intubation include (but are not limited to): use of different laryngoscope blades, LMA as an intubation conduit (with or without fiberoptic guidance), fiberoptic intubation, intubating stylet or tube changer, light wand, retrograde intubation, and blind oral or nasal intubation.

d. Consider re-preparation of the patient for awake intubation or canceling surgery.

e. Options for emergency non-invasive airway ventilation include (but are not limited to): rigid bronchoscope, esophageal-tracheal combitube ventilation, or transtracheal jet ventilation.

Figure 29-1 ■ ASA Difficult Airway Algorithm.

In this setting, non–life-threatening surgical conditions are treated nonoperatively. If operation becomes necessary, pre- and postductal SpO_2 monitoring are necessary. In planning anesthesia, narcotics (fentanyl infusion) and muscle relaxants may facilitate ventilation, but aggressive positive pressure ventilation to attempt lowering pulmonary vascular resistance (PVR) by inducing respiratory alkalosis, may result in lung injury. The induction of metabolic alkalosis is not devoid of problems either. Inhaled or intravenous prostacyclin is a useful pulmonary vasodilator, but it may also cause systemic hypotension during intravenous infusion. A magnesium sulfate infusion to a plasma concentration of 3 to 5 mmol/L provides significant improvement in oxygenation in neonates with PPHN.[80] Adenosine infusion produces useful pulmonary vasodilation and could help improve oxygenation.[81] Nitric oxide can rapidly decrease pulmonary vasoconstriction, decrease right-to-left shunt, and increase systemic oxygenation without causing systemic hemodynamic effects (see Chapter 14).[82-84]

Intraventricular Hemorrhage

Intraventricular hemorrhage (IVH), common in premature and especially VLBW infants, is graded from 1 to 4 depending on the severity of the hemorrhage. In all cases, hemorrhage is thought to originate in the capillary bed of the subependymal germinal matrix, which is fragile in the premature infant. A grade 1 constitutes bleeding in the subependymal area only. A grade 2 is intraventricular bleeding without dilation of the ventricles. A grade 3 is intraventricular bleeding with significant dilation of the ventricles. A grade 4 indicates intraparenchymal blood usually from venous hemorrhagic infarction in association with a grade 3 hemorrhage.

The diagnosis and grading of IVH is made by cranial ultrasound or computed tomography (CT) scan. Grades 3 and 4 portend poor neurologic outcome. One of the major complications of IVH is obstructive hydrocephalus, often condemning the child to multiple CSF shunting procedures. During operation, the anesthesiologist goal is to eliminate fluctuations in blood pressure, thereby maintaining an acceptable cerebral blood flow and intracranial pressure and reducing the risk of IVH.[85,86] To accomplish this, the anesthesiologist establishes and maintains a proper plane of anesthesia during periods of noxious stimulation such as intubation, tracheal suction, mechanical ventilation, and surgical stimulation. For similar reasons, the rapid administration of hypertonic agents is limited.

Neonatal Anesthetic Pharmacology

The neonatal administration of anesthetics and analgesic during the perioperative period not only provides pain relief but also contributes to the maintenance of physiologic stability and prevents protein catabolism, pulmonary hypertension, and intraventricular hemorrhage.[87] The judicious use of these agents takes into consideration the physiologic differences encountered with the neonate. The volume of distribution is larger in neonates due to increased body water. Glomerular filtration and hepatic glucuronidation are far from mature at birth. In addition, protein binding of drugs is limited for several reasons. First, neonates have lower serum albumin levels (that rises to adult level at 5 months). For example, sodium thiopental binding to albumin is significantly decreased whereas propofol is extensively bound to serum albumin and red blood cells.[88-90] Second, alpha-1 acid glycoprotein (AAG) levels remain low during the first year of life. This is important, because most local anesthetics and opioids (such as fentanyl, sufentanil, and alfentanil) are bound to AAG.[91] In general, less protein binding means increased volume of distribution and increased concentration of free drug in the tissue. It is especially relevant to the brain because the immaturity of the blood-brain barrier facilitates the accumulation of drugs in the central nervous system (CNS). In addition, neonates need less concentrated local anesthetics to achieve neural blockade because myelination is not complete.[92] Hepatic metabolism of anesthesia drugs is immature. Thiopental and some muscle relaxants such as pancuronium are some of the few drugs used in anesthesia that are eliminated by the kidney.

Inhalation Anesthetics

The potent, halogenated, volatile anesthetics currently in use include halothane, sevoflurane, isoflurane, and desflurane. These agents are thought to have multiple sites of action including a variety of neuroreceptors (including gamma-aminobutyric acid [GABA] receptors), multiple ion channels, and at lipid protein interfaces throughout the CNS.[87]

In general, the response to a volatile agent is considered to be a function of end-tidal anesthetic concentration. The agent quickly equilibrates between the alveolar and cerebral compartments, making the alveolar concentration of the agent an adequate reflection of the cerebral concentration. The minimum alveolar concentration (MAC) of a volatile agent, is defined as the amount of agent that prevents skeletal muscle movement in response to noxious stimulus (e.g., surgical skin incision) in 50% of patients. The MAC is a commonly used measure of volatile anesthetic potency.[93]

The neonate's myocardium and baroreceptor activity display a greater sensitivity to the depressant effects of inhalation anesthetics. This is why neonates have a greater degree of hypotension in response to anesthetics.[94,95] This response makes for a very narrow margin of safety in their use, particularly in sick neonates or those with congenital heart disease.

Halothane has been supplanted by sevoflurane as the volatile anesthetic of choice for inhalation anesthesia. Like halothane, sevoflurane is nonirritating to the airway, but when compared to other inhalation agents, sevoflurane causes less bradycardia and myocardial depression.[96,97] Because of its low blood-gas partition coefficient, sevoflurane's induction and emergence are faster than halothane. The MAC for most volatile anesthetics is lower in the neonate, increases to about 50% above adult values at about 6 months, and then decreases to adult values by early puberty. The MAC is lower in preterm neonates than in full-term neonates (Fig. 29-2). The quicker onset and offset are due to increased alveolar ventilation, lower blood-gas and tissue-blood solubility, increased cardiac output, faster distribution to vessel-rich organs, and faster

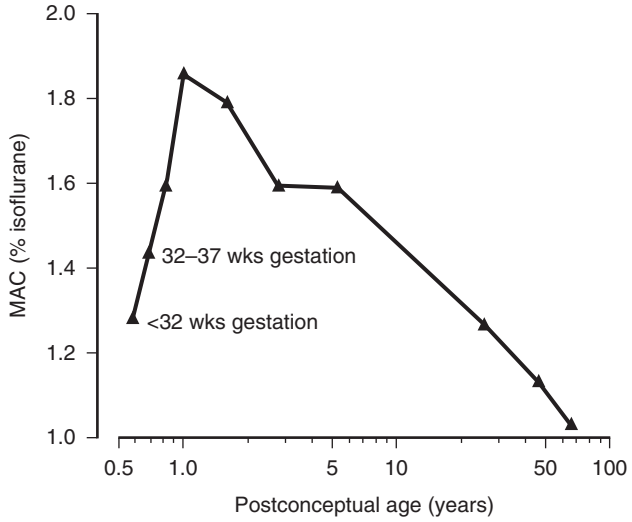


Figure 29-2 ■ The minimum alveolar concentration (MAC) of isoflurance in preterm neonates; Anesthesiology; 1987 September; 67(3):301-7 LeDez KM, Lerman J.

elimination of these volatile agents. Shunting also affects the MAC. Right-to-left shunting slows the rate of rise of the alveolar concentration of an inhaled anesthetic, so the induction of anesthesia is delayed. Left-to-right shunts, however, have no effect on inhaled anesthetic agent uptake. As in adults, inhaled anesthetic depresses the respiratory drive of infants and children in a dose-dependent manner.[98] Because of the immaturity of the neonate respiratory system, it is appropriate to control ventilation during anesthesia.

Nitrous oxide is administered to supplement other, more potent volatile anesthetics. It speeds their uptake and decreases their dosage requirement during surgery. There are caveats to consider when using nitrous oxide. It dilutes inspired oxygen and expands gas-containing space (being 30 times more soluble in blood than nitrogen). When using nitrous oxide, an existing pneumothorax may increase in size rapidly, leading to respiratory and hemodynamic compromise. In prolonged bowel operations, nitrous oxide can cause bowel distension. In the case of venous air embolism, the size of the embolism may be increased by the use of nitrous oxide.

Intravenous Anesthetic and Analgesics

Intravenous anesthetics are administered as a bolus for induction or as an infusion for maintenance of anesthesia. With careful dosing adjustments, they are safely used in neonates. Intravenous anesthetics such as benzodiazepines, barbiturates, and propofol exert their actions on GABA receptors, which activate inhibitory pathways in the CNS.

Propofol is a short-acting agent that has become increasingly popular for induction of anesthesia. Its infusion for routine maintenance is not recommended. Metabolic acidosis and fatal myocardial failure have resulted from propofol infusion in children,[99,100] and this has been termed *propofol infusion syndrome*. Propofol produces greater hypotension and bradycardia than thiopental. Many clinicians pretreat neonates with anticholinergics before giving a bolus of propofol during induction. Significant pain at the injection site is a frequent occurrence.

Induction with thiopental is painless at the injection site and remains a reasonable alternative to propofol, when rapid emergence is not needed. Although redistribution of thiopental is rapid, the action is prolonged due to reduced clearance in neonates. For induction, the curve representing the median effective dose (ED_{50}) of thiopental versus age is very similar to the curve representing MAC versus age for volatile agents.[101,102]

Benzodiazepines are potent hypnotic and amnestic drugs. Midazolam is the most rapid and most commonly used benzodiazepine, but its half-life is considerably longer in the neonate compared with the infant or adult (6 hours in neonates versus 3 hours in infants). The prolonged action is due to developmental immaturity of cytochrome P450 CYP 3A4.

Ketamine is a phencyclidine derivative with *N*-methyl-D-aspartate (NMDA) antagonist activity that is frequently used as a sedative/analgesic in neonates or as an induction agent for general anesthesia. Ketamine releases catecholamines, thus minimally depressing cardiovascular function. Ketamine causes prolonged sedation and is not the best choice when rapid postoperative extubation is planned. Contrary to common belief, ketamine can cause respiratory depression and airway compromise.[103] It is also responsible for an increase in oropharyngeal secretions, often requiring the co-administration of anticholinergics such as glycopyrrolate.

Opioids produce analgesia by stimulating opioid receptors (μ, δ, and κ) located in the brain, brainstem, and in the dorsal horn of the spinal cord. Opioids exert their action on the pain pathways by reducing the release of excitatory neurotransmitters and by inducing a hyperpolarization of postsynaptic membranes. Opioid receptors in the neonate are more vulnerable to exogenous opioids, especially water-soluble agents such as morphine that cross the immature blood-brain barrier and accumulate in the brain more easily.[104]

All opioids (except remifentanil) have decreased clearance in the first 3 months of life, and further reduction in clearance with prematurity.[87] Sedation and respiratory depression are exaggerated with all opioids, and their use may necessitate postoperative mechanical ventilation. Bradycardia and hypotension occur and are dose dependant. Bolus doses may sometimes produce chest wall rigidity, making ventilation difficult. Neonates have the lowest morphine clearance (9.2 mL/min/kg)[105] and do not reach adult clearance levels until 2 months of age. Fentanyl is 100 times more potent than morphine, cleared by the liver, and highly lipophilic, which explains its fast onset and fast effect-site equilibration. Its duration is dose dependent and difficult to predict in neonates. Fentanyl is frequently used as an adjunct to general anesthesia. Very large doses (50-100 mcg/kg) are used in cardiac anesthesia with minimal hemodynamic disturbances.

Remifentanil has an extremely short half-life (3-5 min), does not accumulate during infusion, is metabolized by nonspecific plasma and tissue esterases, and does not have active metabolites. A randomized study of remifentanil versus halothane in neonates and infants undergoing pyloromyotomy showed that intraoperative use of remifentanil did not increase the risk of apnea 12 hours after surgery.[106]

Muscle Relaxants

Neuromuscular blocking agents provide muscle relaxation, optimizing procedures such as intubation and operation without excessive intravenous or inhaled anesthetics. It must be kept in mind that absolutely no analgesia or hypnosis results from neuromuscular blockers. Therefore, care must be taken to have appropriate sedation, analgesia, or anesthesia on board before and during neuromuscular blockade. There are two types of muscle relaxants: depolarizing and nondepolarizing agents. Succinylcholine is the only depolarizing agent used in clinical practice. It is characterized by the most rapid onset of action and the shortest duration of action of all neuromuscular blockers. It provides reliable intubating conditions and is used for rapid sequence induction or emergency situations. A larger dose is required in neonates compared to adults because of a larger volume of distribution and a reduced activity at the neuromuscular junction.[107,108] Because the cholinergic effects of succinylcholine are more pronounced in neonates, atropine is administered first to prevent bradycardia. Most pediatric anesthesiologists avoid the routine use of succinylcholine because of the increased risk of induced hyperkalemic cardiac arrest in neonates with undiagnosed myopathies.

Nondepolarizing neuromuscular blockers are used for intubation and maintenance of relaxation during surgery. Neonates and infants appear to be more sensitive to these agents than adults. The duration of action is longer because the neuromuscular transmission is immature during the first 3 months of life. These agents should be monitored by twitch response, titrated to effect during operation, and reversed at the end of the procedure with anticholinesterases and anticholinergics. Spontaneous neuromuscular recovery times range from 40 to 60 minutes for cisatracurium, rocuronium, and vecuronium, and more than 60 minutes for pancuronium.[109] Cisatracurium is metabolized by Hoffman degradation. Rocuronium and vecuronium are metabolized mainly by the liver. Pancuronium is vagolytic, causing tachycardia, and is mainly excreted by the kidney. Aminoglycoside antibiotics, hypothermia, hypocalcemia, and inhalation anesthetic agents potentiate the action of neuromuscular blockers.

Local Anesthetics

Local anesthetics inhibit sodium-ion flux through voltage-gated sodium channels, blocking initiation and propagation of action potentials in axons. The use of regional anesthesia and analgesia avoid or decrease the side effects associated with the use of opioids, sedative, and general anesthetics by lowering the requirement for these agents. Local anesthetics are either aminoamides or aminoesters. Their metabolism and clearance is decreased in neonates because of enzymatic immaturity. The amides (lidocaine, ropivacaine, bupivacaine) are metabolized by the liver cytochrome P450 (CYP) enzymes. The esters (tetracaine and chloroprocaine) are metabolized by plasma esterases. The neonate requires less concentrated local anesthetics to achieve the same degree of blockade as adults because myelinization is not complete.[110] Bupivacaine and lidocaine are still the most popular local anesthetics used in neonates. Their volumes of distribution are higher, half-lives are prolonged, and there is less protein binding (low level of α–1 acid glycoprotein). Consequently, there is a higher risk of systemic toxicity, especially myocardial depression, arrhythmia, or cardiac arrest with excessive doses or intravascular injection of bupivacaine. Other toxic manifestations include lethargy, agitation, and seizures. Continuous epidural infusion of bupivacaine should not exceed 0.2 mg/kg/hour[87] and concerns have been raised about the safety of epidural infusions lasting longer than 48 hours in neonates.

Effects of Anesthesia on the Developing Brain

The neonate's central nervous system is capable of sensing pain and developing stress responses to surgical procedures.[113-116] These findings have reinforced the practice of administering anesthetics and analgesics during the perioperative period. The safety of anesthetics in the developing brain came into question because exposure to NMDA antagonists and GABA agonists have been found to cause apoptosis of immature neurons in the developing rat brain[117-119] and persistent learning deficits.[118] Similar apoptotic neurodegeneration has been demonstrated in juvenile monkeys exposed to ketamine.[119,120] Commonly used general anesthetics in pediatric anesthesia are either NMDA antagonists (ketamine, nitrous oxide) or GABA agonists (benzodiazepines, volatile anesthetics, barbiturates), and there is no evidence to date of detrimental CNS effect of these agents on pediatric patients. The existing animal data were reviewed at an open public meeting of the Anesthetic and Life Support Drugs Advisory Committee of the United States Food and Drug Administration. The unanimous decision of the committee was that until clinical or neuroimaging evidence of neurodegeneration becomes available, pediatric patients should continue to receive anesthetics during surgery and painful procedures.[121,122]

Preoperative Assessment and Management

Neonatal anesthesia and surgery present special issues that explain why most operations are of an emergent or urgent nature and performed in a specialized environment. The anesthesiologist must understand the surgical pathology and the perioperative implications. Information is gathered through chart review and communication with surgeon, neonatologist, parents, and any other relevant specialist such as the cardiologist. The nurse at the bedside can also give valuable details pertaining to the patient: vital sign trends, IV access, medication status, routine handling, and the patient's idiosyncrasies. Careful physical evaluation and review of relevant laboratory investigations should be performed. Thorough preoperative assessment allows for optimum planning for the neonate's perioperative care.

The history starts with inquiries about gestational age, postconceptual age, weight, birth events (e.g., asphyxia, meconium aspiration, APGAR scores) and sequelae, vitamin K administration, surfactant requirement, associated congenital anomalies, and nothing by mouth (NPO) status.

The maternal history may yield perinatal risk factors such as hypertension, diabetes, substance abuse, prolonged rupture of membranes, and infection. A neonatal history of apnea, periodic breathing, requirement for oxygen, administration of surfactant, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) give an idea of the respiratory status. Inquiries are also made about the degree of hemodynamic stability and the need for fluid, blood, or inotropic support.

The main focus of the anesthesiologist during physical examination is on the airway and the cardiopulmonary status. Difficult intubation may be associated with micrognathia or macroglossia. If the patient is already intubated, it is important to check the size and position of the endotracheal tube and verify that it is securely fixed. When the baby is not intubated, the clinician should recognize signs of increased work of breathing or respiratory distress such as apnea, tachypnea, nasal flaring, tachycardia, and oxygen desaturation. In an intubated patient, the degree of ventilatory support will dictate the initial ventilation settings in the OR. The general cardiovascular examination appreciates skin perfusion, capillary refill, fontanelle fullness, peripheral pulses, heart rate, blood pressure, urine output, and hemodynamic support to assess the degree of resuscitation and the risk of further deterioration. If a congenital heart defect is suspected (by cyanosis, heart murmur or gallop rhythm, tachycardia or bradycardia, absent femoral pulse, hepatomegaly) a blood gas, chest x-ray film, electrocardiogram (EKG), and echocardiogram should be performed and a pediatric cardiologist consulted. The intravenous access is inspected and plans for additional access are made depending on the extent and location of the operation. When there is a risk of decreased venous return from increased intraabdominal pressure, IV access in the lower extremities is not preferable.

Neonates should have a complete blood count and a cross match before surgery. Hemoglobin concentration at birth is related to the degree of placenta-fetal transfusion. Anemia may also occur later because of sepsis, poor nutritional state, growth of the premature infant, or multiple blood drawings for laboratory investigations. Other investigations depend on the baby's clinical condition. Clotting studies are requested in neonates at risk of coagulopathy (perinatal asphyxia, sepsis, jaundice, vitamin K deficiency) and those with a family history of bleeding disorders. An arterial blood gas will assess the adequacy of resuscitation and ventilation. Electrolyte imbalances and hypoglycemia should be corrected preoperatively.

The chest x-ray is useful in any baby with cardiorespiratory symptoms or on mechanical ventilation. A head ultrasound is recommended before surgery in those at risk of intracranial hemorrhage. Neonates scheduled for nonemergent surgery are fed formula, breast milk, or clear fluids up to 6, 4, and 2 hours prior to anesthesia, respectively.

After all information is gathered, anesthetic options are considered. The first decision concerns the urgency of the procedure versus the feasibility of safely optimizing the baby's status preoperatively. Depending on the anticipated need for cardiorespiratory support and hemostasis, a decision is made to proceed with surgery or delay surgery until the baby's status is more stable. For a nonintubated neonate with an anticipated difficult airway, the difficult airway cart should be set up and an airway control strategy determined. Latex precautions are usually declared for myelomeningocele patients. The anticipated need for intraoperative fluids and blood products is established. The possibility of including regional anesthesia in the perioperative plan is discussed.

Next, a decision is made on the operative location. Most procedures are performed in the operating room where optimal conditions for access, lighting, and sterility exist. Transport of a critically ill, intubated, unstable, ELBW neonate, however, exposes him to significant morbidities such as hypothermia, dislodgment of the artificial airway, discontinuation of monitoring, accidental removal of vascular access, and interruption of vital treatment.[123,124] In these cases, operations in the neonatal intensive care unit (NICU) have been proven safe and should be considered.[125-127]

During the preoperative period, optimal care requires that deficits be recognized and reversed prior to surgery. In certain cases, the metabolic, respiratory, or cardiac deficits are caused by the underlying condition requiring surgery and cannot be completely reversed, preoperatively. In these situations, conditions are optimized and the operation performed.

The anesthetic plan is discussed with and informed consent obtained from the parent or legal guardian. The anesthesia equipment is set up and includes appropriate-size facemask, several endotracheal tubes, an oral airway, and straight blade laryngoscopes. The anesthesia workstation and suction are checked for functionality. Drugs are drawn up in appropriate doses (Table 29-1). The intravenous infusion system is meticulously checked and cleared of air bubbles to decrease the risk of paradoxical air embolus. An infusion pump or a burette is used for fluid administration. The operating room is warmed. Active warming devices for the baby, intravenous fluids, and blood products are set in place. Preoperative sedation is not necessary in neonates.

Intraoperative Monitoring

The minimal requirements for intraoperative neonatal monitoring include the basic American Society of Anesthesiology standards for monitoring. This standard is realistic and mandates that the baby's oxygenation, ventilation, circulation, and body temperature be continually evaluated. The standard may be exceeded at any time depending on the patient's clinical condition and anticipated problems during operation. If feasible, a precordial stethoscope is placed on the chest at a site where both heart and breath sounds are audible. The esophageal stethoscope is a valuable alternative when a chest site cannot be used.[128] The degree of neuromuscular blockade is monitored by the twitch or train-of-four response to peripheral nerve stimulators applied to ulnar, facial, or posterior tibial nerves. A urine output of 1 to 2 mL/kg/hr is desirable and can be monitored with an indwelling catheter. Pressure-volume loop assessment is useful in detecting worsening lung function (Fig. 29-3). In critically ill neonates and cases in which major circulatory changes are expected, invasive monitoring such as arterial and central venous catheters provide real-time information about the hemodynamic status. A

TABLE 29-1 Intravenous Anesthetic Drugs for the Neonate: Dosages

Anesthetic Agents	Premedication (mg/kg)	Induction (mg/kg)	Maintenance (mcg/kg)	Intubation (mg/kg)	Reversal (mg/kg)
Anticholinergics					
Atropine	0.01-0.02				
Glycopyrrolate	0.005-0.01				
Hypnotics					
Propofol		2.5-3.0			
Thiopental		4-6			
Ketamine		0.5-2.0			
Midazolam		0.02-0.05			
Opioids					
Fentanyl		0.005-0.010	1-2 mcg/kg/hr		
Morphine		0.05-0.1	10-50 mcg/kg/hr		
Sufentanil		0.0001-0.0002	0.05-0.1 mcg/kg/hr		
Remifentanil		0.0001	1.5-3 mcg/kg/min		
Muscle Relaxants					
Succinylcholine				1-2	
Pancuronium				0.05-0.1	
Vecuronium				0.1-0.15	
Rocuronium				0.8-1.2	
Anticholinesterases					
Neostigmine					0.05-0.08
Pyridostigmine					0.02-0.03
Narcotic Antagonists					
Naloxone					0.005-0.01

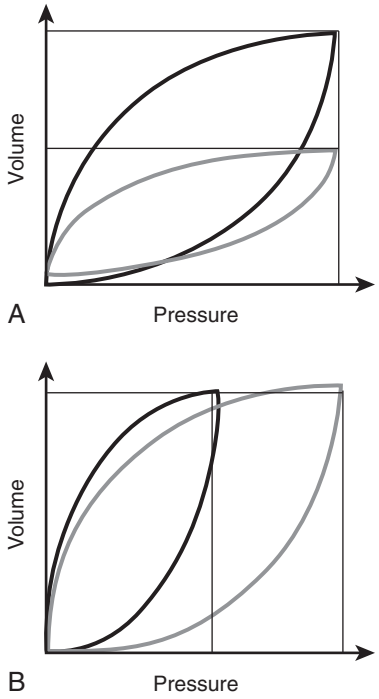


Figure 29-3 ■ **(A)** Pressure-volume loops in pressure-limited ventilation. Pressure is plotted on horizontal axis and tidal volume delivered on vertical axis. In low compliance lung (broken line loop) the tidal volume delivered is lower than compliant lung (continuous line loop). Pressure delivered by the ventilator is same for the two breaths. **(B)** Pressure-volume loops in volume-controlled ventilation. Pressure is plotted on horizontal axis and tidal volume delivered on vertical axis. Tidal volume delivered is same for the two breaths. In low compliance lung (broken line loop) the pressure needed to deliver the set tidal volume is higher than in compliant lung (continuous line loop). (From Singh J, Sinha SK, Donn SM. Volume-Targeted Ventilation of Newborns. Clin Perinatol 2007;34:93-105.)

series of laboratory investigations such as blood gases, hematocrit, ionized calcium, electrolytes, and glucose are crucial for management of the vulnerable neonate and during prolonged surgery.

Induction and Airway Control

Anticholinergics, such as atropine, are administered to neonates with copious airway secretions and/or to prevent bradycardia during induction. There is no ideal drug or combination of drugs to induce and intubate a neonate. The induction technique is based in large part on whether the baby appears to have an accessible airway and whether he/she is an aspiration risk. It should also take into account the degree of cardiovascular stability (congenital heart disease, volume status). A clear plastic mask is applied and properly fitted to the face between the chin and the bridge of the nose to allow for denitrogenation/preoxygenation or bag-and-mask ventilation. Careful observation will detect vomitus or airway secretions. After anesthesia induction, muscle relaxation, and a 2-minute period of mask ventilation with 100% oxygen, intubation must be accomplished because desaturation (SpO_2 less than 90%) occurs within 80 to 90 seconds of apnea.[129]

Awake intubation or rapid sequence induction are useful in babies with a full stomach. Aspirating gastric contents with an oro- or nasogastric tube is useful in emptying the stomach before induction. Awake intubation exposes the neonate to serious complications such as acute hypertensive response, bradycardia or tachycardia, breath holding or apnea, and increased risk of intracranial hemorrhage.[130] The chances of a successful awake intubation after one failed attempt decrease because of associated struggling. Repeat attempts increase the risk of trauma to the airway. If the anesthesiologist deems awake intubation

necessary, there is rarely a reason not to titrate an opioid (or use a short-acting one such as remifentanil).

Rapid sequence induction requires the use of intravenous induction agents (thiopental or propofol), muscle relaxants (succinylcholine or rocuronium) and cricoid pressure. As mentioned above, desaturation is rapid even after preoxygenation. Attempts at bag-and-mask ventilation to mitigate hypoxemia can lead to gastric distension, decrease lung expansion, and an increase risk of aspiration. If the stomach is empty and the airway normal, the anesthesiologist has more options. The IV can be started before or after inhalation induction. Muscle relaxants are given before or after intubation depending on the clinical situation and operative requirements, keeping in mind that an inhalation anesthetic deep enough to provide relaxation by itself is usually associated with an unacceptable level of cardiovascular depression in neonates. In general, an induction dose of a narcotic such as fentanyl accompanied by pancuronium provides a stable hemodynamic condition during intubation of a critically ill neonate or one with congenital heart disease.

We have previously described difficult airway management of the neonate. In those with a previously unrecognized difficult airway, the laryngeal mask airway (LMA) can be life saving, allowing maintenance of a patent airway above the glottic opening (Fig. 29-4). Intubation can then be carried out through the LMA using a flexible fiberoptic bronchoscope. Depending on the nature of the procedure, the baby can then be allowed to awaken or the operation can proceed with the LMA in place, keeping in mind several things:

1. LMA failure rates are high during surgery in neonates[131,132]
2. Anesthesia decreases FRC and alveolar ventilation; increases the closing volume and work of breathing
3. LMA does not protect against aspiration of gastric contents

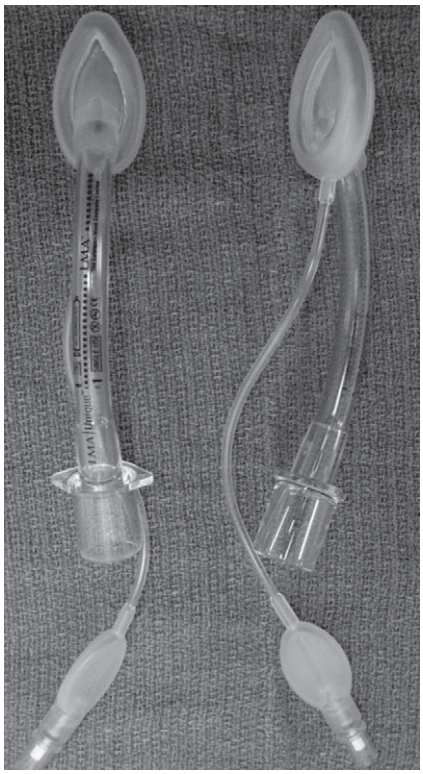


Figure 29-4 ■ Laryngeal mask airway.

The ideal neonatal airway control device is an appropriately sized endotracheal tube (ETT) with an audible leak when providing peak inflating pressure between 15 and 25 cm H_2O. Intubation is confirmed by symmetric chest rise, auscultation of bilateral breath sounds, absence of inflation sound over the stomach, and detection of sustained end-tidal carbon dioxide on the capnograph. After endotracheal intubation, an orogastric tube can be inserted to remove any air introduced during induction and any fluid present in the stomach.

Maintenance of Anesthesia

Intraoperative ventilatory management is performed using an anesthesia workstation (as it is called today) to provide delivery of anesthetic gases, appropriate oxygenation, and assisted or controlled ventilation. The modern anesthesia workstation is a complex integrated system including the anesthesia machine (pressure-regulating and gas-mixing components with their electronic control systems), the vaporizer(s), anesthesia breathing circuit, ventilator, scavenging system, and respiratory and physiologic monitoring equipment.[133]

The anesthesia breathing circuit is the portion that delivers oxygen and inspired gases while removing carbon dioxide. Circle systems are the most commonly used breathing systems in the United States. By allowing rebreathing of anesthetic gases, they facilitate conservation of anesthetic gases, heat, and moisture. In conventional anesthesia systems, the fresh gas flow and the compliance of the system affect the tidal volume delivered to the baby. The exhaled tidal volume, measured at the expiratory valve, measures not only the exhaled gas but also the gas compressed in the system during inspiration. In neonates, the small variations in tidal volume can cause hypoventilation or hyperinflation, volutrauma, barotrauma,[134] or atelectrauma.

Neonatal ICU ventilators are better configured to ventilate newborns, but they cannot deliver volatile anesthetics. Significant improvements in anesthesia ventilation technology have, however, afforded better intraoperative ventilatory management. The following are the improved features of new-generation anesthesia ventilators.[135] First, fresh gas flow is decoupled from the set tidal volume so that the tidal volume delivered is not affected by changes in fresh gas flow. Second, compliance compensation maintains the same tidal volume delivery despite variations in pulmonary compliance, allowing better volume-controlled ventilation (VCV). The new generation of anesthesia workstations also carry some features of the neonatal ventilators that facilitate intraoperative management such as accurate delivery of positive end-expiratory pressure (PEEP) to decrease atelectasis, pressure support ventilation to decrease the work of breathing during spontaneous ventilation, synchronized intermittent mandatory ventilation (SIMV) to facilitate weaning near completion of surgery, and pressure-controlled ventilation (PCV). The choice of VCV versus PCV during anesthesia will depend on the clinical status and the anesthesiologist's experience and

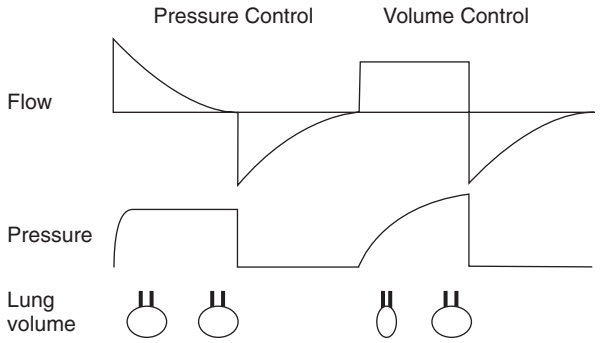


Figure 29-5 ■ Comparison of ventilator output during pressure-control versus volume-control. From Stayer S, Olutoye O. Anesthesia Ventilators: Better options for Children. Anesth Clin of North Am. 2005 Vol 23 Number 4. 655-691.

judgment. As previously mentioned, flow-volume loop assessment may be useful in detecting worsening lung function. Figure 29-5 compares ventilator output during pressure-controlled and volume-controlled ventilation.[136] When comparing VCV and time-cycled, pressure-limited ventilation (TCPLV) in the NICU, benefits of VCV appear encouraging in outcomes such as duration of ventilation, pneumothorax, and intraventricular hemorrhage.[136] There is, however, no similar intraoperative evidence showing VCV is superior to TCPLV in pediatric patients.[134]

Intraoperative management of oxygenation requires monitoring of oxygen concentrations in the inspired anesthetic gases and in the blood. The inspired oxygen analyzer should also contain an oxygen concentration alarm limit. Blood oxygenation is monitored continuously with pulse oximetry and, if necessary, arterial blood gases. In the neonate at risk, it is preferable to have pre- and postductal Spo_2 monitored to detect the occurrence of right-to-left shunting through the ductus arteriosus. During anesthesia, the control of the inspired oxygen concentration may limit the oxidative stress and damage to vital organs (eyes, lung, brain) as a result of high oxygenation[137] in neonates at risk (less than 44 weeks' postconceptual age). Spo_2 should ideally be maintained between 90% and 96%. Evidence abounds that general anesthesia decreases lung volume and produces atelectasis. Administration of 100% oxygen also decreases lung volume during anesthesia.[138,139] It is good practice to apply volume recruitment maneuvers to limit the increase of Fio_2 once the patient is stable.[137]

Intraoperative Management of Cardiovascular Function

A continuous electrocardiogram allows detection of arrhythmias during general anesthesia. The heart rate is indicated by both the ECG and the Spo_2 monitor. When using a precordial or esophageal stethoscope, variations in the characteristics of the heart sounds can warn the anesthesiologist of a decrease in blood pressure or cardiac output. The disappearance of the Spo_2 waveform may indicate poor peripheral perfusion.

All modern anesthesia ventilators include mechanisms with audible signals to detect the disconnection of breathing system components. End-tidal carbon dioxide analysis is monitored by capnometry, capnography, or mass spectroscopy. Capnogram analysis during anesthesia is used to confirm the correct placement of the endotracheal tube and the continuous adequacy of ventilation but also to assist in the diagnosis of metabolic and cardiorespiratory events as illustrated in these next examples.[140,141] Absent end-tidal CO_2 after an intubation attempt is seen in esophageal intubation. A high baseline represents rebreathing of expired gases and is seen with inadequate fresh gas flow in noncircle systems or a malfunction of a unidirectional valve in the breathing system. Sudden loss of end-tidal CO_2 (to zero) occurs with endotracheal tube dislodgement, airway disconnection, or total airway obstruction. Rapid progressive disappearance of end-tidal CO_2 is caused by a loss of pulmonary blood flow as in massive pulmonary embolus, cardiac arrest, or initiation of cardiopulmonary bypass. Increased end-tidal CO_2 is due to either increased CO_2 production (hypermetabolic states, laparoscopy, thoracoscopy, CO_2 embolus) or decreased CO_2 elimination (hypoventilation or decreased pulmonary compliance). End-tidal CO_2 increases transiently after the administration of bicarbonate. The cleft seen on the capnogram plateau usually indicates spontaneous respiratory effort from neuromuscular blockade recovery.

Blood pressure is monitored at least every 5 minutes by a noninvasive oscillometric device. When large hemodynamic changes are anticipated, an intraarterial catheter and a central venous catheter permit beat-to-beat evaluation of the hemodynamic status and are convenient for obtaining serial blood gases and other laboratory investigations. When an umbilical artery catheter is in place, x-ray film should confirm the tip of the catheter at L4 to L5 (above aortic bifurcation and below renal arteries). Adequate urine output (1-2 mL/kg/hr) is a sign of good general perfusion and kidney function. Blood loss is monitored by observation of the surgical field, sponge, suction canister, heart rate, blood pressure, and serial hemoglobin results. Importantly, loss of more than 15% of blood volume is poorly tolerated by a neonate. Therefore, blood replacement should be prompt, with crystalloid being used to temporize (3 mL/mL of blood lost) until blood is available.

Intraoperative fluid and blood management encompasses several components. Deficits are preferably corrected preoperatively. If not, 50% of the volume deficit is provided during the first hour and 50% over the next 2 hours.[142] Maintenance fluids such as total parenteral nutrition (TPN) or combination glucose-electrolyte solution is usually continued. If the fluids are discontinued, serum glucose is monitored during the operation. Third-space losses are replaced by infusion of 1 to 20 mL/kg/hr of isotonic solution (lactated Ringer's or normal saline) depending on the extent of the operation. Controversies about albumin versus crystalloids in neonatal anesthesia abound, but are beyond the scope of this chapter. Hypoglycemia and electrolyte imbalances such as hypocalcemia should be corrected throughout the operation. Blood losses are replaced with packed red blood cells. Other blood product administration such as fresh frozen plasma, platelets, or cryoprecipitate should be based on laboratory or clinical evidence of their need.

Temperature is monitored and every effort should be made to preserve normothermia. Morbidities related to neonatal hypothermia have already been discussed.

Emergence and Extubation

Many factors influence the decision to extubate at the end of an operative procedure. Awakening requires that volatile agents are turned off, complete neuromuscular recovery occurs either spontaneously or pharmacologically (administration of an anticholinergic and anticholinesterase), and that the respiratory depressive effects of anesthetics and narcotics have subsided. A hemodynamically stable, spontaneously breathing, vigorous baby should be extubated. Conversely, a hemodynamically unstable, hypothermic, weak baby (e.g., residual anesthetic effect, preexisting condition, nature of surgery) who had a large intraoperative blood and/or fluid requirement or who has persistent respiratory depression should be taken to the NICU on ventilation. Decision making for any situation in between these two extremes will depend on the clinical specifics and on clinician judgment.

Regional Anesthesia

In practice, regional anesthesia in neonates is generally limited to neuraxial blocks, local infiltration, ilioinguinal/iliohypogastric blocks, and penile blocks. Neurologic and cardiac toxicity are minimized by adherence to maximal dosing guidelines for local anesthetics (see Tables 29-2 and 29-3). Regional anesthesia is avoided in sepsis and bleeding disorders. Benefits of regional anesthesia include the decreased requirement of intraoperative general anesthetics and opioids, thereby limiting the side effects associated with these agents. The neuroendocrine stress responses induced by surgery as well as postoperative pain are better controlled by regional anesthesia.[143-145] This translates into improved neonatal outcomes.[145] The complication rate of pediatric regional anesthesia is extremely low.[146,147] Spinal anesthesia or epidural anesthetics, even as sole anesthetics, do not eradicate the risk of postoperative apnea.[148,149] Even high sympathetic blocks (thoracic level) do not produce significant drops in blood pressure and heart rate as seen in adults. This might be explained by the relatively immature sympathetic nervous system or the relatively small intravascular volume of the neonate's lower extremities.[150-152] To minimize the risks of spinal cord injury, epidural catheters are inserted via the caudal space using various techniques such as fluoroscopy guidance, ultrasonography, or nerve stimulation.

Intraoperative Airway Management of Diseases That Require Surgery

For the sake of brevity and clarity, diseases that require surgery are discussed here within their related organ system: abdominal, neurologic, and thoracic. In addition, the ex utero intrapartum treatment (EXIT) procedure and conjoined twins are discussed under the heading of special situations.

TABLE 29-2 Local Anesthetics: Maximum Doses for Local Infiltration, Peripheral Nerve, and Epidural Blocks

Local Anesthetic	Maximum Dose (mg/kg)
Lidocaine	5 or 7 with epinephrine 1/200,000
Bupivacaine	2.5
Ropivacaine	2.5

Abdominal Surgery

Neonatal abdominal lesions compromise airway management either by increasing intraabdominal pressure or interfering with lung development. Surgical lesions associated with increased intraabdominal pressure include gastroschisis, omphalocele, congenital tumors, and certain urologic disorders (Fig. 29-6). Those that interfere with lung development include congenital diaphragmatic hernia and a wide variety of urinary tract abnormalities (Fig. 29-7).

Neonates with gastroschisis and omphalocele have loss of abdominal domain (Fig. 29-8). The replacement of extraabdominal organs, in this situation, can have deleterious respiratory affects. Replacing the intestines into the abdomen displaces the diaphragm cephalad, decreasing tidal volume (TV) and functional residual capacity (FRC). To maintain oxygenation and ventilation, the child has only one option; increase his/her respiratory rate. In addition to the mechanical effects on respiration, compression of intraabdominal organs can produce metabolic affects that impact respiration. If the abdominal contents are compressed too tightly, intraabdominal organs may become ischemic. This is seen on blood gas analysis as a metabolic acidosis. Respiratory compensation, again, requires an increase in respiratory rate to maintain a normal pH.

Surgical Approach and Care

The care of the neonate takes into account the general considerations previously outlined whether the surgical approach is laparotomy or laparoscopy. Suction is applied to the gastric tube to decompress the stomach before rapid-sequence IV induction is performed with cricoid pressure. Securing a breathing device in the trachea is the only appropriate option for airway control during major abdominal surgery. High doses of narcotics are associated with better hemodynamic stability than a volatile-based

TABLE 29-3 Anesthetics for Neonatal Neuraxial Blockade

Type of Block	Local Anesthetics	Dose	Duration of Analgesia
Spinal	Lidocaine 5%	2 mg/kg	45 min
	Bupivacaine 0.5% with epi 20 mcg	0.8 mg/kg	70 min
	Tetracaine 0.5% with epi 40 mcg	0.5-1.0 mg/kg	80-120 min
Single dose caudally administered	Bupivacaine 0.25%	2 mg/kg	4-6 hr
Epidural blockade	Bupivacaine 0.1%	0.1-0.2 mL/kg/hr	Days
Continuous epidural blockade	Chloroprocaine 1.5%	0.1-0.2 mL/kg/hr	Days

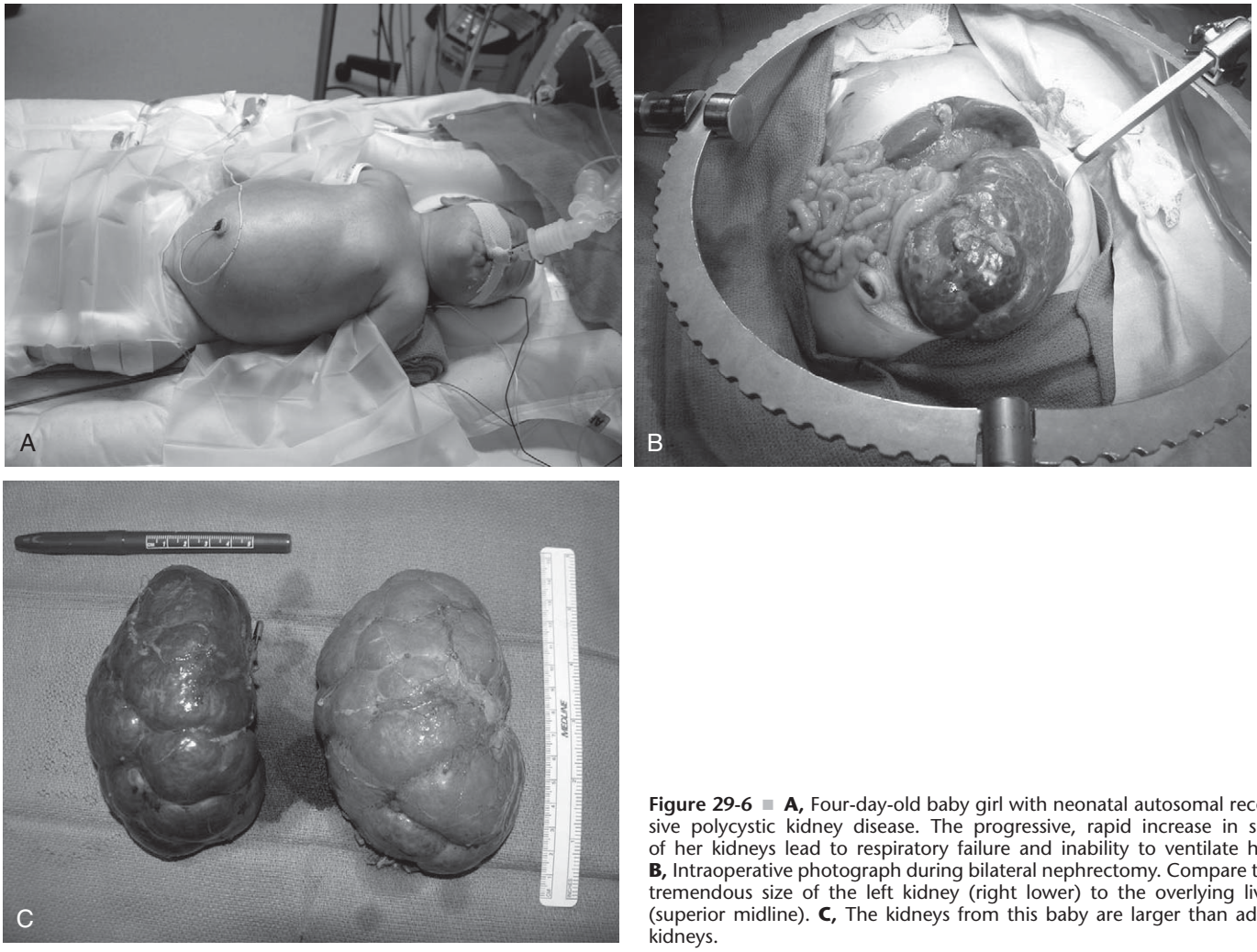


Figure 29-6 ■ **A,** Four-day-old baby girl with neonatal autosomal recessive polycystic kidney disease. The progressive, rapid increase in size of her kidneys lead to respiratory failure and inability to ventilate her. **B,** Intraoperative photograph during bilateral nephrectomy. Compare the tremendous size of the left kidney (right lower) to the overlying liver (superior midline). **C,** The kidneys from this baby are larger than adult kidneys.

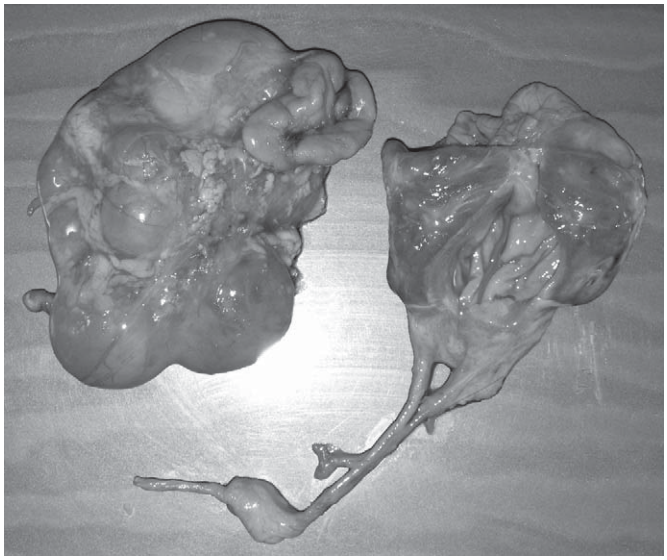


Figure 29-7 ■ Kidneys from a newborn with Potter's syndrome who died from respiratory failure.

anesthetic, particularly in the critically ill neonate and the patient with congenital heart disease. Neuromuscular blockade allows abdominal wall relaxation. Nitrous oxide is avoided to prevent worsening of bowel distension. Third-space fluid and blood losses are anticipated and can be massive. Blood transfusion is started when 10% of the blood volume has been lost. Transfusion of 10 mL/kg of packed red blood cells raises the hemoglobin by 3 g/dL. When justified by clinical observation or laboratory investigations, fresh frozen plasma (10 mL/kg), platelets (10 mL/kg), or cryoprecipitate are also transfused.

If coagulopathy, sepsis, or compromised hemodynamic status has been ruled out, presurgical insertion of caudal epidural anesthesia offers tremendous benefits. It provides outstanding intraoperative and postoperative analgesia, minimizing the use of narcotics or anesthetics as well as providing abdominal wall relaxation, allowing easier exposure and closure. Epidural anesthesia has also been proven beneficial in attenuating surgery-induced stress response. However, the use of an epidural infusion for more than 48 hours in neonates increases the risk of local anesthetic toxicity.

Some major neonatal surgeries present particular management issues that deserve mention. Abdominal wall defects (gastroschisis, omphalocele), when large, are

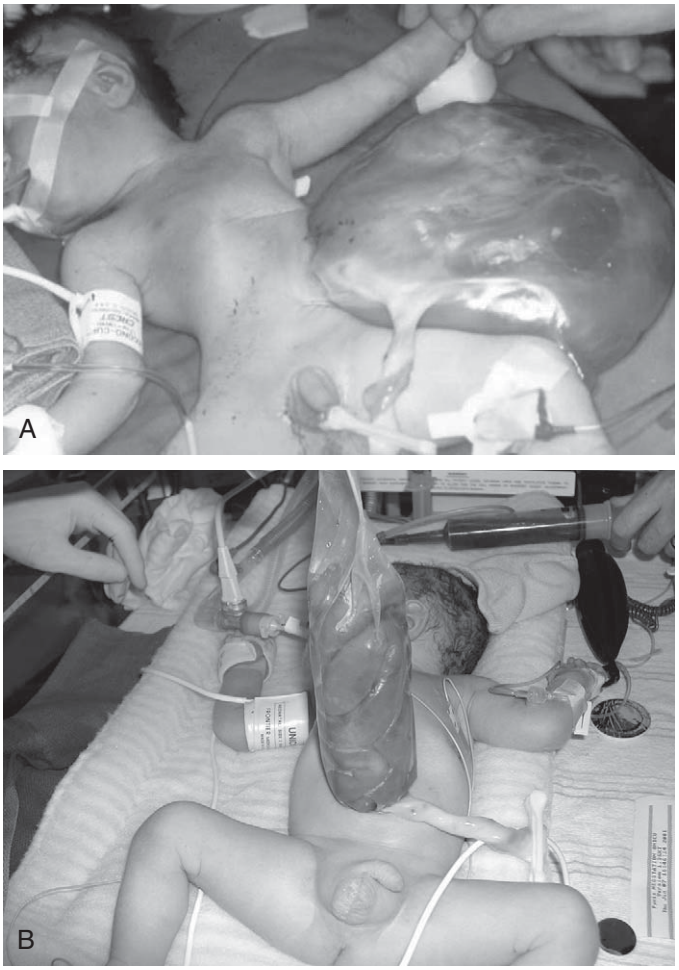


Figure 29-8 ■ **A,** Newborn with giant omphalocele. Compare the size of the omphalocele to the infants' small abdomen. **B,** Newborn with gastroschisis. Compare the amount of intestine in the silo to the small abdominal cavity.

difficult to close primarily. Closure may lead to increased intraabdominal pressure significant enough to limit diaphragmatic excursion and compromise ventilation, compromise cardiovascular status, and impair blood flow to the intraabdominal organs. Perioperative fluid and blood resuscitation requirements can be significant. Omphalocele is associated with a higher incidence of other anomalies including cardiac and thoracic defects (more frequent with epigastric omphalocele), genitourinary defects (more frequent with hypogastric omphalocele), and Beckwith-Wiedemann syndrome. Intestinal atresia is more frequent with gastroschisis.

Necrotizing enterocolitis occurs almost exclusively in the premature neonate. The initial treatment is medical stabilization. Intestinal perforation with free air on abdominal film, abdominal wall erythema, and failure to respond to medical therapy (refractory sepsis, hypovolemia, and persistent metabolic acidosis) are common indications for surgery. These babies are typically hemodynamically unstable, on inotropes, coagulopathic, and anemic when brought to the operating room. The neonate may also present with other complications associated with prematurity. Because of coagulopathy and sepsis, regional anesthesia should not be considered.

Congenital diaphragmatic hernia results in thoracic herniation of the abdominal contents and pulmonary hypoplasia. The most severe cases may require the EXIT procedure and sometimes the EXIT procedure immediately followed by ECMO cannulation.[153,154] The primary cause of respiratory failure is severe pulmonary hypoplasia with persistent pulmonary hypertension. Surgery is delayed until the baby is stabilized with ventilatory strategies that minimize barotrauma: inhaled nitric oxide, surfactant administration, and sometimes ECMO. Operation is performed through an abdominal or a thoracic incision. The baby is typically brought to the operating room intubated. If not intubated, induction is performed maintaining spontaneous ventilation or by rapid sequence, avoiding positive-pressure mask ventilation that could cause gastric distension and inability to ventilate. Placement of an oro- or nasogastric tube allows gastric decompression. Preductal and postductal SpO_2 monitoring will detect right-to-left shunt through the PDA. An arterial line, preferably preductal, is helpful. Conditions that could cause or worsen pulmonary hypertension (acidosis, hypoxia, hypothermia, pain) should be corrected. A caudal epidural catheter with the tip confirmed close to the level of the skin incision will provide excellent intraoperative and postoperative analgesia. Ventilation strategies to minimize barotrauma are implemented. Surgery is sometimes performed in the NICU to avoid disrupting ventilation or when the patient is on ECMO.

Bladder exstrophy heightens the risk of the later development of latex allergy.[155] These patients require latex precautions. The placement of an epidural catheter for bladder procedures facilitates postoperative care.

Laparoscopy Versus Laparotomy

Access to the abdomen can be achieved through either laparotomy or laparoscopy. Neonatal laparoscopy is the result of technologic improvements in instrumentation and previous experience in other fields. Laparoscopy was first used in the 1950s to diagnose gynecological diseases.[156] Over the next 20 years, its use spilled over into the fields of general and pediatric surgery. The development of smaller instruments, better cameras, and the leadership of courageous pediatric surgeons resulted in many open procedures being "converted" to laparoscopic procedures.

Laparoscopy can quickly become laparotomy (conversion rate of about 2%-3%), so preparations are made to make conversion to an open operation safely and efficiently if necessary. Although the incisions are small, the potential for blood loss is equal to that of laparotomy. Therefore, any neonate presenting for laparoscopic surgery deserves, at the very least, a type and screen. Importantly, the pneumoperitoneum and CO_2 insufflation each create physiologic changes that alter normal respiratory, cardiac, renal, and neurologic function.[157-159] The anesthesiologist and surgeon must be familiar with these changes and be prepared to compensate for them. The stomach and bladder are intraabdominal organs in the neonate. To prevent injury, they must be decompressed before the first trocar is placed. The bladder can be decompressed by the

Credé maneuver or by placing a Foley catheter. The stomach is decompressed by placing a nasogastric or orogastric tube. Finally, laparoscopy can cause unique intraoperative and postoperative complications that must be anticipated and treated promptly.

The major effects of laparoscopy are the result of CO_2 absorption and the increased intraabdominal pressure necessary to maintain a pneumoperitoneum. The extent of these side effects are dependent on the intraabdominal pressure, the patient's age, length of the procedure, position of the patient, and the amount of CO_2 absorption.[155-160]

The respiratory effects are both mechanical and CO^2 related. Insufflation of the abdomen pushes the diaphragm superiorly, decreasing the total lung capacity (TLC), FRC, and thoracic compliance.[157] The decreased ratio between FRC and closing volume increases the risk of atelectasis and ventilation-perfusion mismatch. The clinical manifestations of these effects are an increase in peak inspiratory pressure (PIP), a decrease in expired TV, an increase in the end-tidal CO_2 ($ETCO_2$) and transcutaneous partial pressure of CO_2 ($tcpCO_2$), and a decrease in oxygen saturation.[157-159] These effects are made worse by Trendelenburg position and pressure-controlled ventilation.[156,160] They are improved by lower intraabdominal pressure (less than 6 mm Hg in neonates), reverse Trendelenburg position, and volume-controlled ventilation. The displacement of the diaphragm cephalad may push the lungs and trachea superiorly, leading to a bronchial intubation.[160]

Carbon dioxide accumulation in the blood contributes to the adverse mechanical effects of pneumoperitoneum. Carbon dioxide enters the circulation either by absorption or inadvertent intravenous or intraarterial injection. Interestingly, CO_2 absorption is higher with extraperitoneal versus intraperitoneal insufflation, and CO_2 absorption and elimination are both inversely related to age.[157] As the venous CO_2 concentration increases, so will the $ETCO_2$ and $tcpCO_2$. Treatment requires an increase in minute ventilation by increasing the respiratory rate and/or the tidal volume.

The cardiac effects of pneumoperitoneum are mechanical, technical, and CO_2 related. The mechanical effects are related to the intraabdominal pressure (IAP), preload, and patient position. Gueugniaud et al.[161] studied infants undergoing laparoscopy with transthoracic echocardiography (ECHO) and found that at an IAP of 10 mm Hg, aortic blood flow, and stroke volume were decreased and the systemic vascular resistance (SVR) was increased. In a separate study in young children, the same authors found similar results using an IAP of 12 mm Hg.[162] Importantly, these changes in hemodynamics returned to normal when the IAP was lowered to 6 mm Hg.[157-160]

Preload is related to IAP.[156] At low pressures (i.e., IAP less than 15 mm Hg), the splanchnic vascular bed is compressed, pushing blood into the inferior vena cava (IVC), thereby augmenting preload and cardiac output. At higher pressures (i.e., IAP greater than 15 mm Hg), the IVC is compressed leading to a decrease in preload and cardiac output. These effects, however, are short-lived and appear to resolve spontaneously in less than 10 minutes after establishment of the pneumoperitoneum.[157] The clinical manifestations of these changes may include a decrease in cardiac output and hypotension. The best treatment is prevention by keeping the IAP low (less than 6 mm Hg) and ensuring the infant is well hydrated before the abdomen is insufflated.

The technical aspects of laparoscopy that lead to cardiac effects are usually the result of vagal stimulation that results in bradyarrythmias.[157,158] Vagal stimulation can occur with puncturing the peritoneum with the Veress needle or trocar, distension of the parietal peritoneum with insufflation, and applying traction on the bowel or fallopian tube. Conversely, CO_2 accumulation has been associated with the release of catecholamines and tachyarrythmias.

Laparoscopy also affects the central nervous system. Increased IAP, patient positioning, hypercapnia, and the cardiorespiratory effects of pneumoperitoneum affect intracranial pressure (ICP) and cerebral spinal fluid (CSF) absorption. Increased IAP, Trendelenburg position, and hypercapnia increase ICP. An increase in IAP, by elevating venous pressure in the abdomen, may decrease the reabsorption of CSF, thereby further increasing ICP.[157-159]

Laparoscopy has an adverse effect on glomerular filtration, which may decrease urine output. The causes for this are multifactorial and include an increase in antidiuretic hormone (ADH) and plasma renin levels. Again, the best treatment is prevention. The baby must be well hydrated prior to abdominal insufflation.

Complications of Laparoscopy

The major complication rate of laparoscopy is 1% to 2%. Complications include pneumothorax, pneumomediastinum, pain, subcutaneous emphysema, and CO_2 embolization.[158] Pneumothorax and pneumomediastinum are due to inadvertent injury to the diaphragm during operation or dissection of CO_2 into the pleural cavity or mediastinum through the natural openings in the diaphragm. These two complications may remain silent during the case or may result in intraoperative respiratory compromise. Diagnosis is confirmed by auscultating the chest, and if time permits, a chest x-ray. Treatment includes placement of a chest tube and relieving the pneumoperitoneum.

Pain is usually referred to the shoulders and neck and is the result of residual intraabdominal CO_2. Subcutaneous emphysema may be the result of inadvertent infusion of CO_2 into the subcutaneous tissue or residual intraabdominal CO_2 leaking back into the subcutaneous tissue through holes in the peritoneum. This is usually found postoperatively and should be distinguished from rare cases of clostridia infection or bowel injury.

Pneumoperitoneum, through its associated increase in IAP, hypercapnia, and acidosis, may lead to the reopening of right-to-left shunts in the neonatal heart. This return to fetal circulation is manifest by hypoxia and acidosis. Treatment requires relieving the pneumoperitoneum, cardiorespiratory support, and rarely, ECMO.

Carbon dioxide embolization occurs in one of two ways. One occurs when CO_2 is injected directly into an open artery or vein. The other occurs when the rate of CO_2 being absorbed outpaces the ability of the lungs to excrete it. In both cases, CO_2 begins to accumulate in the blood stream. Usually, this is of no clinical consequence. However, if the amount of CO_2 is large enough, pulmonary artery (PA) pressure will rise. If allowed to continue,

the PA pressures can approach and supersede systemic pressures resulting in right heart failure. The clinical manifestations of CO_2 embolism include an increase in $ETCO_2$ and hypotension.

The best treatment for CO_2 embolization is prevention. The anesthesiologist must constantly be monitoring changes in tidal volume, minute ventilation, and $ETCO_2$. Adjustments to ventilation are made to keep up with the excess CO_2 being generated. If CO_2 embolization is suspected, treatment includes relieving the pneumoperitoneum, discontinuing all inhalation anesthetics, ventilating with 100% oxygen, and cardiovascular support with fluids, and if necessary, inotropes. The diagnosis may be confirmed with transesophageal or thoracic ECHO.

Neurosurgery

The most common neonatal neurosurgical problems include hydrocephalus and spinal cord defects.[163] The incidence of associated anomalies in these patients is 20% and includes other CNS, renal, and cardiac anomalies.[164] Neonates with spinal cord defects have a high incidence of hydrocephalus (85%), Chiari malformations (almost 100%), and cardiac defects (37%). Atrial septal defect is the most common cardiac anomaly and is more common in affected females. Chiari malformation is defined as a small posterior fossa, inferior displaced and elongated brainstem, and obliteration of the fourth ventricle. Common renal anomalies include vesicoureteral reflux, hydroureter, and hydronephrosis occurring in up to 30% of neonates with surgical CNS disease.

Preoperative evaluation of these patients is extensive.[165] In prenatal consultation, the maternal history, previous pregnancies, results of amniocentesis, alpha-fetoprotein, and level 3 ultrasound are reviewed. History of teratogen exposure, although uncommon (less than 10%), is important. Postnatal consultation should include a thorough history, physical examination, cardiology and urology consultations, and radiologic evaluation. A history of aspiration, difficulty feeding, signs and symptoms of cardiac dysfunction, the level of neurologic impairment, and the identification of associated syndromes are important to note. Previous aspiration and/or difficulty feeding suggests vocal cord abnormalities, anomalies of the upper aerodigestive tract, or pharyngeal muscle dysfunction and may require additional, preoperative testing.

Some anomalies are difficult to detect on physical examination. Therefore, all neonates with surgical CNS lesions should have a chest x-ray, cardiac ECHO and EKG. Abnormalities on chest x- ray include enlarged heart, bronchitis, or aspiration pneumonia, absence of the 12th rib, and a shortened trachea (up to 36% of patients have less than the normal 17 tracheal rings).[164] Important also is the need to recognize associated cervical spine abnormalities. Magnetic resonance imaging (MRI) evaluation of the CNS is necessary to rule out other associated lesions and determine the need for a preoperative shunt. Finally, renal ultrasound and a voiding cystourethrogram (VCUG) are performed to rule out reflux and obstruction.

There are many intraoperative considerations. The neonate's temperature is maintained by warming the room, using external warming devices, covering nonoperative sites with plastic, and using an in-line ETT humidifier. Latex should not be used because a large number of children (11%-73%) will at some point become allergic to it. In general, premedications are not needed. Intravenous or inhalational anesthesia is provided with great care. In general, nitrous oxide (associated with pneumocephalus), ketamine (associated with increased ICP, cerebral blood flow, and cerebral metabolic rate of oxygen consumption [$CMRO_2$]), and succinylcholine (associated with increased ICP) are avoided. The use of a muscle relaxant depends on clinical circumstances.[163-165]

The size of the head, and the location and size of the lesion can affect patient positioning and the ability to intubate the trachea (Fig. 29-9). In these cases, consideration should be given to intubation in the lateral position. After successful intubation, the child is positioned. Neonates with hydrocephalus are usually supine whereas those with spinal cord anomalies are usually placed prone in the "sea lion" position. When the infant is prone, it is important to adequately pad the chest and abdomen to allow for adequate chest expansion.[163] The neck should be kept in the neutral position to avoid interference with intracranial venous drainage and compression of the brainstem. Securing the ETT, IV access, and all monitoring devices are of utmost importance because it is difficult to correct a problem in the prone baby after draping.

Intraoperative complications include bleeding, air embolus, and acute changes in ICP.[164-166] Air embolus is the result of air entering the venous system and occurs when the head is above the heart. Signs of air embolus include murmur, a decrease in $ETCO_2$ and an increase in end-tidal nitrogen. Treatment includes submerging the operative field in saline, stopping nitrous oxide, and putting the head lower than the heart. Acute changes in ICP (rapid draining of CSF, endoscopy, irrigation, etc.) can lead to acute changes in blood pressure, arrhythmias, and cardiac arrest.

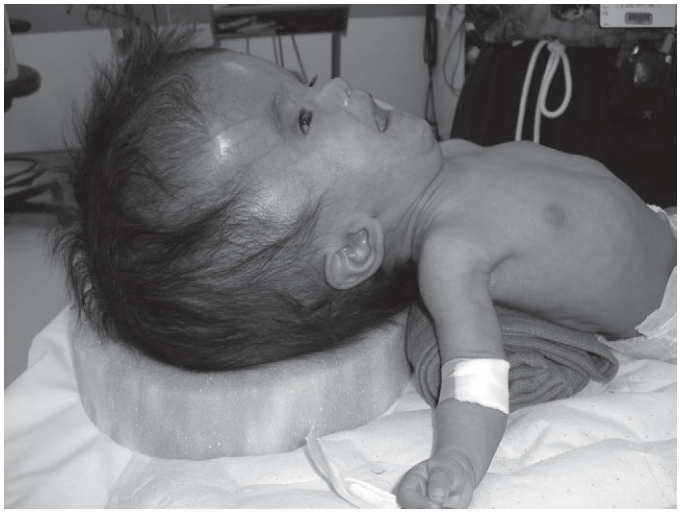


Figure 29-9 ■ Newborn with congenital hydrocephalus. A "ramp" under the head and shoulders is used to improve visualization of the airway.

Thoracic Surgery

Thoracoscopy Versus Thoracotomy

The intraoperative care of an infant undergoing a thoracic procedure is similar to one undergoing a major abdominal operation. In addition to the previously discussed concerns, opening the chest cavity and compressing the lung will lead to major inequalities in ventilation and perfusion. Second, blood should be available for transfusion before the chest is opened because hemorrhage can be sudden and massive. Third, the ETT may be frequently obstructed by blood and secretions requiring frequent suctioning. Finally, preoperative placement of a caudal epidural catheter should be considered because it provides optimum postoperative pain control and facilitates extubation.

The concerns about thoracoscopy are very similar to laparoscopy. Briefly, care must be taken in placing the initial insufflation port. The pressure limit should be between 4 and 6 mm Hg and the flow should be low.[171] Finally, the patient is at risk for hypoxia, hypercapnia, and CO_2 embolization.

Preoperative Concerns

The anesthetic approach to a neonate with a congenial thoracic lesion requires careful consideration. Many of these babies have other associated anomalies that must be identified. Neonatal thoracic procedures can be performed via thoracotomy or thoracoscopy. These procedures include repair of tracheoesophageal fistula with/without esophageal atresia (EA), congenital diaphragmatic hernia, resection of congenital lung lesions (congenital cystic adenomatoid malformation [CCAM]), congenial lobar emphysema (CLE), sequestrations, and bronchogenic cysts (Fig. 29-10), and ligation of patent ductus arteriosus (PDA).[166,167] In addition, some of these lesions will require other intraoperative procedures to be performed, including intraoperative bronchoscopy and one lung ventilation.[168-170] Finally, some of these lesions are best managed with the baby spontaneously breathing. The anesthesiologist must consider these points preoperatively and be prepared to manage the airway accordingly.

Congenital thoracic lesions are usually associated with other congenital anomalies. The classic example is the association of tracheoesophageal fistula(TEF) and esophageal atresia with vertebral, anal, cardiac, renal, and limb anomalies (VACTERL association),[171] but there are many others. Infants with congenital heart disease have a 10% incidence of congenital tracheal anomalies whereas those with congenial diaphragmatic hernia have up to a 50% incidence of associated congenital heart disease.[170] Infants with CLE have a 15% chance of having cardiac anomalies.[171] Preoperative evaluation is aimed at identifying these associated lesions, their accompanying potential complications, and potential impact on the proposed operation.

Intraoperative Management

Airway management during a neonatal thoracic procedure is challenging. The timing (preoperative versus intraoperative), route (nasal versus oral), and method (spontaneous versus mechanical) of ventilation and the need for paralysis needs to be discussed and coordinated with the pediatric surgeon. The patient is small, and positioning can limit access to the airway once the procedure starts. Therefore, the ETT, monitors, and vascular access devices must be properly secured and accessible away from the sterile field. The ipsilateral lung is going to be either retracted (during thoracotomy), compressed (during thoracoscopy), or deflated (during one-lung ventilation) resulting in physiologic changes that must be anticipated, monitored, and corrected. Finally, multiple emergency plans for airway management must be made and discussed preoperatively.

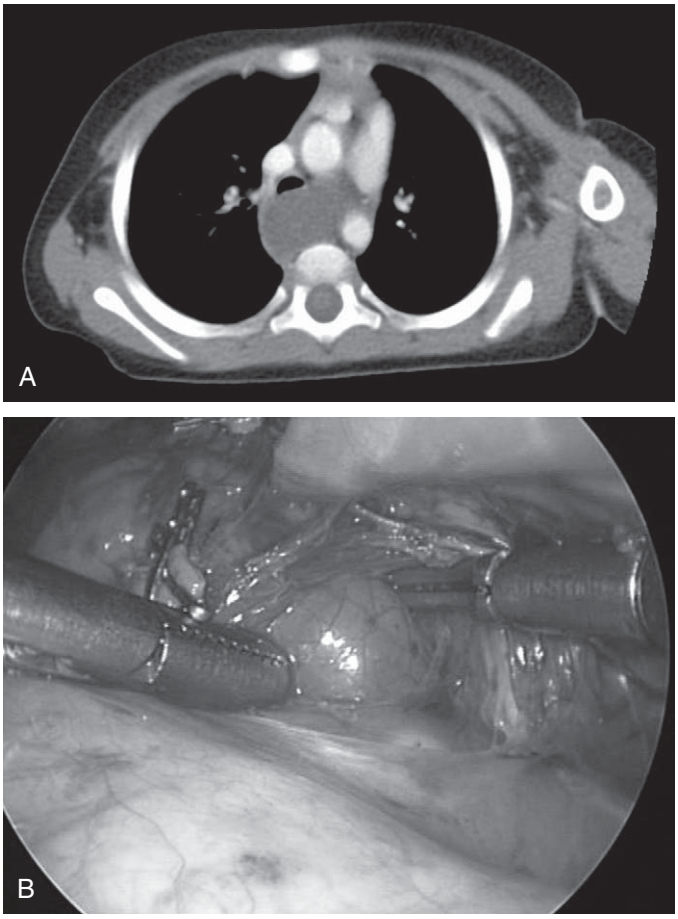


Figure 29-10 ■ **A,** CT scan of a bronchogenic cyst. The cyst is compressing the posterior trachea. **B,** Thoracoscopic resection of a retrotracheal bronchogenic cyst.

One-lung ventilation in the neonate can be accomplished by using a bronchial blocker or more commonly, contralateral, bronchial intubation.[172] In the neonate, there are really only two options for a bronchial blocker; the Fogarty catheter or the Arndt endobronchial blocker.[173] There are several important differences between these two catheters. The Fogarty catheter, although smaller (2 or 3 French), does not have a central lumen. The smallest Arndt catheter is much larger (5 French) but does have a central lumen that can be used to deflate the lung on the operative side, suction secretions, infuse oxygen, and provide continuous positive airway pressure (CPAP). Either catheter can be placed either inside or outside the ETT.[170,171,174]

Placement of a bronchial blocker can be accomplished several different ways. In most instances, the size of the blocker necessitates placement outside the ETT. Placing the blocker outside the ETT can be accomplished in two ways.[170,171,174] Using direct laryngoscopy, the blocker is placed within the trachea and then the trachea is intubated with an ETT. The blocker is then guided into position using bronchoscopy and the balloon is inflated. Alternatively, the contralateral, mainstem bronchus is intubated with an ETT, and the blocker is placed through the ETT. The ETT is then withdrawn and the trachea reintubated with a new ETT. Bronchoscopy is then performed to document correct placement of the blocker and the balloon is inflated. To place the blocker through the ETT, this last step is omitted.

There are several concerns associated with the use of bronchial blockers.[171] Placing the blocker through the ETT effectively decreases the airway available for gas exchange, thereby increasing airway pressure, decreasing minute ventilation and oxygenation. Also, the balloon on the end of the blocker may rupture leading to sudden ventilation of the lung on the operative side. Finally, the blocker may become dislodged from the bronchus and fall or get pulled back into the trachea leading to complete airway obstruction. The first clinical signs of blocker dislodgment include a decrease in the breath sounds over the contralateral lung and an increase in the ventilation of the ipsilateral lung. Therefore, the surgeon may be the first to notice the problem and he/she should notify the anesthesiologist of the increased ventilation of the ipsilateral lung. If the balloon blocker falls into and obstructs the trachea, a loss of $ETCO_2$, hypoxia, and an increase in airway pressure occur. Management depends on the acuity of the situation and timing of the dislocation in relation to the surgical procedure. If the baby is clinically stable and the dislodgement occurs early in the procedure, the blocker may be repositioned using the bronchoscope. If the blocker is dislodged near the end of the procedure or causes clinical instability, the blocker is deflated, ventilation and oxygenation reestablished, and the blocker removed or replaced. It has been suggested that using fluid instead of air to fill the blocker may decrease the incidence of blocker migration.

Intraoperative Concerns

Neonatal thoracic lesions can be divided into those that connect to the airway (TEF, CLE) and those that do not (CCAM, sequestration, bronchogenic cyst, patent ductus arteriosus).[171,172] Recognizing this difference is important because positive pressure ventilation can adversely affect infants with lesions that connect to the airway. In general, neonates with lesions that connect to the airway should be allowed to breathe spontaneously until the lesion (the fistula or emphysematous lung) is controlled. Alternatively, those infants with lesions that do not connect to the lung will tolerate positive pressure ventilation.

The airway management of neonates with CLE and TEF has similar overlying principles. First, they should be allowed to breathe spontaneously as long as safely possible or until the fistula is ligated (TEF/EA) or the chest opened (CLE). Induction of anesthesia can be either IV or inhalation. Lidocaine or propofol are given prior to induction to blunt the autonomic effects of intubation. Once intubated, every attempt is made to allow the child to continue breathing spontaneously. Second, an organized, well-planned, multistep approach to airway management and lesion control is made preoperatively and discussed. Finally, the surgeon needs to be present in the operating room during intubation.

Infants with CLE have respiratory difficult resulting from expansion of abnormal lobe(s). This abnormal lung displaces the mediastinum and normal lung resulting in both hemodynamic and respiratory compromise. Intraoperative maneuvers to avoid or decrease this effect include maintenance of spontaneous ventilation,[174] contralateral mainstem bronchial intubation, and/or use of an ipsilateral bronchial blocker. If these maneuvers fail to control the situation, the surgeon should be prepared to open the chest emergently and deliver the offending lobe(s). In rare cases of bilateral CLE, the same principles are followed and the choice of surgical incisions expanded to include a clam-shell incision.[169-175]

Infants with TEF and esophageal atresia have respiratory difficult related to loss of tidal volume through the fistula and into the stomach. The stomach may then become distended displacing the diaphragm cephalad, decreasing the TV. This effect is most pronounced in neonates with concomitant duodenal atresia (Fig. 29-11).

The majority of neonates with TEF/EA that are brought to the operating room not intubated are induced with an intravenous or inhalation agent, given a muscle relaxant, and intubated.[176,177] The tube is then advanced until breath

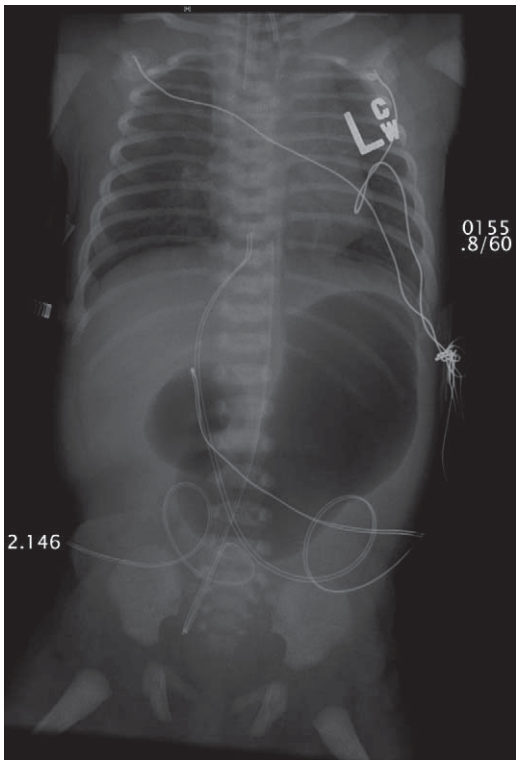


Figure 29-11 ■ Babygram of a newborn with proximal esophageal atresia, distal tracheoesophageal fistula, and duodenal atresia. Positive pressure ventilation will continue to dilate the stomach leading to cephalad displacement, gastric reflux, and aspiration of gastric contents.

sounds are lost on one side and then the ETT is slowly pulled back until bilateral breath sounds return. The tube is then rotated, positioning the bevel anteriorly, to direct ventilation away from the fistula. The ETT is secured, the baby positioned in the right lateral decubitus position, and bilateral breath sounds are confirmed again. The fistula is then ligated and the atresia repaired via either thoracotomy or thoracoscopy.

Bronchoscopy may be performed prior to intubation. The benefits of bronchoscopy include the demonstration of vocal cord function, presence of associated laryngeal cleft, presence of multiple fistula, defining the level and size of the fistula, assisting in fistula control by placement of a Fogarty catheter and for purposes of placing an ipsilateral bronchial blocker. If the fistula is large by visualization or as demonstrated by difficulty in ventilation, a 2 or 3 French Fogarty catheter can be placed through the fistula and into the distal esophagus. The purpose is to prevent loss of tidal volume into the stomach. The balloon is then insufflated, the tube placed on traction, and taped to the ETT.[168-174]

The fistula can also be controlled through the abdomen. The fistula can be occluded by placing a 2 or 3 French Fogarty catheter retrograde through the stomach and into the distal esophagus.[172] Alternatively, the esophagus can be ligated at the gastroesophageal junction. Finally, a gastrostomy tube can be placed in the stomach and connected to water seal. The water chamber is then filled with just enough water to stop the chamber from bubbling during inspiration. This latter procedure is especially useful in emergency situations when the TEF is associated with duodenal atresia.

Special Situations

OOPS and EXIT Procedures

Two methods have been described that allow surgical procedures to be performed on a fetus outside the uterus before clamping the umbilical cord. The first method described was "operation on placental support" or the OOPS procedure.[178] This procedure described infants, born vaginally or via cesarean section whose airways were evaluated and/or treated with the umbilical cord intact. Subsequently, the EXIT procedure (ex utero intrapartum treatment) was described.[180] This procedure, initially developed to remove the tracheal clip placed in utero to treat congenital diaphragmatic hernia, has since been expanded to treat other fetal conditions.[180-188]

Current indications for the EXIT procedure (in descending order of frequency) include reversal of tracheal occlusion, neck masses (Fig. 29-12), lung masses, mediastinal masses, a bridge to ECMO, conjoined twin separation, and congenital high airway obstructions (CHAOS; tracheal atresia and laryngeal atresia).

The combined incidence of congenital problems requiring the EXIT procedure is extremely low, but these lesions require a specialized team and set of resources.[180,182,187] The team should consist of at least the following: two pediatric surgeons, one otolaryngologist, one maternal fetal medicine physician, one obstetrician, one neonatologist, two anesthesiologists (one for the mother and one for the baby), an ECHO technician, and two scrub technicians. Resources include standard surgical instruments for performing a cesarean section, major and minor neonatal neck trays, and neonatal airway (laryngoscopy, bronchoscopy, tracheostomy) equipment. In addition, Miller 0 and 00 blades, armored ETTs, ETT changers, surfactant, 2.5 and 3.0 French feeding tubes, 2.5 and 3.0 rigid bronchoscope, a flexible bronchoscope, appropriate tracheotomy tubes, and a major neck tray are available on a separate back table.[182]

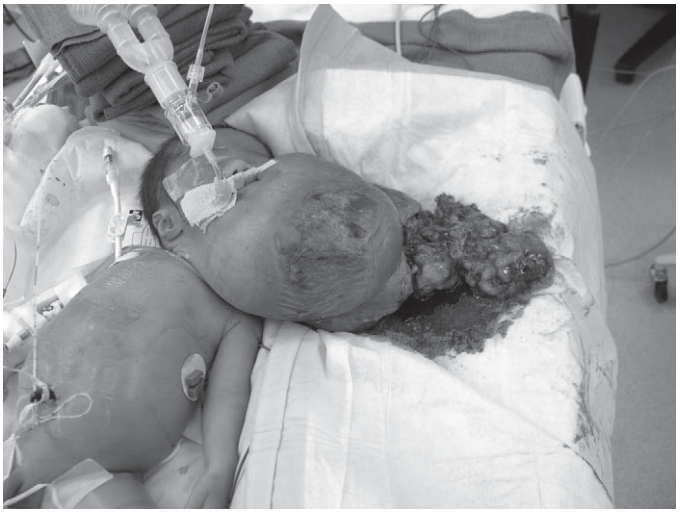


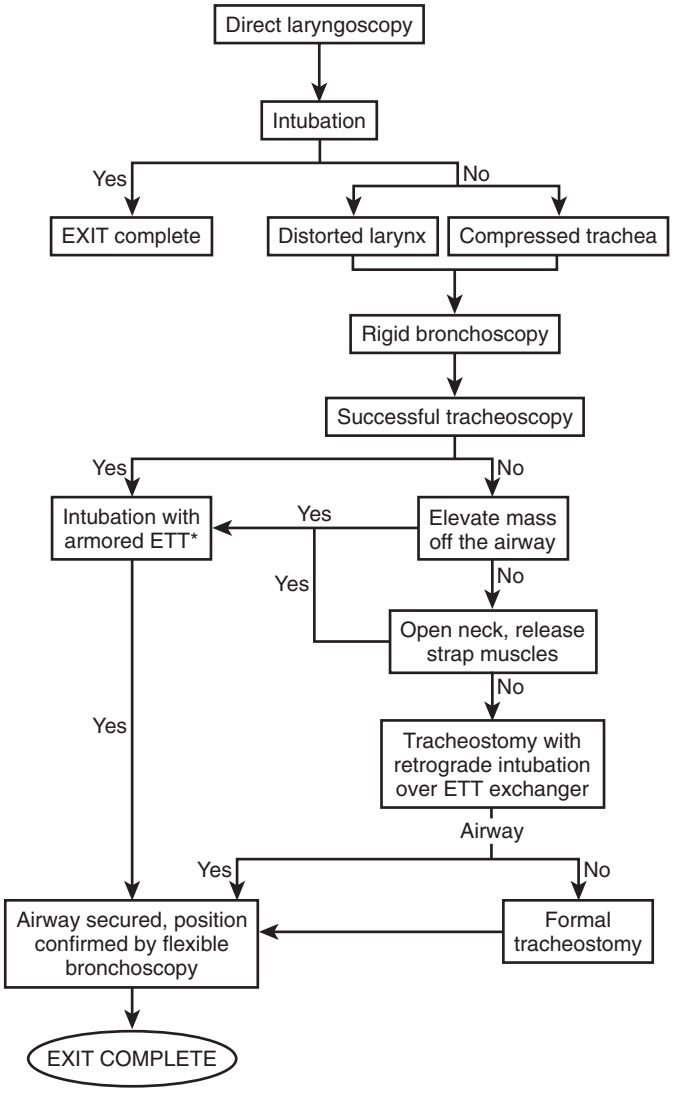
Figure 29-12 ■ Two-day-old infant boy weighing 2.7 kg, with a ruptured epignathus and airway obstruction.

There are four goals of the EXIT procedure: (1) to induce uterine hypotonia, (2) prevent abruption, (3) maintain normal maternal blood pressure, and (4) maintain fetal anesthesia.[189] The procedure has been described in detail elsewhere.[180,182,187] Prior to cesarean section, the mother is positioned with her right hip elevated, displacing the uterus off of the IVC. Rapid sequence induction is followed by a muscle relaxant and an inhalation (isoflurane, desflurane or sevoflurane) anesthetic at 0.5 MAC. This is increased to 2.0 MAC prior to incision. A tocolytic or nitroglycerin[190,191] may be given to assist in relaxing the uterus. The high level of inhalational anesthetic required to relax the uterus may lead to a decrease in maternal blood pressure. In this situation, ephedrine is used to maintain maternal blood pressure to within 10% of preoperative values.

Prior to uterine incision, the level of uterine hypotonia and location of the placenta are determined (by ultrasound). When the uterus is relaxed, the incision is placed on the uterus (low transverse, vertical, or posterior) avoiding the placenta. The fetus is partially delivered (head and shoulders) and uterine volume maintained with rapid infusion of intrauterine warm lactated ringers. The fetus is monitored with a right hand reflectance pulse oximeter, continuous echocardiography (transthoracic or transcutaneous), and a fetal $ETCO_2$ monitor.[37] Fetal oxygen saturations greater than 40% are adequate. Fetal anesthesia[192] is delivered via an intramuscular cocktail of 10 to 20 mcg/kg of fentanyl, 20 mcg/kg of atropine, and 0.2 mg/kg of vecuronium.

The algorithm for the evaluation and treatment of fetal neck masses has previously been described (Fig. 29-13). Initially, the airway is evaluated by direct laryngoscopy. If the airway cannot be adequately visualized and the fetus successfully intubated, rigid bronchoscopy is performed. If the trachea is successfully visualized, it is intubated with an armored ETT and the EXIT procedure is complete. If unsuccessful, the neck mass is manipulated and, if necessary, the strap muscles divided. If the trachea is still not visualized, retrograde tracheotomy and formal tracheotomy are the next two steps.

At the completion of the EXIT procedure and before clamping the cord, the atonic uterus is prepared for delivery. The maternal anesthetic is decreased to 0.5 MAC or discontinued. A bolus of oxytocin (20 units/500 mL) is given followed by a continuous infusion (10 units/liter). If the uterus remains atonic, additional measures include uterine massage, and IM administration of 0.25 mg Methergine and 250 mcg carboprost.



*ETT, endotracheal tube

Figure 29-13 ■ EXIT algorithm.

Maternal and fetal complications of the EXIT procedure have been reported.[180,182,187] Maternal complications are usually related to uterine atony and include bleeding, hypotension, infection, and need for hysterectomy. Fetal complications include loss of placental circulation, inability to intubate, bleeding, tension pneumothorax,[193] and death. Two large reviews of the EXIT procedure have been published. In 2003, Hedrick[194] reported the results of 43 EXIT procedures performed at The Center for Fetal Diagnosis and Treatment at the Children's Hospital of Philadelphia. The indications included neck mass (n = 19), reversal of tracheal occlusion (n = 13), CCAM (n = 5), CHAOS (n = 3), and one each of EXIT to ECMO, pulmonary agenesis, and bridge to separation of conjoined twins. The mean gestational age at EXIT was 34.5 weeks. The mean duration of the EXIT procedure was 33.8 minutes, and the long-term neonatal survival was 69.8%. Maternal complications included abruption, need for blood transfusion, and chorioamnionitis. In 2004, Hirose et al.[187] reported the results of 52 EXIT procedures performed at the Fetal Treatment Center at the University of San Francisco. The indications for EXIT included reversal of tracheal occlusion (n = 45), neck mass (n = 5), and CHAOS (n = 2). The mean gestational age at EXIT was 31.9 weeks. The mean duration of the EXIT procedure was 45 minutes, and the long-term survival was 52%. Maternal complications included infection and excessive blood loss (compared to standard cesarian section cases). Importantly, neither study reported maternal death nor need for hysterectomy.

Conjoined Twins

Conjoined twins occur once in every 50,000 to 100,000 births.[195] Eighteen percent die in utero, 54% are stillborn or die shortly after birth, leaving only 18% to survive the perinatal period. Interestingly, female survivors predominate 3 : 1.

The developmental embryology of this curious condition is unclear. A classification system has been developed based on where the infants are joined (ventrally [87%] or dorsally [18%])[196] and is based on the point of fixation. Conjoined twins are named based on the point of union (the prefix) followed by "-pagus" (suffix), which means fixed. The name and incidence of each are thoracopagus (40%-45%), omphalopagus (33%), pygopagus (19%), ischiopagus (6%), and craniopagus (2%). The diagnosis can be made in utero and portends a worse prognosis. If the lungs are mature, elective C-section between 36 and 38 weeks' gestation is the desired method of delivery.

Postnatally, twins are evaluated radiologically to determine shared organs, rule out associated anomalies, and assist in planning separation. Elective separation is desirable and is best done between 4 and 11 months of age. Indications for emergency separation include damage to the connecting bridge of tissue, when one twin threatens the other, clinical deterioration of both twins, and if a condition in one twin is incompatible with life and the other has a reasonable chance of survival.[197]

The anesthetic management of conjoined twins has previously been described.[185] Two anesthetic teams are required, one for each child. Preoperatively, one to two blood volumes of packed red blood cells are ordered and the need for cardiopulmonary bypass discussed. Drug dosages and IV fluids are calculated based on total body

weight of the twins with ½ dose given to each baby. Depending on the site of fixation, intubation may be easier with the twins on their sides and is done one baby at a time. Induction is inhalational or ketamine with local anesthetic sprayed on the vocal cords. Importantly, muscle relaxants are not given until both airways are secured. Reinforced ETTs are useful, especially for thoracopagus twins. Finally, organs are assigned equally, unless one twin is felt to be nonviable.

Survival depends on the age at operation, urgency of separation, and the point of fixation. Operative survival is improved if the separation is done at more than 4 months of age (90%) versus less than 1 month of age (50%). Compared to elective separation (17%-20%), twins separated emergently also have a higher mortality (71%-91%). The mortality rates associated with each type of twin are as follows: thoracopagus (51%), craniopagus (48%), omphalopagus (32%), ischiopagus (19%), pygopagus (23%).[198]

Conclusions

Pediatric surgeons, neonatologists, and anesthesiologists provide intraoperative care to a diverse group of neonates. Despite this diversity, many management principles remain the same. The preoperative consultation should define the scope of the procedure, the surgical approach (open or laparoscopic), and identify associated diseases that may affect intraoperative management. At operation, the American Society of Anesthesiology (ASA) guidelines for monitoring and management are followed.[199] Finally, the induction and maintenance of anesthesia (IV or inhalation), route of intubation (nasal or oral) and method of ventilation (spontaneously or mechanical), are determined. Following standard intraoperative management principles and working together as a health care team, remarkable advances have been made in the successful treatment and survival of many infants with surgical conditions that even a few years ago were not amenable to therapy.

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30 Neonatal Ventilator Care in Resource-Limited Countries

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The first chapter in this book describes the historical background of the development of neonatal ventilation in the Western world. Despite rapid growth in the United States and other developed countries, neonatal intensive care units (NICUs) have evolved more slowly in resource-limited countries during the last quarter of the twentieth century. Multiple factors such as poor economy, lack of skilled personnel, and lack of equipment have been responsible for the delayed progress. Furthermore, countries with high infant and neonatal mortality rates have rightfully focused more on prevention of common public health issues than on establishing expensive NICUs with ventilator care facilities. However, in recent years, globalization has increased access to new medical knowledge and technology for many developing countries.[1] The twenty-first century will see rapid progression of neonatal ventilator care support in neonatal units around the world, although progress may be uneven.

In this chapter we review the current status of NICUs in resource-limited countries, barriers to development of ventilatory support programs, and possible strategies to overcome these barriers to the development of a functional NICU with respiratory support appropriate for the level of care.

Scope of the Need

High infant mortality rates (IMR) and neonatal mortality rates (NMR) constitute major health problems in resource-limited countries. Over four million newborns die every year, with most (98%) of the deaths occurring in the developing world. Birth asphyxia, low birth weight, prematurity, and sepsis-related problems are the major causes of death. Newborn resuscitation has been estimated to reduce neonatal mortality and morbidity by 6% to 42%.[2] However, after newborn resuscitation, some newborns may require continuous positive airway pressure (CPAP) or assisted ventilation. An estimated 21% of babies presenting with illness in the first 6 days of life have respiratory symptoms that may require respiratory support, indicating the need for neonatal programs equipped with proper ventilator support in these countries.[3] It is recommended that health facilities in rural areas should be equipped with minimal respiratory care tools for resuscitation such as bag and mask and oxygen. The higher-level care hospitals should have the capabilities of CPAP and short periods of mechanical ventilation. To provide CPAP and assisted ventilation, the health facilities have to be staffed by well-trained medical and nursing personnel.

The information about level III and II units in resource-limited countries is scanty. As expected, these countries have the highest infant and neonatal mortality rates, and therefore they have the greatest needs. For example, countries with NMR as high as 40 to 100/1000 (such as India) and countries with deliveries in the magnitude of 20 to 25 million births/year (such as China and India) would require hundreds of level III and perhaps thousands of level II NICUs. It is estimated that in India, a country of approximately 1.1 billion people, one level III NICU with 30 beds is required for every 1 million population.[4] It is expected that there will be additional level II health facilities within the same region. Ideally, to be effective there should be a coordinated regional perinatal program that is responsible for coordination of the clinical activities, education, resource use, and development of best practices.

Limiting Factors

Major barriers to developing regional programs include the limited availability of equipment, properly trained staff, infrastructure support, and the absence of coordinated systems. Health facilities in many developing countries do not meet the basic needs of newborn care. Yet ironically, some of these countries are beginning to open level III units in their district hospitals.[5] A survey of hospitals in India at subdistrict and district levels found that the equipment in the neonatal nurseries was inadequate (Table 30-1). Most district hospitals were equipped with oxygen and suction; however, resuscitation bags and radiant warmers were present in less than half of the hospitals, and oxygen hoods were available in only a small fraction of the district hospitals. In the subdistrict hospitals, resuscitation bags were available in only 20% of hospitals and oxygen hoods were in scarce supply. The primary health centers (PHCs), each of which serve a population of 10,000 to 15,000 and provide basic maternity services, had practically no equipment. These findings show large gaps in the care of the newborn in India but are representative of deficiencies on a global scale. There is an urgent need to

TABLE 30-1 **Survey of Pediatricians and Obstetricians at Health Facilities in Orissa, India, on the Availability of Neonatal Equipment (1997)**

	RESPONDENTS		
Equipment	**District Level Hospital Specialists* (*n* = 33)**	**Subdistrict Level Hospital Specialists† (*n* = 50)**	**Primary Health Center Physicians (*n* = 8)**
Resuscitation bag	13 (39%)	10 (20%)	2 (25%)
Oxygen	32 (96%)	31 (62%)	2 (25%)
Radiant warmer	14 (42%)	8 (16%)	2 (25%)
Mucus sucker	29 (87%)	36 (72%)	4 (50%)
Weighing scale	25 (75%)	37 (74%)	4 (50%)
Phototherapy units	2 (6%)	1 (2%)	0
Oxygen head boxes	6 (18%)	1 (2%)	0

*Includes district hospitals and postpartum centers.
†Includes community health centers, subdivisional hospitals, and upgraded primary health centers.
From Paul VK, Ramani AV: Newborn care at peripheral health care facilities. Indian J Pediatr 67(5):378-382, 2000.

improve these deficiencies to meet the targets set by the Millennium Development Goals[6] effectively by the year 2015. Even though some developing countries initiated neonatal ventilation in the late 1980s, in many resource-limited countries, it is still a novelty. There are several barriers to developing respiratory care services at all levels in these countries.[7] These are described below.

Infrastructure

Physical infrastructure for providing intensive care in an organized fashion is lacking. The hospitals do not have properly designed ICUs for adults, much less for newborns. Even in district and teaching hospitals, the space for the management of high-risk infants is arbitrarily allocated and may lack the basic requirements of running water, a consistent supply of electricity, and controlled environment. There are also problems with maintaining a consistent supply of oxygen and/or compressed air. Some units depend on cylinders for air and oxygen. Maintenance of equipment is irregular at the best hospitals and nonexistent in most units. There are essentially no policies or guidelines either for clinical care or maintenance of equipment.

Skilled Health Care Personnel

Usually there is a shortage of skilled medical and nursing staff in resource-limited countries. The training of nursing staff is quite variable in each country. Training of nurses in neonatal skills is often nonexistent. Very few medical and nursing staff working in teaching hospitals are trained in providing ventilator care. These limitations put constraints on patient care. Physicians have to assume many responsibilities for which they are ill equipped, such as care of the ventilator. Most general pediatricians are not familiar with ventilator care. A few are able to manage mild cases of respiratory distress with oxygen. For the most part, physicians are not trained to provide CPAP, endotracheal tube placement, or ventilation. Most NICUs are managed by general pediatricians who have a special interest or have had previous experience abroad during their training period. Adhikari[8] reports that in many hospitals in South Africa, it is the pediatrician with special training or a qualified neonatologist who provides the respiratory care in level II and level III units. The pediatricians are proficient in providing nasal or endotracheal CPAP and full ventilator care. In all level II units surveyed, nurses were trained to provide oxygen therapy and nasal CPAP and were proficient in managing infants on assisted ventilation. This is quite unique and encouraging. Nurses and pediatricians in other developing countries do not have similar degrees of training and proficiency in managing neonatal respiratory support.

Developing countries also face shortages of doctors and nursing staff because of widespread emigration of skilled health care personnel to the developed world because of better economic opportunities and professional satisfaction, known euphemistically as the "Brain Drain."[9] Innovative programs are needed to retain skilled manpower in resource-limited countries.

Support Facilities and Equipment

Ancillary services such as blood gas machines and microchemistry laboratories are critical to managing infants in respiratory distress. A portable radiology machine is also required for proper diagnosis but is rarely available. Laboratory facilities are not usually available in most of the government hospitals. The availability of pulse oxygen saturation monitors, which are relatively simple to operate, has greatly facilitated monitoring both heart rate and oxygenation. However, these monitors are not available in most of the resource-limited NICUs.

Current Status

During the last quarter of the twentieth century, many developing countries saw the need for establishing NICUs with the capabilities of providing respiratory care. Despite many constraints, some areas have successfully developed NICUs of international caliber. Their reported neonatal outcomes are comparable to outcomes in the developed world. These unique programs were developed mainly through the efforts of committed individuals and concerted effort of professional organizations in the reference country. NICU development was complemented by the phenomenon of "globalization and diffusion of technology" during the last three decades.[1] The evolution of neonatal intensive care and specifically ventilatory care are described below in a few select regions of the world.

China

According to Wei,[10] the first children's intensive care program in China was established by the Ministry of Health of China and the United Nations Children's Fund (UNICEF) in 1983. UNICEF facilitated exchange of faculty from the United States to interact with the leadership of neonatologists in China. Since the development of NICUs in the early 1980s, the infant mortality and morbidity rates in China have declined steadily. However, the incidence of

low-birth-weight (LBW) infants is reported to have increased from 4% to 6% in the 1990s to 10.2% in 2002 (this may be a reporting phenomenon because medical care now is given to more of these infants). This group of infants constitutes most of the NICU admissions at all medical centers. Continuing advances in neonatal intensive care, especially the introduction of mechanical ventilation and surfactant administration, have increased the survival of preterm infants in China. The diagnoses of neonatal respiratory illness, including birth asphyxia, pneumonia, and meconium aspiration syndrome (MAS), accounted for 17.1%, 42.6%, and 3.6% admissions, respectively, mainly in full-term infants. The incidence of respiratory distress syndrome (RDS), pulmonary hemorrhage, and apnea was 2.5%, 0.7%, 3.0%, respectively, seen mostly in preterm infants.

A recent publication reported on neonatal respiratory failure in China.[11] The authors surveyed 23 tertiary care NICUs regarding the incidence, management, cost, and outcome of respiratory failure treated with mechanical ventilation for 1 year (2004-2005). There were a total of 13,070 NICU admissions during this period; 1722 (13%) of babies were treated with ventilation for respiratory failure with the predominant diagnoses of RDS, pneumonia/sepsis, and MAS. In-hospital mortality of ventilated infants was 32%. The mean length of hospital stay for all infants treated with ventilation was 19.2 ± 14.6 days. The median length of stay for survivors was 70 days. Mean hospital cost per survivor was 14,966 ± 13,465 Yuans (equivalent to approximately $2138 US dollars).

The Neonatal Resuscitation Program (NRP) was introduced into China in the 1990s. Since then, the mortality rate from neonatal asphyxia has decreased, from 3.32% in 2003 to 2.15% in 2004. Babies requiring further care are usually transferred to level III hospitals to get additional treatment.

The levels of care in the NICUs differ across the country. Nasal CPAP is most often used earlier in babies with RDS or spontaneously breathing premature infants when oxygen requirements are less than 50%. CPAP is also used for weaning infants from ventilators and in preterm babies with recurrent apnea. Limited data are available regarding the best ways to use CPAP in the country. It is now common practice to intubate and ventilate as an elective procedure in the early stage of most forms of severe neonatal respiratory disease. Synchronized intermittent mandatory ventilation (SIMV) is one of the most widely used modalities of respiratory support. Li and Wei[12] showed that the use of pulmonary mechanics measurement was helpful in guiding the use of ventilator adjustment and decreased the ventilator-associated lung injury in neonatal RDS. High-frequency oscillation ventilation (HFOV) and high-frequency jet ventilation (HFJV) are used in only a few units when infants with respiratory failure do not respond to conventional ventilation. No randomized, controlled studies of HFV versus conventional ventilation are available from China.

With increasing use of ventilatory support in premature infants and increasing survival, the incidence of chronic lung disease (CLD) in China is increasing.[12] A survey of 64 urban hospitals in 16 provinces reported the rate of prematurity has increased from 4.6% to 10% from 1990 to 2002. There is also increasing survival of LBW and premature infants during this period. Survival of infants with a birth weight of less than 750 g is very uncommon. Concurrently, there has been an increase in CLD during this period. In view of increasing CLD and concerns of pulmonary oxygen toxicity, the government of China has developed guidelines for oxygen therapy in the neonatal period. These guidelines call for strict indications for the use of oxygen and using the lowest supplemental FIO_2 to maintain oxygenation saturation between 90% and 95% with pulse oximetry.

As in the United States, preterm infants less than 32 weeks' gestational age should be followed with careful ophthalmic examination after oxygen therapy. Hospitals without equipment for monitoring oxygen concentration should transfer infants to a large medical center after stabilization. Overall, there is a need for the development of standard protocols for the general management of neonatal ventilation and to develop national research networks to track changes in morbidity and mortality. There has been very limited follow-up (either neurodevelopment or pulmonary) of ventilated infants.

India

The development of neonatal intensive care in India has been slow because of constraints[13] such as availability of required technology and skilled personnel. Economic constraints prevent the development of expensive high-technology NICUs in the country. Faced with high IMR and NMR (43/1000), policymakers thought it prudent, and rightfully so, to invest in improving overall health rather than in high-technology medicine. The concept of providing good care to premature infants and LBW infants was well in place as early as the 1950s. However, these units were designed to provide essentially level II care for LBW and premature infants. Respiratory support was limited to providing oxygen in addition to providing incubator care and intravenous (IV) fluids. It was not until the mid 1970s and early 1980s that NICUs in India began to provide ventilator care.

A major impetus to the nationwide growth of neonatal intensive care and therefore neonatal ventilation in India came from the professional organization, National Neonatology Forum (NNF) of India, which was established in 1980.[14] NNF formulated several strategies to improve the care of newborn health at all levels of the health care delivery system. It focused on developing policy guidelines and standardization of care, designation of levels of care, and an accreditation process for neonatal and perinatal care in the country. The NNF developed guidelines for bedside monitoring, equipment use, and assisted ventilation. The organization also placed a great emphasis on the education and training of pediatricians and nurses. In 1987 a national survey by NNF of 28 neonatal units showed very disturbing findings.[15] Many units did not have basic resuscitation equipment. But a later survey of 37 units in 1994 to 1995 showed marked improvement.[13] The impacts of these efforts are becoming increasingly clear today. The survival rates of ventilated babies has improved over time. In 1997 it was noted that half of the units surveyed reported 50% to 70% survival of ventilated neonates.[13] The first surfactant administration in India was given in 1987 at All India

TABLE 30-2 **Neonatal Survival Rates in Different Birth Weight Categories in 1990, 1995, and 2002-2003 at the All India Institute of Medical Sciences, New Delhi***

Birth Weight (g)	1990 *N* = 444 (%)	1995 *N* = 1672 (%)	NNPD 2002-2003
<750	0	0	23.1
750-999	50	73.3	45.9
1000-1249	36.4	77.8	65.7
1250-1499	53.8	95.5	79.0
1500-1749	94.2	85.3	87.5
1750-1999	97.9	96.2	93.9
2000-2499	97.6	98.4	97.6
2500-2999	99.9	99.3	98.7
3000-3999	99.9	100	98.9
4000 or more	93.4	100	98.9

*To be successful, the program requires ongoing commitment from administration and health care staff.
NNPD, National Neonatal-Perinatal Database.

Institute of Medical Sciences. In 2002 NNF again surveyed 27 level III units and published their outcomes.[16]

Over the past two decades, several neonatal units providing complete care with ventilatory capabilities have evolved all over the country, primarily in private settings. The results in these units are comparable to Western units at almost all birth weight groups (Table 30-2). These units are managed by highly qualified medical and nursing personnel. Narang et al.[17] have shown encouraging results after establishing NICUs with ventilator support at their respective institutions in India as described above.

The progress in neonatal ventilation can be indirectly assessed by the number of ventilators purchased in the country. The data provided by MarketStrat, Inc.,[18] a company that analyzes such global information, shows that the number of ventilator purchases in India has been increasing at a steady rate of 3% to 4% per year. This is somewhat higher than the rate of ventilator growth projected in China (2%-3%/year). Based on the number of births (25 million/year), high rates of birth asphyxia, low birth weight, and prematurely born infants (estimated 7% of births or 1.75 million/year), there is a greater need for further development of NICUs across the country.

Nevertheless, ventilator care is labor intensive and expensive. It requires not just the ventilators but also well-trained medical and nursing staff available at all times; both commodities are in short supply. Regionalization of perinatal care and development of specialized neonatal care units at designated centers is appropriate. In vivo economic constrains, low cost, and innovative methods to provide respiratory support short of mechanical ventilation at subdistrict and district hospitals should also be considered.[19]

The conditions described above reflect the conditions in government hospitals. They are the main health facilities accessible to the public in resource-poor countries. Government hospitals usually are ill equipped even for basic needs. In recent decades, there has been a growing trend of opening private hospitals, which are well equipped and are capable of providing the full scope of neonatal ventilator care. Since 1990, several private hospitals have developed well equipped units that meet Western standards of level III NICUs in India. China and other countries are also seeing similar phenomena. Most units meet all the international standards in space, equipment, and skilled medical and nursing staff. A few of these hospitals in the developing countries have been accredited by The Joint Commission (TJC).[20] The high cost of care in these hospitals precludes access by the majority of the country's population.

Other Countries

Bhutta et al.[21] reported an encouraging experience in Pakistan. The provision of ventilatory support to infants with RDS in this developing country resulted in increased survival specifically in infants weighing more than 1000 g. The authors concluded that despite limited resources at the national level, neonatal intensive care and respiratory care can be developed in selected hospitals to successfully manage neonates with RDS. Ho and Chang[22] reported the development and outcomes of a neonatal nursery in Malaysia. They reported that the first NICU was established in 1987 with six ventilators; this unit was expanded in 1993. They analyzed the outcome data from 1993 to 2003. During this period the NICU evolved into a full-fledged unit with respiratory support, electronic monitoring, and facilities for intravascular infusion of fluids. There was a significant increase in survival in the second cohort (2003). The survival of infants weighing less than 1500 g improved from 69% in year 1993 to 81% in year 2003; among ventilated babies survival improved from 53% to 93% during the 10-year study period. Interestingly there was no significant improvement in nonventilated babies, suggesting neonatal ventilation significantly contributed to increased survival among very-low-birth-weight (VLBW) infants. The authors conclude that in spite of inherent barriers to change in a developing country, it is possible to implement ventilatory care and evidence-based medical practices.

The neonatal care practices in Indonesia are slowly evolving, according to Haksari.[23] There is a wide gap in standard neonatal care given between rural and urban areas. Only a few hospitals in large cities have NICUs that provide neonatal ventilator care. Some of these units operate in conjunction with pediatric ICUs for economic reasons. Some hospital ICUs have three-in-one ventilators, which can be used for neonates, children, and adults. There are plans for all teaching hospitals to develop level III NICUs with special equipment for neonates. The Ministry of Health of the Republic of Indonesia encourages all 33 district hospitals and 11 provincial and teaching hospitals to have CPAP devices, which are useful, cheaper, and simpler than ventilators. Major teaching hospitals have developed levels II and III neonatal care units. Teaching hospitals provide CPAP, ventilator care, pulse oximetry, bedside monitoring, and mobile x-ray machines, incubators, radiant warmers, and blood gas analysis capability. They also provide training for both physician and nurses. The lack of availability of repair services and the spare parts needed for equipment repair are often major problems. Respiratory care for the newborns in South Africa is well developed. Adhikari[8] provided survey results of eight hospitals in her state; two were level III units and six were level II. Compared to the other regions described above, these units were well equipped and well staffed with skilled nursing and medical personnel.

Latin America has high IMR and NMR with significant disparities among the countries. In some Latin American countries, the IMR ranges from 9 to 13/1000 births, whereas other countries report IMR as high as 50 to 70/1000 births. Similar to other countries in the world, the major cause of neonatal mortality is respiratory diseases. Most newborns die within days after birth, mostly from inadequate resuscitation at birth and lack of respiratory support after admission to the ward. Argentina reports that 70% of neonates die less than 48 hours after birth in public hospitals. The majority of these deaths could be prevented with development of facilities that provide adequate resuscitation and respiratory support. As far back as 1980, Ventura-Junca et al. in Chile showed the effectiveness of NICU care in reducing neonatal mortality in South America.[24,25] However, such facilities are available mainly in private hospitals.

Developing Ventilatory Care Services

There is a great interest among pediatricians and neonatologists in developing countries in regard to establishing ventilator care for critically ill newborns. This enthusiasm is based on their genuine interest in saving many more babies. However, establishing a ventilator care unit is a major commitment of funds, resources, personnel, and time that would have to be diverted away from other health care needs. A one-time capital investment for the purchase of equipment would seem reasonable. However, it should be understood that establishing a ventilatory care unit requires a ventilator program that includes equipment, care, and maintenance of the equipment, ability to obtain replacement parts, ongoing professional development program for all levels of providers, full-fledged ancillary support systems (e.g., laboratory, radiology) and a regional system of referral that promotes centralized ventilator care. To be cost effective, only regional centers that serve large populations should develop ventilator support systems. Fernandez and Mondkar[4] suggest establishing one such tertiary care NICU per one million population in developing countries. These units should also develop database systems for frequent auditing, maintaining quality control, and addressing ongoing quality improvement of services provided.

Critical to the success of improving neonatal respiratory care in resource-limited countries is training of health care personnel in early recognition of and ability to manage respiratory distress. Because most of the facilities have minimal or no equipment, health care personnel must be trained in clinical skills that help identify infants at risk who require immediate respiratory support, that is, resuscitation and stabilization until the infant can be transferred to a higher level of care. Transport facilities for sick neonates requiring a higher level of care must be developed.

Strategies to Increase Trained Personnel

Worldwide there is an acute shortage of trained health care personnel, particularly in resource-poor countries.[7] Establishment of a neonatal respiratory care program requires innovative methods to overcome this problem. Sen et al.[26] describe a practical solution to overcome the shortage of trained personnel. Their model describes how a rural district hospital under the government auspices was transformed into a functioning regional center for neonatal intensive care including respiratory care by improving physical facilities and training locally available human resources (health care workers) to provide care for infants admitted to the NICU. Over a 2-year period they were able to demonstrate a significant decrease in neonatal mortality in a cost-effective manner. Many of the traditional roles of medical providers were modified in this plan. This model has come to be known as The Purolia Model. This experience may serve as a model for others contemplating improvement of their programs.

Clinical Monitoring

Monitoring of critically ill infants in resource-poor countries is based mainly on clinical observation because very few electronic monitors are available. Several investigators have adopted different methods to train health care personnel in assessing clinical hypoxemia. Bang et al.[27] has shown that lay village workers can be trained to recognize infants in respiratory distress in the community. However, no such studies have been done in the immediate neonatal period.

Downes et al.[28] published a clinical scoring system, the" RDS" score, which correlated with blood gas measurements (Table 30-3). The score consists of hourly assessment for five clinical signs: respiratory rate, grunting, color, retractions, and breath sounds on auscultation. A score of 0, 1, or 2 is assigned according to increasing severity. A zero score would indicate a normal healthy infant. The score is simple and can be learned by almost any health professional; it requires no electronic monitoring or biochemical monitoring and provides a trend of changing clinical status to initiate interventions when required. The score also correlates reasonably well with blood oxygenation.

The score was found to be helpful in assessing the prognosis when recorded in serial fashion. Infants scoring less than 4 in the first 8 hours of life were always normal by 24 hours. The score in RDS reaches its peak by 24 to 30 hours. A score of 7 or more at 12 to 24 hours correlated with severe RDS with a poor prognosis (in the absence of currently available treatment modalities), and was associated with a 50% mortality. The authors in 1970 accurately

TABLE 30-3 Clinical Respiratory Distress Scoring System

Score	0	1	2
Respiratory rate (per minute)	60	60-80	>80 or apneic episode
Cyanosis	None	In air	In 40% O_2
Retractions	None	Mild	Moderate to severe
Grunting	None	Audible with stethoscope	Audible without stethoscope
Air entry* (crying)	Clear	Delayed or decreased	Barely audible

*Air entry is checked by auscultation of chest.

From Downes JJ, Vidyasagar D, Boggs TR Jr, Morrow GM 3rd: Respiratory distress syndrome of newborn infants. I. New clinical scoring system (RDS score) with acid-base and blood-gas correlations. Clin Pediatr (Phila) 9(6):325-331, 1970.

stated, "These are the infants who may eventually require mechanically-assisted ventilation for survival, and in a general hospital could benefit from referral to a neonatal intensive care facility if safe transportation can be provided"[28]

These observations remain true even today. A modified Downes score has been adopted in several resource-poor countries including Indonesia and the Russian Federation-States.[29] In their study, investigators in Indonesia compared the Downes RDS score in infants suffering from hypoxia with pulse oximetry. They found the score had 88% specificity in predicting hypoxemia. In this study, the score showed a sensitivity of 88% (confidence interval [CI] 95%,79-99) and specificity of 81 (CI 85%, 70-91), positive predictive value of 92% (CI 95%,58-86) and negative predictive value of 92% (CI 95%,84-100). The authors concluded that the Downes score could be used to clinically evaluate hypoxemia in neonates with respiratory distress in resource-poor countries where pulse oximetry and blood gas analysis might not be available.

Equipment for Respiratory Care

The basic principles of management of an "at risk" infant include providing warmth and nutritional support. Infants in respiratory distress require oxygen to overcome hypoxemia. In addition, infants may require devices to improve oxygenation. These include oxygen hoods and devices to deliver continuous positive airway pressure (CPAP). Noninvasive transcutaneous pulse oximetry is an important tool for assessing oxygenation in infants with respiratory distress. Using pulse oximetry, Duke et al.[30] in Papua, New Guinea, found that 53% of hypoxemia occurred in neonates with acute lower respiratory infection (ALRI). In this review, neonates with hypoxemia had 3.1 times higher mortality rate. Onyango et al.[31] in Kenya reported on children younger than 3 years of age with ALRI revealing that 50% suffered hypoxemia with mortality rates 4.3 times higher than normoxic infants depending on the degree of hypoxemia.

With globalization and increasing diffusion of technology today, the resource-poor countries have some access to incubators, electronic monitoring systems, pulse oximetry, IV fluids, CPAP devices, and even neonatal ventilators.[1] But they experience difficulty in attaining consumable commodities such as oxygen and in maintaining equipment in working order, both of which are vital to the management of infants in respiratory distress. The lack of ready availability of oxygen has been reported as a major cause of death in Africa and other developing countries.[32]

In developed countries, oxygen is stored at −183° C and is supplied via wall outlets. This requires highly sophisticated cryo technology. In resource-limited countries, oxygen is supplied in pressurized tanks. This is an expensive method and has no reliability of constant supply in remote health facilities with poor transport systems.

In Papua, New Guinea, five hospitals with a total of 20,000 admissions reported the case fatality rate for 2001 to 2003. A total of 1313 neonatal and pediatric admissions were studied prospectively in these hospitals. Of these admissions, 384 (29%) had hypoxemia, defined as a Sp_{O_2} less than 90%. Oxygen was not available on the day of admission for 22% of the patients admitted and was less frequently available in rural compared to provincial hospitals. Based on these results, a program was introduced to provide clinical and technical training in the use and maintenance of pulse oximetry and oxygen concentrators in these hospitals.[30]

In another report, a 3-year experience of using oxygen concentrators in a Nigerian newborn unit was reported by Mekuola and Ajayi[33] Oxygen concentrators absorb nitrogen from air and supply oxygen concentrations up to 85% to 95% at different flow rates. The devices met their needs and were more economical than oxygen cylinders. The cost of oxygen stored in cylinders for 1 year exceeded the initial cost of the oxygen concentrators. A typical oxygen concentrator has a life span of 7 years and is generally maintenance free for the first 26,400 hours of use, a great advantage in developing countries.

In addition, there is a lack of appropriate methods for administering oxygen. Oxygen is administered in the nursery by different techniques—commonly by an oxygen hood. The oxygen hood cannot assure the delivery of an intended high percent of oxygen concentration, especially when there is no oxygen analyzer to check the concentration. It is difficult to achieve concentrations more than 40%, unless the hood is leak proof. There is also a great wastage of oxygen, which adds to the cost. Delivery of oxygen by nasal canula minimizes loss of oxygen and assures direct delivery even at low flow rates. In the absence of nasal cannulas, oxygen can be delivered by face mask. Commercially available face masks, infrequently used in NICUs in the developed world, come in different sizes for term and premature infants.

Sahni and Wung[34] have demonstrated that CPAP devices are important tools in the management of RDS. More and more facilities in resource-poor countries are using CPAP devices to manage infants in respiratory distress.[35] Nasal prongs are simple to use and assure effective oxygen delivery. They can be unilateral or bilateral, although the preferred method is binasal. Prolonged usage may lead to injury of nasal structures and septum. Unless properly managed, nasal prongs may also cause obstruction of airways, and there is an increased risk of infection. The techniques of oxygen delivery and application of CPAP are well described elsewhere in this book (see Chapters 6 and 8).

Physicians and health care workers can use the commercially available equipment (nasal cannula, oxyhoods, and CPAP devices) where feasible and affordable or develop innovative methods using basic principles of physics and physiology combined with ingenuity. Judicial application of CPAP in infants in respiratory distress could be very effective in managing infants with RDS in resource-poor countries. In a study in India,[35] the authors reported that 71% of the 74 babies with RDS improved with early application of CPAP (nasal pharyngeal and nasal CPAP prongs). The remaining 28% required mechanical ventilation and one dose of surfactant. This study suggests that CPAP could be used as the first line of treatment for RDS in resource-poor countries and parallels recent thinking in regions of the world where mechanical ventilators are freely available but attempts are being made to reduce ventilator-induced lung injury. There are a number of commercially available CPAP devices manufactured in the United States and United Kingdom that are available in

the markets of resource-poor countries. However, the cost of commercially available CPAP devices could be as high as 7 times that of indigenously made CPAP devices.

Ventilators and Ventilator Use

It is the ultimate goal of pediatricians and neonatologists around the world to be able to establish an NICU providing ventilator care. Such a venture is labor intensive and expensive. To be successful and cost effective, the planners must consider certain criteria before attempting to establish a neonatal ventilator care program. Box 30-1 lists some basic requirements for establishing a ventilator care program in the hospital. It describes the operational needs, cost of the ventilator, and criteria for choosing a ventilator. In addition to the provision of such basic needs as space and an uninterrupted supply of power and water, the availability of appropriate equipment and skilled staff are critical to the operation of a respirator care program.

Economics play an important role in the purchase of ventilators in resource-poor countries. The initial cost is a major determining factor in establishing a ventilator care program. Typical cost of ventilator and supplies are shown based on the data provided by MarketStrat, Inc.[18] The purchase of ventilators is a major investment for a hospital in resource-limited countries. Therefore choosing the right ventilator is an important undertaking. Often physicians and hospital administrators are heavily pressured into buying expensive equipment based on its brand name recognition. Health professionals and administrators must consider some basic guidelines shown in Box 30-1 in selecting a particular brand of ventilator. Besides a well recognized brand name, simplicity of operation and ease of maintenance, and availability of spare parts should be the important considerations in selecting a specific ventilator. Because of limited funding, ventilators that can serve different age groups may be more economical. The ventilator should have an overall low life-cycle cost.

In addition to the purchase of the ventilator, the purchase of disposables and service contracts are to be taken into consideration in order to maintain a functioning program. Most programs fail to maintain service contracts because of yearly budget constraints, a major barrier faced in all developing countries. Once purchased, the unit should designate a professional (doctor/nurse) in the unit with the responsibility of maintenance of the ventilators and ordering the disposable supplies. Regular maintenance check-ups of the ventilators are important for a smooth operation.

Projected Growth in Neonatal Ventilation—A Global Perspective

It is interesting to note that in spite of aforementioned difficulties, there is a steady growth of the neonatal ventilator market worldwide. Research data from MarketStrat, Inc.[18] reveal an increasing awareness and interest in the purchase and use of ventilator support for adults and newborns around the world. Their recent global market survey shows that although the developed countries have the greatest proportion of the ventilator market share, there also has been a rapid and progressive increase in ventilator purchases during 2005 to 2007, and this trend is projected to continue through 2013 in developing countries, especially China, Latin America, and India (Figs. 30-1 to 30-3). The total world market sales for mechanical ventilators (adults and neonates) and associated disposable and maintenance services is expected to grow from a current $972 million in 2005 to $1.35 billion by the end of 2013. Unit shipment of devices is expected to increase from 51,799 in 2005 to 75,240 units by the end of 2013. The neonatal ventilator market is also expected to grow steadily. The United States is the largest market, whereas India is the fastest growing, followed by Latin America.

Box 30-1 GUIDELINES FOR SETTING UP A VENTILATOR CARE PROGRAM

A. Operational Considerations

- Availability of adequate space
- Uninterrupted availability of power and running water
- Continuous availability of a pediatrician trained in ventilator care
- Availability of sufficient nursing staff trained in ventilator care in the ratio of 1 nurse to 2 or 3 patients
- Availability of maintenance staff trained in ventilator repair
- Continuing education of staff
- Acquisition, review, and analysis of data for quality improvement

B. Typical Cost in US Dollars of a Ventilator in a Developing Country*

Cost of ventilator:	$30,000
Cost of disposables/year	$250
Cost of service contract	$200
First-year cost	$30,450
Recurrent yearly cost	$450

C. Choosing a Ventilator

- Simplicity of operation
- Cost considerations
- Ease of maintenance, availability of replacement parts
- Brand name
- Lower overall cost of ownership and life cycle cost

*Data from MarketStat, Inc. These cost estimates do not include costs of oxygen supply or delivery systems such as CPAP devices or high flow devices, 2005.

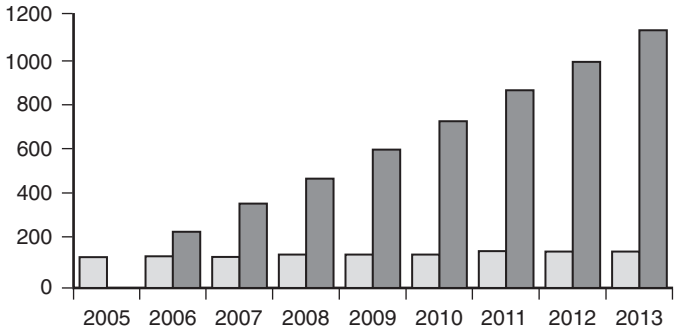

Figure 30-1 ■ Neonatal ventilator purchases in China. Small bars represent projected number of purchases per year and tall bars cumulative number of ventilators in China in that year. (Data from Marketstrat[18])

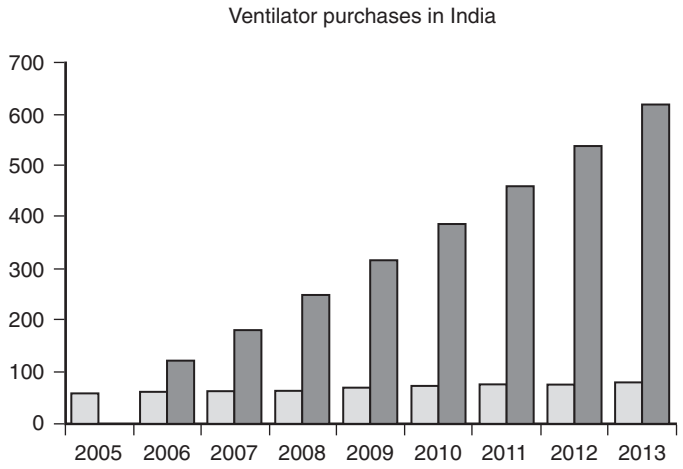

Figure 30-2 ■ Neonatal ventilator purchases in India. Small bars represent projected number of purchases per year and tall bars cumulative number of ventilators in India in that year. (Data from Marketstart[18]). Note that number of purchases per year and cumulative number of neonatal ventilators in India are lower than observed in China (see Fig. 30-1).

Globally, neonatal ventilator units account for about 10% to 11% of all ventilators sold. The sale of conventional neonatal ventilators is expected to grow from 4557 units in 2005 to 5485 in 2013, a cumulative growth rate of 2.3%/year. Sales of high-frequency ventilator (HFV) units are expected to grow from 1310 units in 2005 to 1442 units by year 2013 at a growth rate of 1.3%/year. The Americas have the largest market share, followed by Europe, and then the Asia Pacific countries.

Even though neonatal ventilator purchases are increasing in developing countries such as India, China, and Latin America, these acquisitions are far fewer than these countries need. For example, India, with yearly births of 25 million, and China, with 20 million births/year, are estimated to have a total of only 300 and 600 ventilators, respectively, by year 2010. Expressed per million births, India will have one ventilator per 80,000 live born babies, China will have one ventilator per 30,000 live births as compared to one ventilator per 500 births in the United States. Considering higher neonatal morbidity from LBW and birth asphyxia rates in India and China, the requirements of ventilators are many times higher than the above estimates. At the current estimated rate of purchases of 100 ventilators per year in each country, it will take a very long time to meet the clinical demands and reach the ratio level of the developed world.

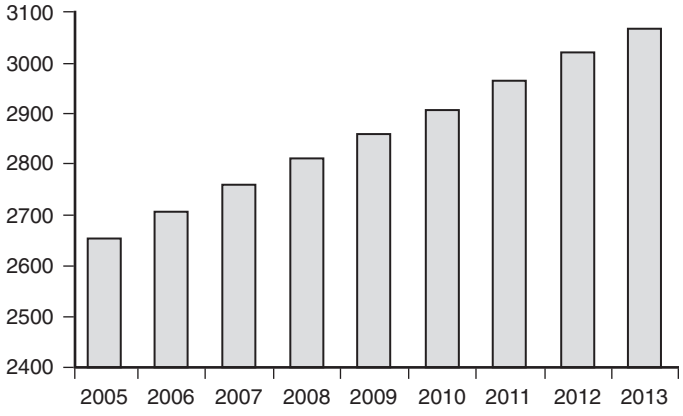

Figure 30-3 ■ Figure shows number of Neonatal ventilator purchases per year in the United States. Please note only purchases/year are shown in this graph. The neonatal ventilators purchased per year in the United States are many folds higher than in India (about 100/yr) and China (about 200/yr). Also note that these are based on projections made in 2007. (Marketstrat[18])

Outcomes of Neonatal Ventilation

The outcome results of infants treated with neonatal ventilation in developing countries in some NICUs have been published in recent years. Investigators of the national neonatal-perinatal database (NNPD)[36] from India in a study of 10 tertiary care NICUs reported that 45% of babies admitted to the NICU required oxygen therapy, and 16% required assisted ventilation. Of the 3831 newborns admitted to NICUs, 87% were delivered at small private hospitals and 68% of admissions were male. Half of the admissions were LBW, 32% were preterm, and 7.5% left against medical advice. Common causes of death included sepsis (36%), prematurity (26%) and perinatal asphyxia (10%). Among the causes of death, prematurity and RDS were the major causes.

In a report from Pakistan, Bhutta et al.[21] concluded that ventilatory care of the newborn is feasible with good results. In a 12-month period, 200 babies were admitted to the NICU with RDS, and 79% required assisted ventilation. Overall mortality was 39%. The mortality rate for infants weighing less than 1000 g was 70% but only 30% for infants weighing greater than 1000 g.

A recent report from Ghana showed that establishment of a ventilator support program in the NICU at a teaching hospital led to a dramatic decrease in mortality of infants admitted to the unit.[37] The authors reported improvements in outcome of infants weighing less than 1500 g who would have otherwise not survived. The significant finding of this report was that the major single intervention in an already existing NICU was the addition of ventilators and improved physical facilities. This was a one-time capital budget commitment. No new nurses were added; however, the existing staff was given on-site additional training in ventilator care. These observations suggest that it is possible to develop NICUs with ventilatory support even in developing countries with minimum investments.

Initiating ventilatory support is associated with emergence of new morbidities, that is, chronic lung disease (CLD) and retinopathy of prematurity (ROP). Wei in China noted that improved survival of infants weighing less than 1500 g was associated with an increase in chronic lung disease.[10,11] Similarly, there are reports of increasing occurrence of ROP in survivors after ventilation in resource-poor countries.[38,39] However, the programs in these resource-poor countries lack the required pediatric ophthalmic services. Considering these limitations, one should take a cautious approach in developing ventilator care programs in resource-limited countries.

Box 30-2 ETHICAL QUESTIONS TO CONSIDER IN RESOURCE-POOR COUNTRIES

- Should the best interest of the baby or the global interest of the family determine the care given?
- Should each country decide a cut-off weight below which no NICU care is given?
- Should NICU ventilator care be denied to those who cannot afford to pay?
- Can therapy be stopped when a family cannot afford to pay for further care?
- Should expensive NICU care be given to extremely or very-low-birth-weight infants of parents who do not have basic amenities at home and where social support from the government is not available?

Modified from Singh M: Ind J Pediatr 70:417-420, 2003.

Ethical Dilemmas

The introduction of neonatal and critical care services poses several economic and ethical dilemmas. In a national study in India, NNF found that 7.5% of infants from the NICU were discharged against physician advice.[36] These discharges were most likely caused by economic, social, and family reasons (e.g., the family could not afford the continuing cost of care).

Moazam and Lakhani[40] discussed the dilemmas of providing neonatal intensive care in a resource-limited country. Their concerns were related to the high cost of NICU care. The outcome and costs of 200 infants admitted to an NICU in Karachi, Pakistan, were analyzed. They found that the cost of care for premature infants with RDS was, on average, a total cost of 23,260 RS (equivalent to $788 US) with a daily cost of 1050 RS ($55). In addition, one needs to consider the associated disease burden secondary to associated morbidities of chronic lung disease, neurodevelopmental disabilities, and unavoidable ROP in developing countries. The ethical question remains this—"Is it justifiable to invest a country's meager resources to benefit a few sick infants?" With increasing awareness of available technologies to save critically ill infants, there is higher expectation from parents. But daily expenses incurred for the care given in the NICU challenge the parental support. The mounting daily hospital costs may exceed the capabilities of the family. Therefore every attempt should be made to honor distributive justice.

The physician should define a priority and decide the level of care based on the resources available. All babies must be given the basic care available in the country. Decisions to employ heroic measures such as ventilator care should be based not only on immediate clinical needs but also on the implications of long-term needs of health care and the availability of support systems in the community once the infant recovers from the acute illness.[41] Singh,[41] in an article on ethical and social issues in the care of the newborn, offers some serious thoughts and suggestions regarding the ethical issues faced by pediatric and neonatal practitioners in resource-limited countries (Box 30-2). Clearly, each society must develop guidelines based on its local values and resources. In addition, there are regional and cultural variations in allocation of resources for adults and pediatric patients.

Conclusions

It is clear that developing countries have the highest neonatal and infant mortality from respiratory problems and that there is a great unmet need for respiratory care and ventilatory support. Yet these are the same countries that lack the most essential minimum equipment such as bag and mask for resuscitation, continuous supplies of oxygen, and oxygen delivery devices. It is suggested that the World Health Organization (WHO) designate this life-saving equipment as part of the essential equipment, similar to the WHO Essential Drug List.[42] Such policies would make a major impact on neonatal survival internationally. Health care workers at primary health care centers and hospitals should be trained in providing basic respiratory care, that is, clinical assessment using the RDS score, basic principles of care including clearing the airway, bag and mask ventilation, and proper oxygen therapy. The staff at level II units must be routinely trained in providing oxygen therapy, applying CPAP. Staff in level III units should be capable of providing ventilatory support using mechanical ventilation.

Countries with high birth rates and high NMR require the establishment of regional NICUs with ventilatory support. These centers of excellence must provide nationwide training of health care personnel in providing basic resuscitation, stabilization with nasal CPAP, and triage and transport to hospitals that can provide higher levels of respiratory care. The market research data also shows that developing countries are rapidly acquiring neonatal ventilators; however, there is a shortage of skilled personnel and also a lack of guidelines for the appropriate use of ventilators. China has developed a model in which health policies are implemented in top down fashion by the government. The NNF of India provides a model in which a professional physician organization has started a major initiative to improve newborn care in the country. A combination of the models may work well for other developing countries.

Because of the large global need, it is important that professionals, organizations, institutions, and government agencies in developed countries extend their services and participate in global programs to accelerate the transfer of knowledge and skills of ventilatory care to resource-limited countries. These goals can be achieved through bilateral exchange of medical faculty and nurses between institutions in developing and developed countries. In our own experience, these approaches have made an enormous impact in several countries.

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31 Transport of the Ventilated Infant

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Expanding Role of the Transport Team

The development of regional neonatal intensive care centers and interhospital transport services for critically ill infants has been an important factor in decreasing perinatal morbidity and mortality. In the 1970s, the growing recognition that regionalization of care improved patient outcomes resulted in the formation of regionalized centers for perinatal and neonatal care. With this development of regionalized care, the need for a skilled transport team was realized. Today, as advanced technologies have become more available and portable, the transport team has become an extension of the intensive care unit, and transport teams now initiate the comprehensive specialized care in the referral hospital that will be continued in the tertiary care center. Transport teams bring the intensive care environment to the child, stabilizing the infant to ensure a safe and effective transfer.

As advanced technologies have been approved and adopted, sophisticated treatments such as high-frequency ventilation (HFV) and inhaled nitric oxide (iNO) are often now available; these are initiated in intensive care units that do not offer extracorporeal membrane oxygenation (ECMO). Infants who continue to fail after receiving these therapies and then require transfer to a tertiary care unit are difficult to transport, due to their instability and need for complex care.

The transport team of today has adapted to meet the needs of these children. Teams now have the ability to provide intensive therapies such as surfactant therapy, HFV, iNO, and even mobile ECMO in some cases. Team members competent in the critical care of an ill newborn must be able to provide a rapid response to the referral hospitals who request their services. They must provide appropriate stabilization of the infant for transport and expedient but safe transport of the infant. Importantly, as the skills and technologies of transport teams continue to change and develop, it is becoming evident that comprehensive care and therapies initiated during transport can improve patient outcomes.

Regionalized Care

Almost 40 years ago, neonatologists and obstetricians recognized that neonates treated at tertiary centers had improved outcomes, and the push for regionalized care began. Usher[1] demonstrated a 50% reduction in mortality for critically ill newborns that received care at tertiary centers. Other studies confirmed these results and also showed improved mortality rates for infants transported to regional care centers.[2-3]

Although the previous studies supported the early transfer of high-risk mothers and fetuses to tertiary centers, the birth of high-risk infants in nontertiary centers has continued to occur, and current data suggest that 14% to 30% of very-low-birth-weight (VLBW) infants are delivered in nontertiary hospitals.[4-6] Current studies of such infants further support the fact that outborn infants experience significantly higher morbidity and mortality when compared to infants delivered at tertiary perinatal centers. Chien et al.[7] found that outborn infants were at higher risk of death, severe intraventricular hemorrhage (IVH), patent ductus arteriosus (PDA), respiratory distress syndrome (RDS), and nosocomial infections, even after adjusting for perinatal risks and illness severity using SNAP-II scores.

Lui et al.[8] performed an interesting study comparing inborn and outborn infants born between 23 and 28 weeks 6 days of gestation before and after the development of centralized care in their geographic region. They compared outcomes for infants born from 1992-1995 to those born from 1997-2002. They showed that optimization of in utero transfers resulted in 25% fewer nontertiary hospital births and that with provision of perinatal advice, increased provision of antenatal steroids, and centralization of the neonatal retrieval system, outborn mortality rates decreased significantly from 39.4% to 25.1%. Rates of severe IVH and necrotizing enterocolitis (NEC) also decreased in outborn infants between the two periods after interventions were started. Importantly, however, morbidity for outborn infants continued to be significantly higher than that for inborn infants, especially with regard to severe (grade 3 or 4) IVH (19.4% outborn versus 10% inborn, $p = 0.002$) and radiologically or surgically proven NEC (7.2% outborn versus 1.7% inborn, $p < 0.001$). All together, these data demonstrate that implementation of a coordinated system to provide perinatal advice and appropriate neonatal transport improves outcomes, but outborn infants continue to face higher morbidity despite these interventions. Thus in utero transfer of high-risk pregnancies to a tertiary center still remains the best option. When maternal transfer cannot be accomplished because of rapid labor progression, pending delivery, or fetal or maternal compromise, the specialized services offered by the neonatal transport team play an important role in optimizing outborn infant care.

Make-Up of the Transport Team

Multiple models have been used when determining the make-up of the transport team. Each institution must determine the most appropriate model for their facility based on the volume and types of local transports, travel times, the skills required for efficient and safe transfers, the availability of team members, and the overall costs. The American Academy of Pediatrics (AAP) has recommended that transport teams consist of at least two providers, with one member being a nurse who has 5 years or more of nursing experience.[9] Team make-ups can include emergency or intensive care nurses, pediatric respiratory therapists (RT), paramedics, and physicians, including attending staff, fellows, or residents in training. Most commonly teams are made up of RT-nurse pairs or nurse-nurse pairs with paramedic support. Given the significant number of neonatal transports requiring respiratory interventions, many teams find the skills of a respiratory therapist helpful and often necessary. However, all transport team members should be cross-trained and capable of supporting all transport procedures and interventions.

Several studies have compared different team models and their effect on patient care outcomes. Lee et al.[10] found no difference in patient care outcomes when comparing three different models: two nurses, one nurse and one RT, or two paramedic team members. The results of this comparison may be skewed by the fact that physicians were present for over 40% of transports and were present when intubation was required. However, the presence of a physician did not alter patient outcomes in this study.

Multiple other studies have supported the idea that non-physician teams are capable of providing care that is effective, and potentially timelier, than teams accompanied by a physician. Beyer et al.[11] demonstrated that non-physician teams were able to provide care and transport intubated neonates without problems. In their cohort, 20% of infants were intubated by a transport nurse or RT at the referring facility. They concluded that there was a low incidence of complications in intubated neonates when transported by personnel trained in pediatrics. Leslie and Stephenson[12] found that transports directed by advanced neonatal nurse practitioners were as effective as those directed by physicians, and King et al.[13] found that there was no change in mortality or complications when teams were converted from nurse-physician teams to nurse-nurse teams, but that response time did improve. Voluntary reporting by pediatric and neonatal transport teams to the AAP Section of Medical Transport team database indicates that almost half of the teams providing information (37 of 82 teams) do not include physicians on transport.[14] Thus with a well-trained, experienced transport team, availability of a medical control physician by telephone is all that is required.

Regardless of the model chosen, however, team members should be specialists in neonatal and pediatric care because specialized teams have been shown to make a significant difference in outcome. Early studies demonstrated that dedicated neonatal transport teams reduced both morbidity and mortality in VLBW infants that required transfer to a tertiary center,[15-16] and that outborn infants who were not transferred by a specialized transport team experienced a 60% greater mortality rate.[17]

More recent studies confirm that the incidence of transport-related morbidity increases when personnel without specific pediatric training transport critically ill children. A study by Edge et al.[18] demonstrated that adverse events during interhospital transport, such as loss of the endotracheal tube or IV access, were significantly higher in transports performed by a nonspecialized team (20%) compared to transports performed by a specialized pediatric team (2%). Similarly, Macnab[19] demonstrated a higher rate of secondary complications in children transported by nonspecialized transport teams when compared to pediatric transport teams.

High-volume transport services have the advantage of being able to develop full-time transport teams dedicated solely to neonatal transport, where experience is greater and skills are more easily maintained. Smaller services that use team members on a more infrequent basis must invest significantly in continuing education to maintain their knowledge base and technical skills in order to provide specialized services. Data from the AAP voluntary registration of transport teams suggests that the majority of teams provide combined pediatric and neonatal transport services.[14] Although this is often necessary and allows the maintenance of a dedicated team, team members should track the number of neonatal transports they perform to be sure they are maintaining adequate exposure to the unique circumstances involved in neonatal resuscitation and transport. A lack of exposure should be offset by continuing education.

Transport teams are frequently called to attend and participate in the delivery of high-risk preterm infants that occur outside of the tertiary center. Although all delivery hospitals should have at least one attendant certified in neonatal resuscitation available at all times, transport personnel may be asked to support referral staff, or in some cases, may be the primary resuscitator at a preterm delivery. Although this is often a stressful situation, recent data demonstrate that the presence of a dedicated neonatal retrieval team can improve delivery room resuscitation of these outborn premature infants.[6] In this study, neonates that were resuscitated by a specialized transport team were intubated more promptly with fewer attempts, had better positioning of the endotracheal tube, and were more likely to receive surfactant.

Neonates cared for only by the referring hospital team had a high rate of hypothermia, lack of vascular access, and more extensive resuscitation. Despite having the same average gestational age, infants resuscitated by the referral team received longer chest compressions (6 min versus 0.5 min), longer bag-mask ventilation (13.5 versus 7 min) and longer continuous positive airway pressure (CPAP) (14 versus 2 min), all of which may reflect a delay in intubation by the referral team. These differences are not surprising, because referral hospitals that appropriately transfer high-risk mothers and fetuses lack a critical mass of preterm births and experience in resuscitation of extremely low-birth-weight (ELBW) and VLBW preterm infants.

Dedicated teams with specialized training and increased experience are able to provide better specialized care and resuscitation. Given the evidence that the first few minutes of resuscitation and early oxygen exposure can influence

long-term outcome, the need to optimize resuscitation is evident.[20-22] These studies reinforce the fact that transport teams should be made up of members with specific training in comprehensive neonatal care and resuscitation and also suggest that the use of the transport team as a neonatal resuscitation team for outborn infants may be desirable (see Chapter 4).

Transport Education

The need for extensive education of team members who transport neonates is clear, because team members are expected to recognize and treat a wide array of disorders. They must be able to resuscitate and stabilize neonates in critical condition, and accomplish their safe transport, often under conditions that may be suboptimal. Although no standard curriculum exists, guidelines for team education have been published by the AAP Section on Transport Medicine.[23] Education of transport team members includes a requirement for resuscitation training through the Neonatal Resuscitation Program (NRP; American Academy of Pediatrics and American Heart Association provider course) or a similar program, as well as continuing education in neonatal pathology and disease. Continuing medical education (CME) and transport review conferences ensure that team members maintain their skills in neonatal stabilization and exposes them to new topics in neonatal care. CME opportunities should include a skills lab, with stations focusing on skilled intubation, effective bag-mask ventilation, handling of the difficult airway, chest tube placement, and vascular access, including IV line placement, umbilical line placement, and intraosseous line placement.

Unique to the education of transport team members are the requirements for knowledge about flight physiology and its contribution to disease states, the physical and mental stresses of transport, and the need for a significant focus on safety that includes both team and patient safety. Given the many unique challenges encountered during transport (excessive noise, vibration and rotation forces, low-level lighting, variable ambient temperatures/humidity, and the need for specific safety measures), team members should receive extensive supervised orientation and then must participate in transports with sufficient regularity to maintain their skills in all transport settings. Team members may also benefit from training on ethical issues such as the withdrawal of support, because they may be involved in situations where support is stopped after resuscitation or where infants are deemed appropriate for withdrawal of care at the referring facility, where the family can participate, rather than transport to a distant facility. Training should also be given regarding the social aspects of transport to help team members work more compassionately with families and help raise team awareness of the many emotional issues that are faced by the family during the crisis precipitated by a neonatal transport.

Transport Physiology

The effect of altitude and the stresses of flight can have a significant impact on the neonate during fixed-wing or helicopter transport, especially in the already compromised infant. The transport environment itself, including ground transport, introduces unique stressors such as noise, vibration, and temperature variation. Transport team members must understand altitude physiology and the physiologic stresses of transport in order to anticipate and properly treat problems that may occur during transport. Each of these factors can affect team members as well. The most significant concerns include the following:

1. Hypoxia
2. Air expansion
3. Noise and vibration
4. Thermoregulation

Hypoxia

As an aircraft ascends, the partial pressure of gas decreases. As the altitude above sea level increases, the barometric pressure falls, and the partial pressure of ambient oxygen and thus the alveolar oxygen partial pressure decrease. During this time, infants may develop hypoxia. This is demonstrated using the simplified alveolar gas equation, $P_{AO_2} = (P_B - 47) \times F_{IO_2} - Pa_{CO_2}/0.8$, where P_{AO_2} is the partial pressure of alveolar oxygen, P_B is the barometric pressure, 47 is the partial pressure of water vapor, F_{IO_2} is the inspired oxygen concentration, Pa_{CO_2} is the partial pressure of arterial CO_2, and 0.8 is the respiratory quotient. If an infant receiving 50% inspired oxygen with a Pa_{CO_2} of 50 is transported from sea level (barometric pressure = 760) in a nonpressurized plane that must achieve 8000 feet for the transfer (barometric pressure = 570), then the alveolar oxygen partial pressure will drop from 294 at sea level to 199 at altitude, if you assume no change in minute ventilation, F_{IO_2}, or Pa_{CO_2}. In reality, the partial pressure of arterial CO_2 will decrease at altitude as well, making the alveolar oxygen partial pressure slightly greater than that calculated by the equation.

$$P_{AO_2} = (P_B - 47) \times Fi_{O_2} - Pa_{CO_2}/0.8$$

$$P_{AO_2}\ (\text{sea level}) = (760 - 47) \times 0.5 - 50/0.8 = 294$$

$$P_{AO_2}\ (8000\ \text{ft}) = (570 - 47) \times 0.5 - 50/0.8 = 199$$

Preterm infants, infants with respiratory diseases, and infants with high oxygen demands (sepsis, shock) are at particular risk of developing hypoxia. Careful monitoring of oxygen saturations helps with identification of infants experiencing hypoxia, who usually respond to increased F_{IO_2} levels or increased positive end-expiratory pressure (PEEP). For infants already receiving oxygen prior to transport, the need for increased oxygen during flight should be anticipated. The anticipated adjustment in oxygen administration can be calculated using the following equation:

$$\text{Adjusted } F_{IO_2} = (F_{IO_2} \times P_{B1})/P_{B2}$$

where F_{IO_2} represents the current F_{IO_2} being administered, P_{B1} is the current barometric pressure, and P_{B2} is the barometric pressure at the highest anticipated altitude during transport.

Air Expansion

As an aircraft ascends and barometric pressure falls, the volume of gas within a closed space expands. Gas in an

enclosed space at sea level (i.e., a pneumothorax) will expand by a factor of 1.5 at 10,000 feet. This is most significant for the infant with a pneumothorax or a pneumopericardium, although it may influence the status of the infant with a pneumoperitoneum or pneumatosis as well. Ideally, air leaks are treated prior to flight because of the concern of further expansion at higher altitudes.

Noise and Vibration

Noise and vibration are significant problems encountered during both air and ground transports. Studies have shown that neonates are exposed to very high levels of sound during transport, and that mean sound levels for all modes of transport exceed the recommended levels for neonatal intensive care.[24,25] Similarly, neonates experience high vibration accelerations within the transport incubator.[25] Configuration of the transport unit should be optimized to reduce vibration, and ear protection should be considered for neonates during transport, particularly during air transport, where sound exposure is greatest.

Thermoregulation

Ambient temperatures change significantly with altitude variation and with seasonal variation during ground transport. Proper thermoregulation has been shown to be critical for the intact survival of VLBW infants,[26,27] whereas hyperthermia can be detrimental to infants with perinatal acidosis and hypoxic-ischemic encephalopathy.[28,29] Temperature variation will also increase metabolic and oxygen demands, which can cause further compromise in the hypoxic or septic patient. Transport members must be thoughtful about optimizing the thermal factors they can control. Conductive heat loss can be minimized by preheating the transport incubator and blankets and using a chemical heating mattress. Evaporative heat losses are minimized by keeping the skin surface dry, using a polyethylene bag for ELBW/VLBW infants, and heating and humidifying inspired gases. Additional efforts to control cabin temperature may be required during specific seasons.

Stabilization

The goal of the transport team is to initiate definitive care for the ill neonate and to bring the resources of the tertiary center to the infant. Ideally neonates should be transported when they are stable, so that transport can occur in a safe and controlled manner. This means that the ill neonate should be stabilized in the referring hospital environment, which offers the advantages of space; easy access to the infant; good lighting and visibility; access to personnel, equipment, and support (laboratory and radiology); thermal stability for the infant; and ease of communication with the tertiary center neonatologist. Stabilization involves identifying and treating factors that could lead to deterioration of the infant's condition. Procedures or interventions that are needed, such as intubation, chest tube placement, or vascular access, should be anticipated as much as possible and performed prior to transport. Given the limitations of the transport space, and the complexity added to the transport environment by vibration and noise, only rarely should a major intervention such as intubation need to be performed during the course of transport itself. Despite the inherent desire to expedite the transport process, time spent stabilizing an infant at the referring facility is an important investment to ensure a safe and effective transport. There are rare situations (e.g., transposition of the great vessels with intact ventricular septum) where definitive treatment can be offered only at the tertiary institution and the benefit of rapid transport outweighs the risk of transporting an unstable infant.

Clinical Issues

The members of a specialized transport team must recognize and treat a wide array of neonatal disorders. Although each transport is different, there are a standard set of broad issues that must be addressed in every neonatal transport. These include the following:

1. Respiratory support and airway issues
2. Cardiovascular support
3. Vascular access
4. Glucose stability
5. Thermal regulation
6. Infection risks and treatment

The most common problem encountered by neonatal transport personnel is respiratory distress. Kronick et al.[30] performed a 2-year review of neonatal transports and found that over 80% of neonates that were transported received some form of assisted ventilation, and transport teams performed intubation and initiated ventilation in 34.7% and 38% of transported infants, respectively. Newborns most commonly present with respiratory diseases, so it is not surprising that airway interventions (intubation, mechanical ventilation) are the most common interventions performed by the transport team.[30] Transport personnel must be skilled in establishing and maintaining an airway in a neonate. Airway skills should include not only intubation but also appropriate bag-valve mask (BVM) ventilation, use of nasal and oral airways, placement of CPAP prongs, use of a laryngeal mask airway (LMA), and options for handling a difficult airway. Skills in basic chest x-ray interpretation are needed for diagnosis and optimal management of respiratory diseases.

Transport personnel must also understand the concepts of mechanical ventilation. They should be able to recognize and treat complications encountered with the use of positive pressure and an endotracheal tube, because endotracheal tube or ventilator problems occur in almost 10% of transports.[31] Priority must be given to properly securing the endotracheal tube to avoid accidental extubation in transit. Team members should be able to recognize and treat pulmonary air leaks, and need to have experience in needle thoracentesis or chest tube placement. Optimization of ventilation and oxygenation prior to and during transport is important for maintaining stabilization and for achieving the goal of providing comprehensive care. There is room for improvement in transport ventilator management; recent studies have shown that 15% to 25% of transported infants have suboptimal pH or P_{CO_2} levels at tertiary center arrival.[32-34]

From a cardiovascular standpoint, transport personnel must be able to recognize and appropriately stabilize

infants with congenital heart disease. Differentiating severe pulmonary disease from cyanotic congenital heart disease can be difficult, but proper recognition and initiation of prostaglandin can significantly influence outcome (see Chapter 26). Team members must be well-versed in the use of prostaglandin and its complications. Teams in communication with medical control must make a decision about intubation of infants on prostaglandin E_1 (PGE_1) based on the stability of the infant, the dose of medication being used, and the length and mode of transport. Little evidence exists regarding the need for intubation of infants on PGE_1 prior to transport. Apnea has been reported to occur in 12% to 30% of infants treated with PGE_1, but the incidence can be as high as 42% in infants weighing less than 2 kg.[35,36] Browning-Carmo et al.[37] evaluated 93 of 300 infants with congenital heart disease undergoing transport that did not have mechanical ventilation initiated at the beginning of the PGE_1 infusion. Of these infants, 17% went on to require intubation for apnea within 1 hour of PGE_1 initiation, and 2.6% of the remaining infants developed apnea during transport. Overall, 25% of infants were able to be successfully transported without intubation, but these infants were receiving very low doses of PGE_1 at less than 0.015 mcg/kg/min. Although each situation must be individually assessed, in general, term infants who are receiving standard PGE_1 doses may be transported short distances safely without intubation. Transport teams also have the ability to supply nitrogen or CO_2 to unstable infants with hypoplastic left heart physiology during transport, but extensive education is needed before this approach is implemented.

The ability to establish vascular access is a critical skill for transport team members to possess. Team personnel must be able to place an umbilical venous line emergently during resuscitation for the purpose of administering epinephrine and volume, as well as nonemergently for administration of IV fluids, medications, or blood products. Some centers expect that transport personnel will be able to place umbilical arterial lines as well; however, the time necessary for umbilical arterial line placement should be weighed against earlier transport to the tertiary center where the procedure can be done under more ideal circumstances. Team members also should have the training and skills required for intraosseous line placement for emergent situations.

Maintenance of normal glucose levels and maintenance of thermal stability have both been shown to be critical for neonatal morbidity and mortality prevention.[26,28,38] Transport team members must recognize the importance of glucose stability and thermal stability in neonates, and should have protocols that address these two key issues for every transport. Although glucose and temperature alterations are problems that are usually easily treated or controlled, they are also easily overlooked. Several studies evaluating optimization during transport have shown that approximately 10% of neonates have hypothermia and 10% of neonates have hypoglycemia on arrival following transport.[31-33]

Finally, the incidence of infection in newborn infants is high, and transport teams must consider these risks in order to perform appropriate evaluations and initiate antibacterial or antiviral therapy in a timely manner.

Equipment

The equipment carried by the transport team must be lightweight, durable, compact, and easily secured, but most of all it must be complete to meet the needs of transport. The assumption should be made that the referring hospital will not have equipment needed to stabilize the neonate prior to transport. Medications and basic support supplies for interhospital transport are listed in Boxes 31-1 and 31-2. A variety of durable equipment bags exist for organizing consumable supplies and medications. Supply bags should be checked and replenished after every transport.

Transport systems have now been specifically designed to incorporate all of the critical life support systems and technology in a single mobile unit, including the transport incubator, ventilator, monitoring systems, suction apparatus, and infusion pumps. Medical gas tanks are usually stowed on the bottom of the transport sled to provide compact storage but easy accessibility. Equipment used during transport can be run via an AC/DC power source or via internal battery if necessary. Transport ventilators may be powered pneumatically or by AC/DC power with battery backup. These complete systems have been designed to promote ease of movement, security within the transport vehicle to minimize the effect of vibration and motion, clear visualization of both monitors and the baby, and easy access to the infant.

Monitoring during transport of the ventilated infant has become significantly easier with the development of the pulse oximeter. Current models available provide adequate readouts despite the vibration contributed by the transport environment. Monitoring with pulse oximetry and electrocardiograph leads is standard during all transports. Target ranges for oxygen saturation should be adhered to during transport, especially for the ELBW infant. Several teams have also used noninvasive end-tidal CO_2 detectors or

Box 31-1 MEDICATIONS FOR INTERHOSPITAL TRANSPORT

Adenosine 6 mg/2 mL
Albumin 5%
Alprostadil (PGE1) 500 mcg/mL
Ampicillin 100 mg/mL
Atropine 0.1 mg/mL
Calcium chloride 10% 100 mg/mL
Calcium gluconate 10% 100 mg/mL
Cefotaxime 100 mg/mL
Clindamycin 150 mg/mL
D10W 250 mL
Digoxin 100 mcg/mL
Dobutamine 250 mg/20 mL
Dopamine 400 mg/5 mL
Epinephrine 1:1000
Epinephrine 1:10,000
Fentanyl 0.05 mg/mL
Flumazenil 0.5 mg/5 mL
Fosphenytoin 100 mg/2 mL
Furosemide (Lasix) 10 mg/mL
Gentamicin 10 mg/mL
Heparinized saline
Lacri-lube
Lidocaine 1% 10 mg/mL
Lorazepam (Ativan) 2 mg/mL
Magnesium sulfate 1 g/2 mL
Midazolam (Versed) 1 mg/mL
Morphine 2 mg/mL
Naloxone (Narcan) 1 mg/mL
Nipride 50 mg/2 mL
Normal saline
Phenobarbital 65 mg/mL
Rocuronium 10 mg/mL
Sodium bicarbonate 4.2%
Sodium chloride, 3 mEq/mL
Sterile water
Surfactant
Vecuronium 1 mg/mL

Box 31-2 SUPPLIES FOR INTERHOSPITAL TRANSPORT

IV Supplies

Alcohol and Betadine swabs
Chlorhexidine prep
Gauze (2 × 2 and 4 × 4)
Cotton balls
Band-Aids
Label tape
Clear tape (½ inch, 1 inch)
Self-adherent wrap (1 inch)
Tegaderm, small and large
Needles (23 gauge, 19 gauge)
IO needles (18 gauge)
IV catheters (14, 16, 18, and 24 gauge)
Butterfly needle (19, 23, and 25 gauge)
Syringes (blood gas, 1, 3, 5, 10, and 30 mL)
Arm board
IV extension tubing
Y-adapter and T-connector
IV pump tubing
Three-way stopcock
Heparin lock
Catheter adapters (18, 20, and 21)

Umbilical Line Supplies

Catheters (3.5 and 5 Fr with double lumen 5 Fr)
Umbilical tape
Umbilical line tray
Suture
Umbilical line bridges

Phlebotomy Supplies

Lancets
Capillary tubes
Heparin tubes
Tourniquet
Blood culture bottles
Chemstrips
Chemical warmers, small

Monitoring Supplies

ECG leads
Oximeter probe
BP cuff (1, 2, 3, and 4)
Thermometer

Airway Supplies

Resuscitation masks (various sizes)
Anesthesia bag
Endotracheal tubes (2.5, 3.0, 3.5, and 4.0)
Stylet
Skin protector (DuoDERM)
Adhesive and adhesive remover
Adhesive tape
CO_2 detector
Suction catheters (6, 8, and 10 Fr)
Laryngoscope and blades (00, 0, and 1)
Spare laryngoscope bulb and batteries
Magill forceps
Nasal CPAP prongs (10.5, 12, and 15 Fr)
Endotracheal tube bridge
Laryngeal mask airway (1 and 1.5)
Nasal trumpet
Oral airway (00, 0, 1, and 2)
Thoracostomy tubes (8, 10, and 12 Fr)
Thoracostomy tray
Heimlich valve
5-to-1 (Christmas tree) adapter
Vaseline gauze
Nasal cannula
Normal saline bullets
Bulb syringe
Meconium aspirator

GI Supplies

Replogle catheters (6, 8, 10, and 12 Fr)
Feeding tubes (5, 6.5, and 8 Fr)
Sterile specimen (bowel) bag

Other

Soft restraints
Stockinette cap
Safety pins
Rubber bands
Scissors
Hemostats
Penlight
Flashlight
Sterile gloves

transcutaneous CO_2 monitors for evaluation during transport and found them to be effective, although some have noted problems with specific monitors being cumbersome and difficult to secure during transport.[39-41] Tingay et al.,[42] however, found that end-tidal CO_2 monitoring underestimated arterial CO_2 levels and did not trend reliably over time. Transport teams must still evaluate these adjuncts individually to determine their benefit, because no single standard has been adopted. Colorimetric CO_2 monitors that are placed briefly on the end of the endotracheal tube have been more universally adopted and have proven useful for confirming initial endotracheal intubation and for confirming continued intubation after movement from the isolette to warmer and back during transport.[41]

Quality of care and efficiency during transport has been greatly improved by use of the i-STAT analyzer (Abbott Laboratories, Illinois, USA), a handheld device that allows point-of-care analysis of blood gases, hematocrit, glucose, electrolytes, and ionized calcium on a small amount of blood (0.3 mL). Compact and easy-to-use, this instrument is easily carried in the equipment pack and provides rapid analysis at outlying hospitals, where blood gas measurements may be difficult to obtain in a timely manner. Macnab et al.[43] demonstrated that there is significant cost efficacy with the use of this technology, and that use of point-of-care testing can reduce stabilization times and improve quality of care.

One piece of equipment not carried by all transport teams but receiving greater use is the laryngeal mask airway, or LMA. The laryngeal mask is a supraglottic airway device that fits over the laryngeal inlet to provide a means for positive pressure ventilation. The deflated mask is inserted into the mouth of the infant using two fingers and is guided blindly along the hard palate without laryngoscopy or instrumentation. Once resistance is met, the mask is seated by inflating the rim with 2 to 4 mL of air, occluding the esophagus while covering the laryngeal opening (see Chapter 4). The most frequently reported use of laryngeal masks in neonates is for airway rescue when facemask ventilation and endotracheal intubation have failed. Multiple single case reports or small retrospective series have described successful use of a laryngeal mask as a lifesaving maneuver during management of a difficult airway. In a meta-analysis, Mora and Weiner[44] concluded that a fairly strong recommendation could be made to attempt laryngeal mask ventilation during resuscitation when other methods fail, based on the fact that placement of the laryngeal mask is fairly noninvasive, is easily placed by most providers, has a relatively low incidence of reported complications, and may be life-saving.

There are several case reports on the use of the LMA during transport. These case reports have documented the use of the LMA to resuscitate, and in some cases transport, infants with congenital anomalies and difficult airways, including descriptions of its successful use for choanal atresia,[45] severe micrognathia,[45] and laryngotracheoesophageal clefts.[46] The International Guidelines for Neonatal Resuscitation state that the LMA may be an effective alternative for establishing an airway if bag-mask ventilation is ineffective or attempts at intubation have failed, but routine use of the LMA is not currently recommended.[47] Given the unpredictable nature of difficult airway presentations and the challenge of providing optimal resuscitation in sometimes suboptimal conditions, transport teams may consider including an LMA in their equipment box and providing training to personnel in the use of the LMA. The smallest size LMA (size 1) is appropriate for most term and larger preterm neonates, but is too large for infants weighing less than 1500 g.

Transport Ventilators

The Bio-Med MVP-10 ventilator has been the prototypic ventilator used for transport for some time, and is still the "workhorse" ventilator used by many transport teams and

TABLE 31-1 Characteristics of Portable Gas Cylinders

SPECIFICATIONS OF OXYGEN CYLINDERS (E, M, H TYPE)						
	CAPACITY					
Cylinder Type	**(cu ft)**	**(gal)**	**(L)**	**Height (Inches)**	**Diameter (Inches)**	**Weight of Full Tank (lb)**
E	22	165	620	20	4¼	15
M	122	900	3450	46	7⅛	86
H	244	1800	6900	55	9	130

VOLUME AND FLOW DURATION OF OXYGEN IN THREE CYLINDER SIZES												
	FULL			¾			½			¼		
Cylinder Type	**E**	**M**	**H**	**E**	**M**	**H**	**E**	**M**	**H**	**E**	**M**	**H**
Contents (cu ft)	22	107	244	16.5	80.2	193	11	53.5	122	5.5	26.8	6
Liters	622	3028	6900	466.5	2271	5175	311	1514	3450	155.5	757	172
Pressure (psi)		2000			1500			1000			500	

APPROXIMATE NUMBER OF HOURS OF FLOW IN THREE CYLINDER SIZES												
	FULL			¾			½			¼		
Cylinder Type	**E**	**M**	**H**	**E**	**M**	**H**	**E**	**M**	**H**	**E**	**M**	**H**
Flow Rate (L/min)												
2	5.1	25	56	3.8	18.5	42	2.5	12.5	28	1.3	6	14
4	2.5	12.6	28	1.8	10.4	21	1.2	6.3	14	0.6	3.1	7
6	1.7	8.4	18.5	1.3	6.3	13.7	0.9	4.2	9.2	0.4	2.1	4.5
8	1.2	6.3	14	0.9	4.6	10.5	0.6	3.1	7	0.3	1.5	3.5
10	1	5	11	0.7	3.7	8.2	0.5	2.5	5.5	0.2	1.2	2.7
12	0.8	4.2	9.2	0.6	3	6.7	0.4	2.1	4.5	0.2	1	2.2
15	0.6	3.4	7.2	0.4	2.5	5.5	0.3	1.7	3.5	0.1	0.8	1.7

is configured into many modular transport incubators (Bio-Med Devices Inc., Guilford, Conn., USA). The MVP-10 is a pneumatically powered ventilator that provides time-cycled pressure-limited ventilation. It is capable of meeting standard ventilation needs and provides intermittent mandatory ventilation (IMV), positive end-expiratory pressure (PEEP), and continuous positive airway pressure (CPAP). A number of other ventilators are now available for use on transport.

Previously, transport ventilators lacked the versatility found in ventilators used in the intensive care nursery. Today, however, most ventilator modes can be replicated in transport, and ventilators providing pressure or volume ventilation with Control, Assist Control, SIMV (synchronized IMV), PEEP, CPAP, and pressure support modes are all available. Patient-triggered systems that respond to pressure or flow are also available. Ventilators may be pneumatically powered or have AC/DC operation with internal battery backup.

During transport, it is essential to be able to deliver oxygen concentrations between 21% and 100%, in order to limit oxygen exposure for preterm infants and infants with congenital heart disease, yet provide high oxygen concentrations for infants with pulmonary hypertension and hypoxic respiratory failure. Air-oxygen blenders are available and should be used to adjust oxygen delivery. Medical gases for the ventilator are provided by cylinders mounted on the transport system frame during transfer or by larger cylinders that are part of the ambulance or aircraft configuration during transport itself. Table 31-1 lists the characteristics and expected life of various gas cylinders at differing flow rates. Team members should be familiar with cylinder capacity and the number of hours of flow provided, particularly for long transports or for infants requiring high concentrations and high flows of inspired oxygen.

High-Frequency Ventilation

High-frequency ventilation (HFV) has been shown to be useful for the treatment of many respiratory disorders, including respiratory distress syndrome, meconium aspiration syndrome, and persistent pulmonary hypertension.[48-50] Many intensive care nurseries use HFV for infants who have failed conventional management, whereas others use it as their primary ventilator strategy for preterm infants at risk for chronic lung injury (see Chapter 11). Delivery of inhaled nitric oxide has been shown to be more effective with high-frequency oscillatory ventilation (HFOV) for infants with hypoxic respiratory failure,[51] and it is this scenario that can pose difficulties for transport, when an unstable infant must be converted from high-frequency ventilation to conventional ventilation for transfer. Risks associated with such a conversion include loss of lung recruitment, atelectasis, and subsequent hypoxic respiratory failure. To maintain stability for infants already being treated with HFV at the outlying institution, as well as to extend a standard tertiary resource out to the transport environment, high-frequency ventilators providing

high-frequency jet ventilation (HFJV) or high-frequency flow interruption are now available for use on transport.

Although high-frequency ventilators are now available, few studies have been performed to evaluate the risks and benefits of transport HFV. In a retrospective study, Mainali et al.[52] compared the use of HFJV, with or without inhaled nitric oxide (iNO), to that of conventional ventilation. Twelve infants were transported on HFJV alone, 17 on HFJV with iNO, and 9 infants were transported on conventional ventilation with iNO. The infants transported on HFJV, regardless of the use of nitric oxide, demonstrated significant improvement in ventilation during transport after conversion to HFJV without an escalation in support. This included infants converted from conventional ventilation and HFOV. Infants on HFJV also demonstrated a trend toward improved oxygenation and oxygen index (OI), but this did not reach statistical significance. It is important to note, however, that there was an increased incidence of pneumothorax both pre- and post-transport in the infants that received HFV when compared to those receiving conventional ventilation (7/29 HFJV versus 1/9 conventional pretransport and 3/29 HFJV and 0/9 conventional post-transport), although the presence of a pneumothorax pre-transport may have biased decision making towards the use of HFJV. The authors concluded that HFJV with or without iNO is safe and efficacious during transport and may even be preferred to conventional ventilation.

Honey et al.[53] recently reported their experience transporting 134 infants using HFV with flow interruption. Sixty percent of the infants were less than 37 weeks, and 16% were less than 28 weeks gestational age. Infants were successfully transported on HFV 96% of the time. Reassuringly, there were no pneumothoraces in any of the transported infants. For the small number of infants that had pre- and post-transport blood gases available ($n = 24$), pH improved significantly after the initiation of HFV whereas oxygenation and ventilation remained stable. Insights that were provided by the study include the fact that extensive training and education are needed for implementation of HFV on transport, and that there is a steep learning curve with its use. Differences in ventilator readouts and the need for fine-tuning of ventilator settings further complicate training, even for those with prior experience using HFV. Finally, point-of-care testing for blood gas analysis and complete monitoring with cardiorespiratory (CR), O_2 saturation, and CO_2 monitoring are necessary for optimal management of an infant on transport HFV. Our own institutional experience mirrors these insights. We have found frequent blood gas analysis to be essential, with overventilation being a common problem encountered during the use of HFV (Children's Mercy Hospital Transport, Kansas City, Mo.).

Continuous Positive Airway Pressure

The increasing use of continuous positive airway pressure (CPAP) for the respiratory support of newborn infants has necessitated that transport teams become more familiar and facile with its use. Despite a large body of evidence supporting the use of CPAP in the delivery room and intensive care unit, little data exists regarding its use during transport. The few studies that have been done suggest that CPAP can be delivered safely and effectively in appropriately selected infants during transport. Simpson et al.[54] reported their experience with seven preterm neonates from 2002 to 2003 and reported no complications during transport. Bomont et al.[55] reviewed their experience with 100 infants transferred on CPAP. Infants required minimal intervention during transport and were safely transported on CPAP with adequate blood gases on arrival. Five out of 100 infants required stimulation or prong repositioning for apnea, bradycardia, and desaturation, but no major intervention was needed.

Several limitations of the transport environment make the use of CPAP more difficult, however. Visual and auditory assessment is limited in the transport environment, and it can be difficult to achieve proper infant positioning in the transport isolette for adequate CPAP delivery. The use of more extensive transcutaneous or end-tidal CO_2 monitoring may facilitate the evaluation of the infant on transport CPAP. Due to these limitations, however, careful consideration must be given to the safety and stability of an infant being transported on CPAP, and factors such as the length of transport, mode of transport, and the gestational and chronologic age of the infant may all influence decision making regarding the appropriateness of CPAP in transport. Given the increasing use of CPAP in the delivery room for preterm infants, further study of the safety and efficacy of CPAP on transport should be undertaken.

Surfactant Administration

The administration of surfactant to infants with surfactant deficiency has had a significant impact on the morbidity and mortality of infants with RDS.[56,57] Experience with surfactant replacement in the transport environment has not been widely reported, but has been adopted as part of the standard care offered by most transport teams. Costakos et al.[58] found that surfactant could be administered safely prior to the interhospital transport of preterm infants, but was unable to identify significant benefits in terms of ventilator days, time to discharge, or incidence of bronchopulmonary dysplasia (BPD) for infants who received surfactant prior to transport.[58] Endotracheal administration of surfactant is associated with the risk of respiratory compromise (desaturation, hypoxemia, bradycardia)[59] and should be performed by personnel with adequate experience in administration. Moreover, the change in lung compliance that usually follows surfactant administration should be carefully monitored by the transport team; however, it may be difficult to discern in a transport vehicle.

Inhaled Nitric Oxide

Inhaled nitric oxide (iNO) has been shown to improve oxygenation and reduce the need for ECMO in near-term and term infants with persistent pulmonary hypertension (PPHN) and hypoxemic respiratory failure.[51,60,61] Since the US Food and Drug Administration (FDA) approved use of inhaled nitric oxide for respiratory failure, iNO has become available at most level III neonatal intensive care units. Although this benefits most infants, 30% to 40% of infants fail to show a sustained response to iNO and may require transport to an ECMO center.[62] Further, rapid withdrawal of iNO can precipitate rebound hypoxemia, thereby further compromising an already unstable infant.[63] The need to

continue iNO initiated at the outlying institution has prompted transport teams to become capable of delivering iNO during transfer.

Several studies have evaluated the use of inhaled nitric oxide during transport.[62,64-66] Kinsella et al.[64] and Goldman et al.[65] first demonstrated that critically ill infants with hypoxemic respiratory failure could be safely transported on inhaled nitric oxide, and that ambient levels of the gas were maintained well below levels of risk in a closed transport vehicle. Since that time, all studies have demonstrated safe transfer of infants on iNO. Kinsella et al.[64] was able to show that inhaled iNO acutely improved oxygenation in hypoxemic infants and that the effect was sustained during transport. Inhaled nitric oxide was also used to support the conversion from HFOV to conventional ventilation, because it minimized the pulmonary vasoreactivity associated with the change and decreased the lability associated with PPHN. These results were confirmed by Westrope et al.,[66] who retrospectively reviewed their experience in transporting 55 patients on iNO to a tertiary center for ECMO consideration. They found that oxygenation improved after the initiation of iNO, as demonstrated by significant improvement in both PaO_2 and oxygen saturations, and that iNO delivered in transport maintained the stability of patients previously on iNO.

Therapies should be initiated on transport with the goal of providing appropriate stabilization for safe transport, but ultimately with the goal of improving patient outcome. With this in mind, Lowe et al.[67] evaluated whether iNO initiated during transport showed benefit when compared to iNO initiated at arrival at the receiving facility. Although they found no difference in mortality rates or the need for ECMO for infants who received iNO prior to transfer, they did find a significantly shorter hospital stay for survivors that had iNO initiated in the field, suggesting that iNO initiated in transport may be cost-saving.

For teams that decide to offer inhaled nitric oxide, two FDA-approved delivery systems are commercially available—the AeroNOx device (Pulmonox Medical Inc., Tofield, Alberta, Canada) and the INOvent device (Datex-Ohmeda, Madison, Wis.). Safety during transport is of the utmost importance, and teams must be careful when transporting with a hazardous gas. Kinsella et al.[62]has shown that in a "worst-case scenario," where a full "D" cylinder of nitric oxide is completely released, maximum concentrations of nitric oxide would be 25.3 ppm, 34 ppm, and 94 ppm in a fixed-wing jet, ambulance, and helicopter, respectively. Maximum allowable transient exposures are 25 to 100 ppm, and in a helicopter, completely released levels approach Occupational Safety and Health (OSHA) and National Institute for Occupational Safety and Health (NIOSH) levels that pose an immediate danger to life or health.[68] Transport teams should develop a system in which the choice to carry nitric oxide can be made during the preparation for the transport run, in order to avoid carrying a hazardous gas unnecessarily for all neonatal transports.

Extracorporeal Membrane Oxygenation

Uncommonly, a neonate may require transport while receiving extracorporeal membrane oxygenation (ECMO). This occurs most often when an infant is unable to be weaned off ECMO but requires specialized services, such as organ transplantation, at another institution. It also may occur in an infant too unstable to survive transport, necessitating cannulation at the referring facility prior to transport. Currently 12 centers in the United States offer transport ECMO. Wilford Hall Medical Center provides global transport ECMO, and recently reported their 22-year experience with 68 children transported on ECMO by ground or fixed-wing aircraft.[69] All children survived transport. Survival to discharge was 65% for transported ECMO infants, which was equivalent to a survival rate of 70% for in-house patients receiving ECMO. Given the increasing use of extracorporeal cardiopulmonary resuscitation,[70,71] the need for transport ECMO may increase in the future, but will likely continue to be a specialized service offered by only a few institutions.

Future Directions

The neonatal transport team plays a critical role in providing optimal care to the ill outborn neonate. The role of the transport team has expanded as technology has advanced and has made it possible to deliver sophisticated therapies to infants out in the field. We have now begun to consider that earlier initiation of specific therapies, beginning in transport, may influence long-term outcomes. Although it is more difficult to conduct studies in the transport arena, prospective studies are possible and are now being done. The transport environment will continue to change as new technology and therapies develop. The expanding use of clinical simulators should be useful for transport team education and should be used to promote technical and clinical skill maintenance for team members. The emerging use of telemedicine, and its use on transport, may significantly change interactions with outlying practitioners and team communication with medical control. As changes come, the neonatal transport team will continue to play a vital role in stabilizing and transferring infants who require specialized care.

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32 Pulmonary Outcome and Follow-Up

Cheryl Marco Naulty, MD

According to data published by the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network, neonatal and infant mortality rates have decreased significantly in all birth weight categories over the past several decades, and particularly for very-low-birth-weight (VLBW) infants.[1-3] Contributing factors to the overall decrease in mortality were the use of exogenous surfactant, antenatal antibiotics, antenatal steroids, and more physiologically based ventilator strategies. Fanaroff et al.[2] compared mortality rates for infants of birth weight 501-1500 g for three epochs: 1987-1988, pre-surfactant use; 1993-1994, postsurfactant use and moderate use of antenatal corticosteroids; and 1999 to 2000, postsurfactant use and widespread use of antenatal corticosteroids. Mortality rates decreased from 23% to 17% to 14% for VLBW infants between each of the epochs (Fig. 32-1). Despite this major improvement in survival over that period, survival free of major morbidity did not change significantly. The major contributor to the long-term morbidity of these VLBW infants was chronic lung disease (CLD).[3,4] The acute pathophysiology of this complication of assisted ventilation is more fully discussed in Chapter 23.

Before addressing pulmonary outcomes and the long-term follow-up of neonatal survivors, it should be recognized that there are multiple issues that affect and influence the interpretation of outcome studies in general. At the very least, any report of the effect of a particular therapeutic strategy on a cohort of infants, at an age when full outcome measures can be assessed, may yield data on therapies that have long since changed. Hence, outcome studies are like a moving target, whose baseline is constantly changing. To have the best clarity of what constitutes long-term pulmonary outcome, there should be a clear understanding of the nature of chronic lung disease, how to define the severity of the neonatal pulmonary morbidity, and the potential contribution of the degree of prematurity to the overall outcome.

In 1967, Northway et al.[5] first recognized that not all infants with hyaline membrane disease (HMD) recovered completely. Some went on to develop a chronic pulmonary syndrome. Northway named the syndrome bronchopulmonary dysplasia (BPD). The definition of BPD or CLD has evolved significantly over time. The original criteria for BPD reported by Northway et al.[5] were based on an orderly progression of clinical, radiologic, and pathologic changes, beginning with severe HMD during the first week of life (stages I and II). Stages III and IV defined the progression over the next several weeks to a severe chronic obstructive pulmonary disease, frequently complicated by cor pulmonale.[6] However, as smaller, less mature infants have survived and the approach to ventilator management has changed, the distinct stages as described by Northway have become less clear. The radiologic abnormalities in extremely low-birth-weight (ELBW) infants do not seem to be similar to the original descriptions of Northway.

In 1979, Tooley[7] introduced a new definition of CLD. He proposed that any infant who required additional oxygen at 1 month or 30 days of age, with any radiologic abnormality of the lung parenchyma, could be considered to have CLD or BPD. It should be recognized, however, that the length of time required for additional oxygen might be as much a function of immaturity and the policies of the particular nursery unit as reflective of the severity of the lung pathology. Shennan et al.[8] found that, irrespective of gestational age at birth, the requirement for additional oxygen at 36 weeks' postmenstrual age (PMA) was a better predictor of abnormal long-term outcome and more likely to reflect an increased probability of abnormal pulmonary signs and symptoms in infancy. However, this definition has its limitations as well.

A definition of BPD based on oxygen therapy at 36 weeks' PMA may not accurately identify all infants with BPD.[9] Infants treated with oxygen for more that 28 days but not requiring oxygen at 36 weeks PMA may have residual lung disease.[9] The presence of BPD has become a surrogate for long-term pulmonary morbidity and should reflect the increased likelihood of abnormal pulmonary signs and symptoms in infancy, which has not proved to be the case.[10] Moreover, methods to assess the need for supplemental oxygen are not standardized between neonatal intensive care units (NICUs) or physicians; they vary with clinical practice.

The definition of BPD/CLD was reviewed at the National Institute of Child Health and Human Development (NICHD)/National Heart, Lung, and Blood Institute Workshop in June 2000.[11] Although these terms, *BPD* and *CLD*, are often used interchangeably, BPD was chosen to clearly distinguish this pulmonary morbidity from multiple chronic lung diseases in later life.[9] A severity-based definition for BPD was proposed. The severity-based diagnostic criteria recognized that some infants with oxygen requirements below the threshold of Shennan's definition have residual lung disease. Infants had to be less than 32 weeks' gestational age and were assessed at 36 weeks' PMA or at discharge. The criteria for mild, moderate, or severe BPD were based on the need for oxygen at all or at a level less or greater than 30%, recognizing that some children, who do not require any supplemental oxygen at discharge, still

may have mild residual disease. No specific radiologic findings were required because they did not increase the diagnostic sensitivity or specificity.[9]

This newest approach to defining BPD has its own limitations: variations in oxygen use with different respiratory support modalities; differing use of drugs such as respiratory stimulants, diuretics, and corticosteroids; and no uniformity on the acceptable level of oxygen saturation and no standardized physiologic test to confirm the oxygen requirement.[12] In any case, this concept of the "new BPD" captures the "change in the nature of the condition from failure of resolution of acute lung injury to an arrest in pulmonary alveolar development."[10] However, it has been recently noted that an additional predictor of long-term pulmonary morbidity in discharged prematures who have been ventilated and are no longer on positive pressure is the pCO_2 level at 36 weeks' PMA.[12a]

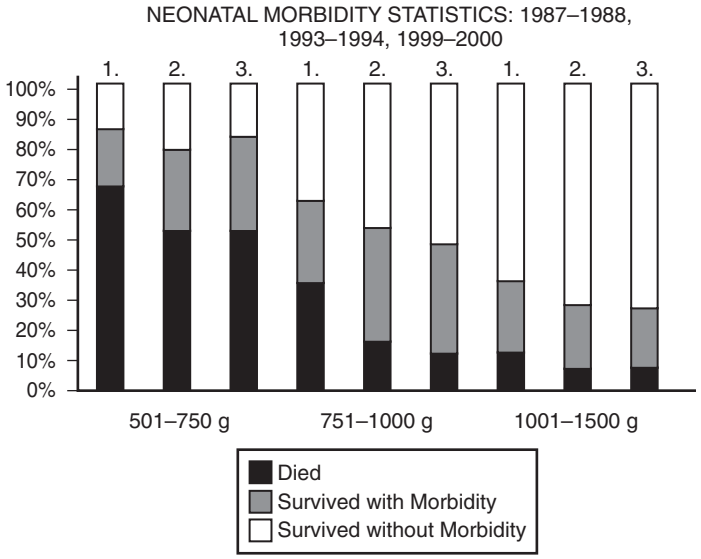

Figure 32-1 ■ *1,* Mortality rate for very-low-birth-weight (VLBW) infants cared for in National Institute of Child Health and Human Development (NICHD) Neonatal Research Network Centers ($n = 5$) in 1988 and 1994 by 250-g birth weight intervals. *2,* Major morbidity for all VLBW infants cared for in NICHD Neonatal Research Network Centers ($n = 5$) in 1988 and 1994 by 250-g birth weight intervals, including severe intracranial hemorrhage, chronic lung disease, and confirmed necrotizing enterocolitis. *3,* Major morbidity among VLBW survivors cared for in the NICHD Neonatal Research Network ($n = 5$) in 1988 and 1994 by 250-g birth weight intervals, including severe intracranial hemorrhage, chronic lung disease, and confirmed necrotizing enterocolitis (Reprinted from Stevenson DK, Wright LL, Lemons JA, et al: Am J Obstet Gynecol 179:1635, 1998).

The timing and choice of lung function measurements are important variables that influence the reporting of long-term outcome. The timing of the measurements will reflect the dominant changes occurring at the time of the testing: acute lung injury during the first 6 months and healing, remodeling, and growth in later childhood. It is not until 5 to 6 years of age that pulmonary function tests become more reliable. Total lung capacity (TLC) and vital capacity (VC) are related to overall body weight and increase with growth. Obstructive airway disease is a primary component of pulmonary dysfunction in BPD, and the best way to assess this is through forced expiratory maneuvers. With more severe disease, there is a rapid decrease in flow, expiration ends prematurely secondary to the narrowing of the small airways, and the flow-volume curve is concave after the point of maximum flow (Fig. 32-2).[13] A major limitation in measuring TLC and VC is the ability of subjects to cooperate before 3 to 4 years of age.

Further complicating the picture is the difficulty in separating out the influence of prematurity and low birth weight alone on pulmonary function in later childhood. Where does the role of various antenatal factors fit into the puzzle: fetal nutrition, exposure to cigarette smoke in utero, and a history of family atopy and asthma? Finally, consideration must be given to the relationship of lung functions to clinical symptoms, as well as the interaction of pulmonary dysfunction with later respiratory illnesses, and overall growth and health status and neurodevelopmental factors.

Pathology

The literature seems to suggest that BPD does not interfere with parenchymal lung growth,[14-17] but there is reported evidence of small airway obstruction suggestive of dysanaptic lung growth, that is, normal growth of lung volume but not of airway size.[18] A look at the pathology of those infants who die as a result of their respiratory disease beyond the acute phases of BPD might provide some

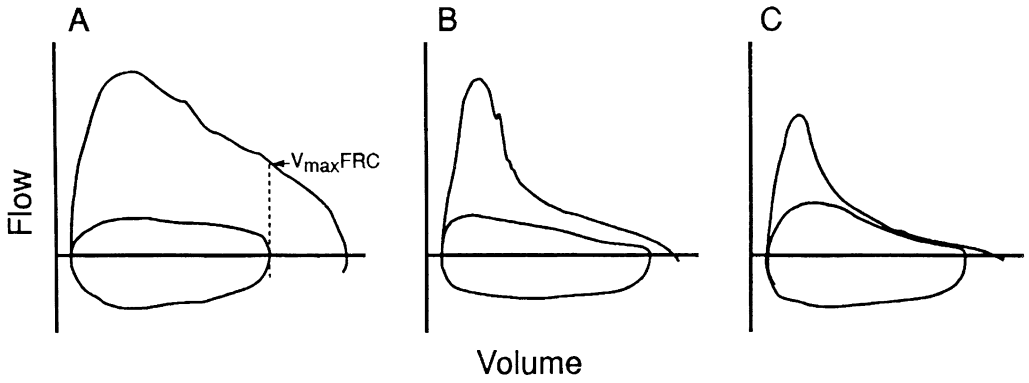

Figure 32-2 ■ Schematic of typical partial expiratory flow-volume loops. **A,** Normal infant. **B,** Infant with mild airflow limitation (infant with history of respiratory distress syndrome). **C,** Infant with bronchopulmonary dysplasia. (Reprinted from Bhutani VK, Abbasi S: Clin Perinatol 19:649, 1992).

insight into the morphology associated with the abnormal pulmonary function findings.

In 1986, Stocker[19] described the pathology of 28 infants born between 1974 and 1984, who all had severe BPD and died at 3 to 40 months of age. The cause of death was progressive respiratory failure in 68%, and an additional 18% died of pneumonia superimposed on long-standing BPD. The original lung injury leading to BPD was characterized by necrotizing bronchiolitis, alveolar cell hyperplasia, and bronchiolar squamous metaplasia. The main residual feature in the "healed" stage of BPD was focal alveolar septal fibrosis. The degree of fibrosis and parenchymal involvement varied considerably, with severe fibrosis in one area and normally inflated or hyperinflated lung in adjacent lobes. Stocker postulated that the variability might be related to a "protective effect" of the necrotizing bronchiolitis. The occlusion of the bronchioles by the inflammatory debris might actually shield the distal sublobule from the high oxygen tensions and ventilatory pressures. With healing, there might be absorption and recanalization, leaving a normal or less damaged parenchyma "downstream." Alternatively, the exudates might be absorbed into the alveolar wall, resulting in fibrosis, or the debris might become organized tissue, resulting in total obliteration of the alveolar space (Fig. 32-3). The morphologic features as described in this study might account for the clinical studies on infants who demonstrated increased small airway resistance, increased functional residual capacity, maldistribution of ventilation, and airway hyperreactivity.

With the continuing advancement in mechanical ventilation and the current widespread use of surfactant, the classic pathologic features of BPD are now seldom seen. The characteristic lung injury of BPD currently is one of minimal-to-moderate diffuse alveolar septal fibrosis.[20] The pathologic alterations are thought to be primarily

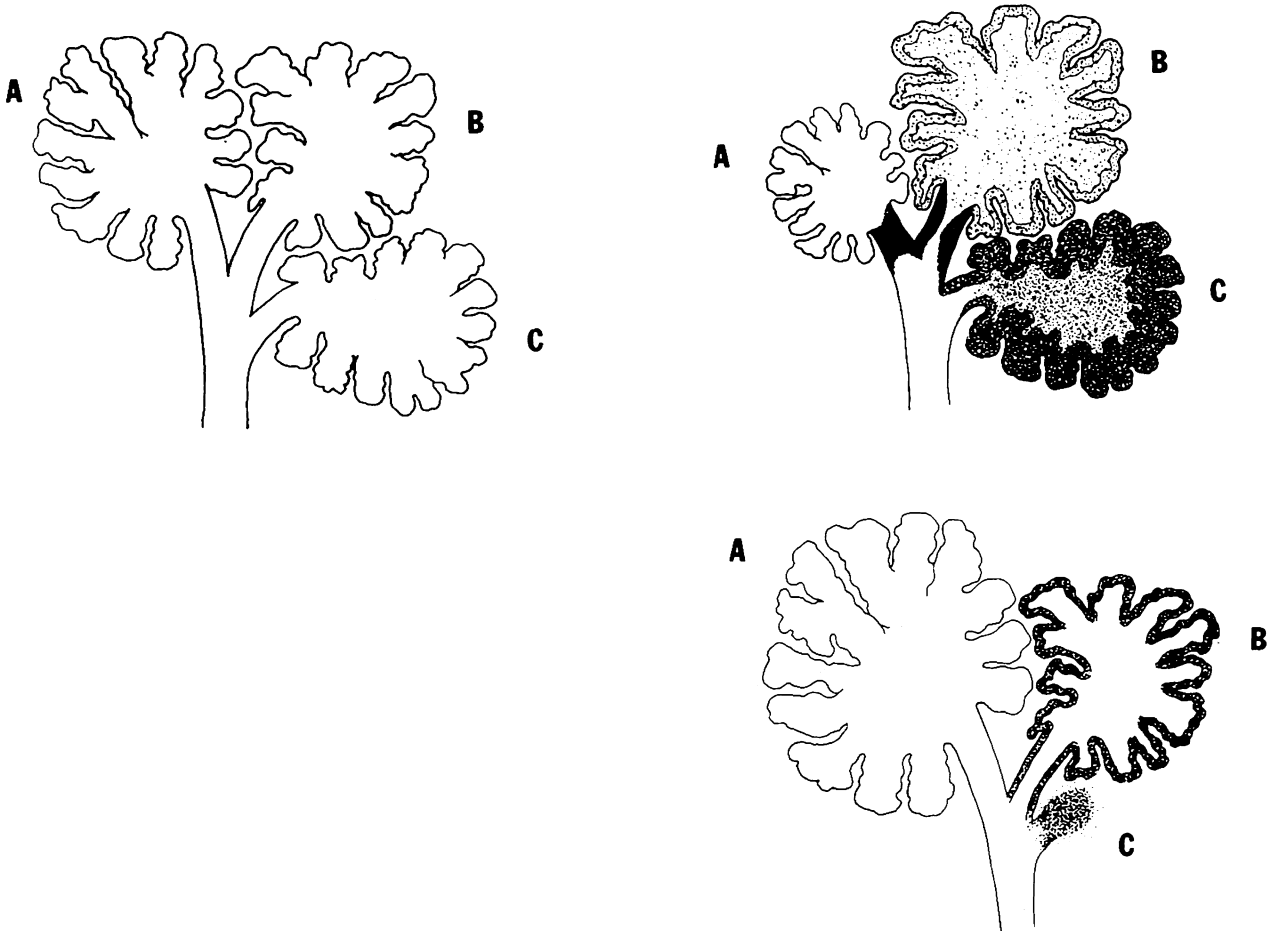

Figure 32-3 ■ *Top left,* Schematic drawing of normally expanded and aerated pulmonary lobules. *Top right,* Acute bronchopulmonary dysplasia. *A,* Necrotizing bronchiolitis occludes the bronchiolar lumen, "protecting" the parenchyma distal to it from the high oxygen tension and pressure used in maintaining adequate oxygenation. *B,* The bronchiole is narrowed by mucosal hyperplasia and muscular hypertrophy, thereby reducing the amount of pressure and oxygen tension in the lobule distal to it. Alveolar cell hyperplasia, septal fibroplasia, and alveolar macrophage dysplasia occur to a mild-to-moderate degree. *C,* The bronchiole is widely patent, exposing the distal sublobule to the full ventilatory pressure and oxygen tension. The alveolar lumina are largely obliterated by alveolar macrophages, alveolar cell hyperplasia, and marked septal fibroplasia. *Bottom right,* Long-standing "healed" bronchopulmonary dysplasia (LSHBPD). *A,* With resolution of the necrotizing bronchiolitis that occluded the lumen of the bronchiole, the uninjured sublobule overexpands to compensate for the less expansile injured portions of lung (*B, C*). *B,* With resolution of the mild-to-moderate injury incurred by the parenchyma during the acute stages of bronchopulmonary dysplasia, the sublobule displays the hallmark of LSHBPD—septal fibrosis. *C,* The sublobule is virtually obliterated by organization of the severe acute bronchopulmonary dysplasia (Reprinted from Stocker JT: Hum Pathol 17:959, 1986).

mediated by highly reactive oxygen species after respiratory therapy.[21] Husain et al.[20] found that the alveolar septal fibrosis was a mild diffuse injury that resulted in slowing of alveolar saccular and alveolar development. They reported that the ratio of the radial alveolar counts to the mean linear intercept (RAC/MLI), which reflects the comparison of the number of alveoli and their size, was significantly lower in the infants with BPD than in non-BPD controls. RAC is a measure of the complexity of alveolar development, and these values were significantly decreased in infants with BPD. In contrast, MLI, which is a measure of alveolar size, was significantly increased, reflecting hyperinflation of the alveoli.[20,22]

This suggests that there is an "acinar arrest" during the time when normal infants have rapid alveolar development. There is a failure to increase the complexity of the acinus and a compensatory hyperexpansion of the lung with growth of the thorax. This combination of hyperinflation and decrease in alveolar number would explain the seemingly normal TLC but otherwise severe impairment in lung function. These authors postulate that, in the absence of necrotizing bronchiolitis, there are no "protected" acini. All acini are uniformly exposed to the ventilatory pressures and oxygen tensions, leading to this partial or complete arrest in acinar development. Further, they found that surfactant therapy did not alter this inhibited development in infants with severe BPD.[20] To add to this picture, early postnatal dexamethasone (Decadron) therapy in rats was found to inhibit outgrowth of new interalveolar septa, leading to a mature but emphysematous lung with larger and fewer air spaces.[23,24] In summary, " infants with BPD, whether or not they have been treated with prenatal steroids and/or surfactant, still show a lack of increased complexity (a decrease in alveolarization), an abnormal capillary morphology, and an interstitium with variable cellularity/fibroproliferation."[25]

Role of Airway Injury in the Development of Chronic Pulmonary Sequelae

Mucosal and submucosal necrosis with inflammation have been described at the vocal cords, in the subglottic region of the larynx, and in the trachea after endotracheal intubation for assisted ventilation.[26,27] The severity of the lesion was related to the duration of intubation and to the presence of bacterial infection.[26] No lesions were seen in children who had not been intubated.

At the more extreme end of the spectrum of airway injury from endotracheal intubation is the development of subglottic stenosis.[28,29] Movement of the endotracheal tube has been judged to be a contributing causative factor, and orotracheal intubation has been associated with a higher incidence of subglottic stenosis than has nasotracheal intubation.[30,31] After mechanical injury to the ciliated respiratory epithelium, squamous metaplasia may occur.[32] This may lead to impaired clearance of pulmonary secretions and thus to a predisposition toward pulmonary infection. In addition, the potential for premalignant change, particularly with regard to the propensity for the occurrence of neoplasia in the area of the larynx and vocal cords, needs to be evaluated on a prospective, long-term basis.

Squamous metaplasia of the respiratory epithelium occurs in vitamin A deficiency.[33] Premature infants have been reported to have levels of vitamin A that are in the deficient range.[34,35] In the study of Hustead et al.,[34] the ventilated premature infants who developed BPD had lower levels of vitamin A at birth and at age 3 weeks than those who did not have BPD. In addition, the dietary intake of vitamin A has been reported to be lower in the mothers of premature infants who developed BPD.[36] Shenai et al.[37] reported that supplementation with vitamin A resulted in an approximately 50% decrease in the incidence of BPD and a decrease in the incidence of respiratory illness. However, Pearson et al.[38] did not find a reduction in the incidence of BPD with vitamin A supplementation. Theses researchers have speculated that this differing experience may be a result of the greater use of exogenous surfactant and postnatal steroids in the more recently studied patients of Pearson et al.[38]

More recently, in a large multi-institutional study, Ambalavanan and colleagues[38a] found that intramuscular vitamin A supplementation for ELBW infants reduced bronchopulmonary dysplasia without increasing mortality or neurodevelopmental impairment at 18 to 22 months. However, this study was not powered to evaluate small magnitudes of change in long-term outcomes.[38a] At this time it may be premature to make a recommendation for the routine use of vitamin A to prevent BPD.

Exposure to high FIO_2 damages ciliated epithelial cells in the bronchi[39] and the trachea[40] and decreases the velocity of the tracheal clearance of mucus.[41] Free oxygen radicals, including the superoxide anion (O_2), accumulate, producing inhibition of cell growth and cell damage.[42] Injury to the pulmonary alveolar macrophages results in a release of chemoattractant substances that causes an outpouring of polymorphonuclear leukocytes.[43] These leukocytes contain collagenases and elastases that can cause further damage to connective tissue in the lung. The administration of liposome-encapsulated catalase to experimental animals prevented the histologic changes of chronic pulmonary O_2 toxicity.[44] The administration of superoxide dismutase to premature infants with RDS has been reported to reduce the incidence of,[45] but not totally prevent, the development of BPD.

It appears likely that the prevention of BPD will require a multifaceted approach, and attention will need to be devoted simultaneously to several factors related to their ability to cause disease either separately or acting synergistically. The accumulating information suggests that prematurity is such a strong determinant of these sequelae that a reduction in its incidence itself might be expected to result in a reduction in the frequency of later pulmonary sequelae.

Family and Genetic Factors and Later Respiratory Abnormalities

In 1980, Nickerson and Taussig[46] reported an unusual incidence of a family history of asthma in ventilated RDS patients who developed BPD. They compared 21 RDS survivors without BPD with 23 with BPD and found that the BPD infants were significantly younger and smaller. In

addition, 17 of the 23 infants (77%) with BPD had a family history of asthma compared with only 7 of 21 infants (33%) without BPD. Nickerson and Taussig[46] speculated that the development and/or severity of the BPD might be related to a genetic predisposition of airways to become highly reactive after exposure to one or more etiologic factors. It should be noted, however, that their incidence of a family history for asthma in 33% of the infants without BPD is high in comparison to the normal population.

The relationship between a family history of asthma and/or atopy and the development of BPD is controversial at best. To add to the confusion, various associations are made among a variety of genetic and perinatal factors and later respiratory abnormalities, including gender, ethnicity, prematurity, RDS, BPD, and familial history. Riedel[47] reported that bronchial hyperreactivity elicited by histamine inhalation had significant statistical correlation with the duration of neonatal ventilation, birth weight, and gestational age. Several studies showed a high prevalence of a family history of asthma or atopy among prematurely born children, who had recurrent respiratory symptoms or wheezing in early childhood.[48,49] In a large epidemiologic study, males with birth weight less than 1500 g, prematurity, and RDS were significant predictors of childhood asthma up to 4 years of age.[50] Von Mutius et al.[49] found that premature female infants had a higher prevalence of asthma and decreased lung function at 9 to 11 years of age, especially if they required mechanical ventilation. An ethnic influence on lung function has been described in normal, full-term children.[51] Forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) were found to be significantly lower in children of African and Indian origin than in those of European origin.

Bertrand et al.[52] studied the role that familial factors may play in the long-term sequelae of RDS. They looked at prematurely born infants with and without RDS and their full-term siblings as controls. An additional group of full-term children with no personal or family history of asthma or allergies was studied. They found that premature children, regardless of a previous history of RDS, and their full-term siblings had increased airway hyperreactivity. In a 1995 study, Hagen et al.[53] examined the relationship between a family history of asthma, neonatal CLD, and oxygen dependency in a group of infants of 24 to 30 weeks' gestation. They found that prematurity, and not a family history of asthma, was the dominant factor in the prevalence of CLD. However, infants with a family history of asthma were more likely to be oxygen dependent at term (odds ratio [OR] 11.0; 95% confidence interval [CI] 2.3, 53.0). They concluded that infants with CLD and a family history of asthma were more likely to develop severe CLD and experience a delay in recovery, as measured by the need for prolonged supplemental oxygen.

Hyperreactivity in both bronchial and uterine smooth muscle might account for the association between asthma and premature births.[54] Parents with a family history of asthma might be more likely to give birth to VLBW infants. Kramer et al.[55] described an association between spontaneous preterm labor and maternal asthma. In 1988, Chan et al.[56] reported that increased airway responsiveness to histamine in LBW infants and a full-term reference population was significantly related to a history of asthma in first-degree relatives (natural parents and siblings). However, they found no increase in the prevalence of maternal asthma or of airway responsiveness to histamine in the mothers, thus failing to support the hypothesis that maternal smooth muscle hyperreactivity (both uterine and airway) has a causative role in premature labor and subsequent bronchial hyperresponsiveness in their prematurely born children.

To date, available studies have not been able to conclusively associate a maternal or family history of asthma and neonatal respiratory disease in premature infants. The role of maternal bronchial hyperreactivity or asthma in the etiology of premature labor remains controversial.[57] Data do seem to support, however, a strong association between a family history of asthma and childhood asthma in VLBW infants, regardless of the development of RDS or BPD. On the other hand, BPD is associated with childhood asthma regardless of the family history. Finally, there may be a link between a family history of asthma or atopy and the severity of the CLD or the duration of oxygen dependence.

Pulmonary Status of Prematurely Born Infants

The literature is clearly divided on the independent correlation of birth weight and neonatal pulmonary disease with pulmonary abnormalities in later childhood. As early as 1928, long before the availability of assisted ventilatory support, Capper[58] commented on an increased incidence of respiratory infections in surviving premature infants. Later, a national survey of the health of a group of prematurely born and full-term infants conducted in England revealed that almost twice as many premature infants as full-term infants died or were admitted to a hospital, most frequently because of pneumonia.[59] The question is whether it is the effect of the type and severity of the neonatal lung disease, the evolving neonatal treatment and the subsequent interaction of intercurrent respiratory illness, or the child's individual constitution as reflected in birth weight and prematurity that puts these infants at risk for childhood pulmonary morbidities.[60]

A 1991 study published in the *British Medical Journal*[61] reported that low birth weight (LBW) in infants might be an independent predictor of lung function and death from chronic obstructive pulmonary disease in adult life. These data, known as the Barker effect, were based on a retrospective study of more than 6000 adult males, born between 1911 and 1930, with known recording of birth weight and childhood illness. Death from chronic obstructive airway disease in adult life was strongly associated with low birth weight alone.

Various studies relative to LBW and VLBW infants argue for the contribution of prematurity alone to later evidence of obstructive airways disease and hyperreactivity. Chan et al.[62] reported abnormal flow measurements and increased airway responsiveness in LBW infants compared to full-term controls at 7 years of age. The increased airway responsiveness was clinically significant and irrespective of neonatal respiratory illness or treatment. Similar data were reported from studies by Tammela et al.[63] and Mansell

et al.[64] They reported no differences in TLC and FVC between LBW and term infants but significantly lower flow values in LBW children at 6 to 10 years of age. In school-aged children, reduced lung function and respiratory symptoms, especially wheezing, were associated with LBW, regardless of respiratory complications at birth.[65,66] Every additional week of gestation reduced the risk of wheezing by 10%.[66] In a very well-designed study, Galdis-Sebaldt et al.[67] found decreased FEV_1, air trapping, and increased airway responsiveness to methacholine in all VLBW infants with or without HMD, but not in infants with HMD whose birth weight was greater than 1500 g. In 1995, Rojas et al.[68] reported CLD as a frequent sequela in VLBW infants with mild or no RDS. In this population, the development of late episodes of patent ductus arteriosus (PDA) in association with a nosocomial infection seemed to play a role.

More recently, Anand et al.[69] studied the lung function and respiratory health of a geographically defined population of adolescents at 15 years of age, who were born preterm with birth weight less than 1500 g. Compared to matched controls, the adolescents who were VLBW showed medium and small airways obstruction as measured by a significant reduction in FEV_1/FVC ratio and forced expiratory flow (FEF_{25-75}). This reduction in airflow indices was associated with a significant increase in the prevalence of chronic cough, wheezing, and asthma. These findings were related to prematurity alone rather than intrauterine growth restriction or having received respiratory support during the neonatal period. Hjalmarson and Sandberg[70] compared lung function in preterm infants with mean gestational age of 29.5 weeks, who had no signs of illness at birth and no supplemental oxygen past 3 days of life, with healthy full-term infants. The preterm infants showed decreased specific compliance and specific conductance, but increased gas mixing efficiency relative to the term infants. These measures reflect dysfunction of terminal respiratory units and higher elastic recoil. These same researchers[71] reported similar ventilatory impairments in preterm infants with BPD, and the magnitude of impairment correlated to the severity of BPD using the new classification system. The authors speculate that preterm birth alone and early exposure to extrauterine conditions may affect alveolarization and formation of elastic tissue in the lungs, and that acinar growth is hampered, whereas airways grow more normally.

Outcome of Infants After Assisted Ventilation and Bronchopulmonary Dysplasia

Equally compelling are those studies that relate HMD and mechanical ventilation in the neonatal period to later abnormal lung function. The severity of the neonatal respiratory illness, along with the occurrence of complications such as prolonged ventilation and pneumothorax, has been associated with increased respiratory morbidity and significantly lower FEF measurements in VLBW infants with BPD at ages up to 18 years.[72-75] In a study of VLBW infants with and without BPD compared to controls at age 11 years, Kennedy et al.[76] found only a small contribution of gestational age and birth weight to decreased expiratory flow rates. Together birth weight and gestational age accounted for only 16% of the variance in FEV_1. The best predictors for abnormal lung function were number of days receiving supplemental oxygen and a reported family history of asthma, which together accounted for a 43.4% reduction in FEV_1. In addition, Kennedy et al.[76] reported a "dose effect" of supplemental oxygen on the subsequent FEV_1, with little effect associated with less than 20 days of O_2 but a decline of 3% in FEV_1 for every extra week of supplemental oxygen beyond 20 days. It should be noted, however, that, although there were statistically significant reductions in flow values, the overall lung function measurements were within the published norms for full-term children of similar age.

In 1990, Northway et al.[14] reported in the New England Journal of Medicine the follow-up to adolescence of 26 children with BPD who were born between 1964 and 1973. The majority had abnormalities in pulmonary function testing, with evidence of hyperinflation and small airway obstruction. Most of the abnormalities were mild to moderate, and only 6 of the 26 were clinically symptomatic. The chest x-ray findings were subtle, but computerized tomographic findings revealed multifocal areas of reduced lung attenuation and perfusion[77] These data, along with other reports of populations from the 1970s and 1980s,[15,16,78,79] found that BPD did not appear to interfere with parenchymal lung growth, because TLC and FRC increased normally with age, but BPD did result in small airway obstruction and hyperreactivity. One may conclude from these findings that infants with BPD have normal alveolar formation but also have persistent damage to their small airways.

In comparisons of large cohorts of VLBW children to healthy term infants at school age, abnormalities in lung function were present only in those with BPD.[80,81] Preterm infants without BPD, even if they had been treated with intermittent positive-pressure ventilation, showed no differences in lung function from the term infants. The abnormalities found in the children who had BPD included higher residual volumes, indicative of air trapping, and significant decreases in FVC, FEV_1, and FEF_{25-75}, reflecting airflow obstruction. These differences increased when BPD was defined as oxygen dependence at 35 weeks' postconceptional age (PCA). However, although various pulmonary function measurements were significantly reduced in infants with BPD, the values were either within or close to the normal range and, therefore, not clinically significant.

In outcomes that focus on infants with more severe BPD, there is clear evidence of more significant long-term sequelae. Mallory et al.[82] looked at 11 infants with BPD and tracheostomies at up to 3 years of age and compared those ventilated for less than 5 months with those ventilated for more than 10 months. All showed an increase in FVC with age, reaching normal values by 3 years. In contrast, mean expiratory flows ($MEF_{25\%}$) were very abnormal in all patients. Those with shorter ventilatory times and less severe BPD had a gradual increase in expiratory flow rates of up to 40% of predicted by 3 years, whereas those with more severe disease had no change in flow values and remained at only 10% of predicted at 3 years of age. Jacob et al.[83] described a population with severe BPD in which

all infants were on oxygen at 44 weeks PCA and all were discharged home on O_2. At 11 years of age, these children all showed significant gas trapping and hyperinflation, and mean FEV_1 was 65% of predicted compared to preterm infants without BPD. The severity of these abnormalities was inversely related to the duration of O_2 exposure.

Exercise Tolerance

Although many studies have found statistically significant, but not clinically relevant, abnormalities in pulmonary function measurements in children with BPD, there is some evidence suggesting that exercise tolerance in these children may not be normal. Maximum oxygen consumption and the anaerobic threshold are recognized markers of exercise performance. The failure of an adequate increase in minute ventilation during exercise to meet the high metabolic demands equals the hallmark of the cardiorespiratory response to exercise in children with BPD.[84] This certainly raises concerns about possible declining exercise capacity into adulthood.

Bader et al.[85] described 10 BPD survivors who underwent exercise testing at a mean age of 10.6 years. These patients had a decrease in arterial O_2 saturation to pre-exercise levels at maximum workload, whereas six age-matched normal controls born at term did not. No differences in maximum O_2 consumption were noted between these two groups. The pre-exercise transcutaneous carbon dioxide tension was higher and remained high at maximum workload in the BPD group compared with the control group. Later studies demonstrated BPD patients, tested at up to 12 years of age, had limited ventilatory reserve, a lower anaerobic threshold, and were more likely to have O_2 desaturations during exercise.[84,86,87] Even when no significant cardiopulmonary limitations to exercise were found, those with BPD had higher respiratory rates with normal tidal volumes in response to exercise, rather than an increase in tidal volume, as occurred with control children. There may be certain qualitative adaptations to cardiopulmonary responses to exercise in children with BPD that are distinct from term infants.[88]

Kriemler et al.[89] reported on pulmonary and exercise-related effects of BPD at 5 to 7 years of age in VLBW children born 1988 to 1990 with and without CLD versus term controls. Both preterm groups had some pulmonary dysfunction at rest and after exercise and a higher prevalence of exercise-induced bronchospasm with no reduction in maximal aerobic exercise performance. Those with CLD had higher oxygen uptake at a given mechanical power than those without, which may cause early fatigability during prolonged exercise even when aerobic performance is normal. Similarly, Kilbride et al.[90] found that 20% of ELBW children (less than 801 g) at 9 to 15 years of age had clinically abnormal pulmonary function compared to normal birth weight (NBW) children. Pulmonary function abnormalities consistent with obstructive lung disease were more frequent in children with CLD; however, O_2 consumption measurements were significantly lower for ELBW infants independent of CLD. This is suggestive of a lower level of fitness for ELBW children compared with NBW children.

In conclusion, data on the influence of prematurity on long-term pulmonary function are conflicting. All infants with BPD seem to have some degree of small airway obstruction, but the abnormalities may not be clinically relevant in many cases. Long-term studies on the combined effects of surfactant therapy, use of antenatal and postnatal steroids, and application of new modes of ventilation are just being done. Berger et al.[91] recently reported that, over a 15-year period, the survival rate of VLBW infants improved significantly without increasing the incidence of moderate-to-severe pulmonary morbidity, using the new definition of BPD. The authors attribute this finding to the increased use of antenatal corticosteroids and changes in respiratory support strategies from pressure-limited, time-cycled, continuous flow ventilation to synchronized intermittent mandatory ventilation (SIMV), high-frequency oscillation using a high-volume strategy, and the concept of permissive hypercapnea. However, they cannot determine to what extent each of these protective lung strategies has played a role in the improvement in outcome. Finally, there is still the question of whether there are more subtle abnormalities that can be discerned only by challenging the capacity and endurance of lung function in children, and whether these subtleties will lead to increasing problems with age on into the adult years.

Postnatal Growth and Later Respiratory Illness

It has generally been accepted that growth failure is a major problem in infants with CLD. Markestad and Fitzhardinge[92] found growth retardation associated with severe and prolonged respiratory dysfunction in 26 survivors with BPD. The average height and weight at term were at or below the third percentile. Subsequent growth occurred at an accelerated rate after improvement of respiratory symptoms. Vohr et al.[93] and Meisels et al.[94] both reported that infants with BPD were at greater risk for growth retardation in the second year than those with RDS alone. This growth failure is thought to be related to increased oxygen consumption and increased respiratory energetics secondary to abnormal pulmonary mechanics.[95] Additional contributing factors are decreased caloric intake related to abnormal sucking patterns, palatal abnormalities, and iatrogenic fluid limitations.

Later studies do not necessarily support these observations. Vrlenick et al.[96] criticized prior reports based on problems with small sample size, short length of follow-up, timing of the follow-up, variable definitions of growth failure, and failure to consider confounding neonatal, neurologic, and demographic risk variables. Although their data initially supported differences in growth outcome among VLBW infants with and without BPD, no difference in any growth parameters was found when accounting for all covariates.[93,94] Likewise, Chye and Gray[97] and Davidson et al.[98] reported growth patterns of infants with BPD similar to other VLBW infants who were ventilated but did not develop BPD. All VLBW infants who were ventilated, with or without subsequent BPD, had significant growth delays in all parameters, and growth velocity at 21 months was similar in both groups.[98] Birth weight, not respiratory

status, was the best predictor for postterm growth measurements at 12 and 21 months.

Is poor nutritional health related to factors other than BPD per se? Data reported by deRegnier et al.[99] indicated that growth patterns are established early. By the first 2 to 4 weeks of life, infants with BPD had lower protein and energy intakes. They took longer to achieve full enteral feedings and were lower in all growth parameters, as well as in arm muscle and fat measurements, than VLBW infants without BPD. When BPD infants were able to tolerate full enteral intake, they were able to accrete muscle and fat at a normal rate but were unable to catch up to their peers.[99] VLBW infants both with and without BPD have a bone mineral content well below that of full-term infants in the first year.[100] Singer et al.[101] assessed the feeding patterns of VLBW infants close to term gestation. The infants were more difficult to feed and spent less time sucking and more time in nonfeeding behaviors than VLBW infants without BPD, as well as healthy term infants. As a result, the BPD infants ingested lower volumes and fewer calories; however, no long-term growth data was reported.

Infants with LBW, especially those with chronic sequelae of assisted ventilation, are believed to have an increased risk of developing frequent and severe infections, especially in the lower respiratory tract. As early as 1968, Lewis[102] reported that 11 of 63 RDS survivors in London, England, required later hospital admission for bronchiolitis or bronchopneumonia. Preterm infants during the first 1 to 3 years have increased and recurrent symptoms of coughing and wheezing, an increased need for antibiotics and other medical care, and were more often hospitalized than full-term infants.[48,74,103-105] In a large series that followed RDS survivors for at least 3 years, Stahlman et al.[106] reported that 23% were found to have experienced repeated episodes of wheezing or pneumonia or chronic respiratory symptoms. Data from a questionnaire survey of the respiratory history of 7-year-old children whose birth weight was less than 2000 g was compared with those from a reference group of local school children.[107] The comparison showed frequent cough was significantly more common among VLBW children who had received neonatal respiratory treatment. The prevalence of cough correlated with the neonatal O_2 score (based on the duration and the fractional inspired oxygen concentration used), but not with the use of mechanical ventilation.[52] The incidence of wheezing was not increased in this group of prematurely born children.

The rate of lower respiratory tract infections in infants with BPD has been reported to be significantly higher in comparison with that for the positive-pressure-ventilated RDS survivors without BPD.[93] Kitchen et al.[108] followed three cohorts of infants (group 1: 500-999 g birth weight; group 2: 1000-1500 g birth weight; group 3 greater than 2500 g birth weight) up to 8 years of age. They found that all VLBW infants had more wheezing illnesses and more hospital admissions for respiratory problems in the first 2 years than the normal term infants. From 2 to 8 years, however, respiratory health and decreased expiratory flow measurements, indicative of obstruction, were not related to birth weight, but they were associated with continuing respiratory illnesses at 8 years, especially asthma and bronchiolitis.[108] Beyond 5 years of age, Korhonen et al.[104] found respiratory infections were more common only in infants who had BPD. deKleine et al.[73] associated increased treatments for pneumonia and increased hospital admissions for respiratory infections during the first 4 years with the diagnosis of BPD. After 8 years, BPD patients did not have increased respiratory symptoms over children who had HMD but no assisted ventilation, indicating improvement with age.

Furman et al.[109] reported that infants with CLD had a mean hospital stay in the first year of 153 days, the majority of which was the initial neonatal stay. However, up to 50% were rehospitalized within the first year and 37% in the second year. Cardiac and respiratory causes predominated as the primary reasons for rehospitalization, with respiratory causes representing the majority. They concluded that the duration of neonatal stay and the total duration of hospitalization in the first year were significantly associated with all measures of the severity of CLD, and the duration of hospitalization in the first year might be the more useful index of overall morbidity.[109]

In summary, the evidence indicates that later respiratory illness is more common among those who were born prematurely, appears to be increased in frequency in the children who had RDS, and is further increased in those who develop BPD. Encouragement can be taken from the fact that there seems to be improvement with age in all categories. It is particularly important that these children avoid smoking and environmental pollutants to minimize their risk for later impairment of pulmonary function. The impact of maternal smoking of one or more packs per day on lowering the age of onset of lower respiratory infections and on increasing the incidence of wheezing and nonwheezing illness in infancy needs to be emphasized when the parents of these children are counseled.[110]

Respiratory syncytial virus (RSV) is one of the major causes of respiratory morbidity in premature infants, especially those with CLD.[111] In general, an immunologic factor may contribute to the increased incidence of lower respiratory tract infections in prematurely born infants. Maternal immunoglobulin G is transferred to the fetus during the third trimester of pregnancy,[112,113] and serum immunoglobulin G levels at birth correlate directly with gestational age.[112,114] Hypogammaglobulinemia in infants weighing less than 1500 g at birth has been observed at 6 months of age and was associated with an increase in respiratory infections.[115] Premature infants of less than 28 weeks' gestation have been found to have significantly lower levels of specific antibodies against RSV and lower mean titers of neutralizing antibody than term infants.[116] This possibility has been suggested as an explanation for the higher incidence of RSV infection observed in prematurely born infants,[117,118] but these authors believed that the lower specific antibody levels did not entirely account for the increased incidence of infection and that other immunologic factors or structural differences must also be involved.

In the first year of life, 15% to 22% of all children, regardless of birth weight, develop lower respiratory tract infections, and 0.5% to 2% of previously healthy children who become infected require hospitalization. The mortality rate in hospitalized infants is 0.5% to 1%. RSV infection is the major cause of hospitalization of infants with BPD

during the winter months,[119] with rates ranging from 2.7% to 45%.[111,120]Meert et al.[121] found that of all infants hospitalized secondary to RSV infections, those with BPD had an increased length of stay, increased days on the ventilator and on supplemental oxygen, increased physiologic instability, and an increased rate of nosocomial infections. Infants with BPD are clearly more susceptible to more severe and prolonged illness from RSV than the healthy term population and may develop severe pulmonary compromise as a result of their infection at an older age than children without BPD.

The use of RSV immune globulin intravenous (RSV-IGIV), RespiGam (Massachusetts Public Health Biologic Laboratories and MedImmune, Inc., Gaithersburg, Md, USA), and the more recently developed intramuscular monoclonal antibody palivizumab (Synagis, Med Immune) provide an approach to the prevention or amelioration of RSV infections in high-risk infants.[122] Prophylactic use of palivizumab in a high-risk pediatric population resulted in a 55% reduction in the risk of hospitalization attributable to RSV infections. Infants and children with CLD and prematurely born infants without CLD experienced a reduced number of hospitalizations and a decrease in the severity of illness.[123] The American Academy of Pediatrics currently recommends that palivizumab or RSV-IVIG prophylaxis be considered monthly during RSV season for infants and children younger than 2 years of age with CLD, who have required medical therapy for their CLD within 6 months before the anticipated RSV season.[122] In addition, infants born at 32 weeks of gestation or earlier without CLD may be at high risk based on gestational and chronologic age at the beginning of the RSV season and should also be considered for prophylaxis.

Neurodevelopmental Outcome

The impact of CLD or BPD on long-term neurodevelopmental outcome is unclear (also see Chapter 28). As in most long-term outcome studies, the sample size, heterogeneity of the population, lack of controls, timing of the assessments, and what was measured and the variables considered, strongly influence the results. What is the effect of long-term ventilation? Is the outcome no different from the rest of the preterm population but only influenced by the degree of intraventricular hemorrhage (IVH)? How do socioeconomic and environmental factors affect the equation? Is the impact on motor developmental performance, cognitive performance, or both?

Early studies were discouraging. LBW infants with BPD did not function as well as those with RDS alone.[94] They had lower scores on both the Bayley[124] mental developmental index (MDI) and psychomotor developmental index (PDI) and a higher rate of neurologic impairment.[125] At 36 months, children with BPD and/or IVH were functioning in the subnormal range for their mental scores and in the low-average range for motor development, significantly below infants with RDS and no IVH.[126] Perlman and Volpe[127] described an extrapyramidal movement disorder that was observed in 10 premature infants with severe BPD. The natural history was partial or complete resolution or a static course. These studies, however, did not separate out the effect of BPD from other important perinatal variables, especially IVH.

Long-term follow up studies in older children have revealed a hidden morbidity not apparent until the school-age years. Vohr et al.[128] reported lower scores in perceptual motor integration, more problems with motor coordination, and a greater need for academic support in a group of 10- to 12-year-old children who had BPD, even after eliminating those with cerebral palsy from the analysis. Others described CLD associated with long-term effects on cognitive functions related to visuomotor integration and visuospatial problem solving,[129] lower full-scale intelligence quotient (IQ) and performance IQ scores,[130] and lower scores in the cognitive domains of language and memory, which persisted even after controlling for birth weight, gestational age, and severity of IVH.[131]

Katz-Salamon et al.[132] found that CLD alone had a deleterious effect on the early development of certain psychomotor functions such as hand-eye coordination, but they did not have any longer term correlations. Majnemer et al.[133] assessed outcome in VLBW infants with and without BPD at 10 years of age. Neurologic abnormalities, including subtle neurologic signs, cerebral palsy, microcephaly, and behavioral difficulties, were highly prevalent in the BPD group (71% compared with 19% in the control group). Severe IVH occurred with equal frequency in both groups. BPD infants were twice as likely to have difficulties in gross and/or fine motor skills and postural stability than their peers. The overall motor function correlated with the severity of the lung disease, as measured by the duration of hospitalization, duration of home oxygen therapy, and decreased lung function at school age, and not the degree of prematurity.[133]

In 1997, Singer et al.[134] reported the outcome of three groups of infants at 3 years of age: VLBW infants, with and without BPD, and full-term controls. BPD was a significant independent predictor of poorer motor outcome, associated with a 10- to 12-point decrement in the PDI scores. BPD and the neurologic risk score together accounted for 21% of the variance in the motor outcome. Minority race, lower social class, lower birth weight, and neurologic risk predicted poorer mental developmental outcome at 3 years. After controlling for these risks, BPD did not predict the MDI. In terms of mental outcome, children with a history of VLBW and BPD and who did not have neurologic sequelae, had similar outcomes to VLBW infants without BPD.[134]

In contrast, there are several reports of infants with CLD whose outcomes were more associated with central nervous system complications or prematurity than BPD, the duration of mechanical ventilation, or oxygen therapy.[135-137] Children, who had BPD had lower mean psychometric scores compared to controls, but the differences disappeared when those with severe IVH were excluded.[135] Giacoia et al.[138] studied preterm children at 11 to 12 years of age. Although all preterm children scored lower with regard to performance and full-scale IQ scores compared with the term controls, there was no difference in the proportion of children with borderline or low IQ between those with and those without BPD. In a later study, Gregoire et al.[139] compared the outcome of children with BPD based on the two different definitions: oxygen

dependent at 28 days and not at 36 weeks' PCA versus oxygen dependent at 36 weeks' PCA. These children were compared at 18 months to other VLBW children who did not meet either definition for BPD. The children with milder BPD (oxygen dependent at 28 days and not 36 weeks' PCA) were comparable to those without BPD in terms of neurodevelopmental outcome. Those with more severe BPD had a statistically significant lower mean developmental quotient, although their scores were still within the normal range. This difference remained significant even when excluding severe IVH and periventricular leukomalacia (PVL).[139] Robertson et al.[140] also found some subtle variance in IQ and psychoeducational scores associated with more severe BPD. These data suggest that oxygen dependence at 36 weeks PCA might be a better predictor of later developmental delays than gestational age alone or the older BPD definition of oxygen dependence at 28 days.[139,140]

As more children of extremely low birth weight (ELBW, less than 1000 g) are surviving, the long-term outcome of this birth weight group must be considered as yet another variable in the equation. Marlow, et al.[141] studied infants less than 25 weeks' gestation at 6 years of age. They found a high prevalence of impairments in visuospatial, perceptual-motor, attention-executive, and gross motor functions among all ELBW infants at early school age. These deficits indicate poor spatial judgment, poor concepts of orientation and directionality, which denote important perceptual deficits. How these problems contribute to overall performance and school achievement has yet to be determined.

Inhaled nitric oxide (iNO) has recently been used in the preterm population in an attempt to decrease mortality and the incidence of chronic lung disease. Early reports on the neurodevelopmental outcome of infants from these trials are mixed. Mestan et al.[142] indicated that at 2 years of age patients treated with iNO had approximately half the risk of abnormal neurodevelopmental outcomes as those in the placebo group. The decreased incidence for abnormal neurodevelopmental outcome persisted, even after adjusting for the decreased risk for CLD, severe intraventricular hemorrhage, or periventricular leukomalacia. Conversely, Hintz et al.[143] reported that rates of death or neurodevelopmental impairment for both iNO and placebo groups were high. A post hoc analysis suggested higher risk of death or cerebral palsy (CP) particularly in infants with birth weight less than 1000 g with iNO treatment. The differences between these studies may be a reflection of the more routine approach to intervention with iNO and its use in a less severely ill population in the Mestan study.

A discussion of long-term outcome would not be complete without addressing the recent concerns of the effects of postnatal corticosteroids on neurodevelopmental outcome and the incidence of CP. Because inflammation plays a major role in the pathogenesis of CLD, corticosteroids, particularly dexamethasone, have been widely used to prevent or treat CLD.[144] In 2001, Barrington[145] conducted a meta-analysis of eight long-term outcome studies and concluded that the relative risk for developing CP was 1.92 with use of postnatal steroids compared to controls. Even with a widely differing timing of steroid administration and dosage schedules, the homogeneity of the results suggested potent pharmacologic doses of steroids at any age and at any dose might not be safe for the brain of premature infants. Magnetic resonance imaging done at 38 to 41 weeks' PCA showed that preterm infants treated with dexamethasone had marked reduction in cerebral cortical gray matter.[146] An 8-year follow up of children, from a randomized controlled trial of postnatal dexamethasone therapy for CLD, found that those who received dexamethasone had poorer motor performance, significantly lower full scale IQ scores, and significantly lower scores for perceptual organization and visual-motor integration.[147] In 2002 the American Academy of Pediatrics Committee on Fetus and Newborn and the Canadian Paediatric Society Fetus and Newborn Committee reviewed the short- and long-term effects of systemic and inhaled postnatal corticosteroids for the prevention or treatment of CLD and issued a joint statement.[144] The committees concluded that treatment of infants with VLBW with dexamethasone is associated with an increased risk of both short- and long-term complications, including impaired growth and neurodevelopmental delay. They advised that the *routine* use of systemic dexamethasone for prevention or treatment of CLD in infants with VLBW is not recommended.

As a result of this joint statement, "further trials of dexamethasone seem unlikely, although new information suggests benefits in specific circumstances."[148] Nixon et al.[149] found improved respiratory outcome at 8 years in infants treated with dexamethasone compared with placebo, likely mediated by the facilitation of early extubation and shortened exposure to mechanical ventilation. Others[150,151] have shown no differences at school age in neurocognitive and motor performance in children treated with hydrocortisone versus controls for CLD. Hydrocortisone is a less potent glucocorticoid than dexamethasone, and it is possible that the use of low-dose hydrocortisone would result in significantly improved neurodevelopmental outcomes compared with dexamethasone or other synthetic glucocorticoids.[148]

Overall the incidence of severe prematurity is not decreasing, and infants of less than 1000 g birth weight are surviving more frequently. Everyone involved with the care of high-risk neonates would like to be able to reliably predict the long-term outcome. Short-term, 2-year outcomes can be predicted by the "alphabet soup of neonatal diseases": BPD, PDA, IVH, PVL, RDS, NEC.[152] The more diagnoses and the greater the severity, the more likely the surviving infant will have adverse findings on assessment at 18 to 24 months. However, the early predictors of disease severity and adverse outcomes at 18 to 24 months are not strong predictors of behavioral and school-age problems. Parental education, parental socioeconomic status, and other indicators of the environment take on more significance with age.[152,153] Ultimately among the strongest predictors of a good outcome are better parental education, childrearing by two parents, a stable family composition, and geographic residence at one location for greater than 10 years.[153] "Over time the neonatal risk factors become less critical as environmental influences play a synergistic relationship between biologic and environmental risk factors, making preterm

children especially vulnerable to non-optimal environmental influences."[153] Furthermore, there is essentially no information on very late outcomes into adulthood and aging.

Extracorporeal Membrane Oxygenation

Medical Morbidity

The general criterion for extracorporeal membrane oxygenation (ECMO) use is a predicted high mortality rate (greater than 80%) related to the severity of the underlying illness. The most common diagnoses for which ECMO has been used are meconium aspiration syndrome (MAS), persistent pulmonary hypertension (PPHN), RDS, congenital diaphragmatic hernia (CDH), and group B streptococcus or other disease states resulting in cardiopulmonary failure (see Chapter 16). The illnesses leading to the need for ECMO treatment plus the treatment itself are all significant factors for the long-term sequelae. Underlying the diagnoses are the various physiologic problems related to the severity of the disease: hypoxia, stress, acidosis, hypotension, and the problems related to treatment before initiating ECMO (hyperventilation-induced alkalosis, seizures, and intracranial hemorrhage).[154] Finally, the potential complications of ECMO itself, including risks related to heparinization, equipment failure, and ligation of the carotid artery (if venoarterial cannulation is used), must be factored into the equation.

Studies of the long-term outcome after ECMO often report just the ECMO population without reference to non-ECMO survivors. The outcome of ECMO survivors should really be compared to the outcome of infants with similar underlying diagnoses who were not treated with ECMO, to try to sort out the compounding effects of the ECMO therapy itself on the outcome.[155] Walsh-Sukys et al.[156] compared outcomes of ECMO-treated children and children treated with conventional ventilation. They found an increased incidence of CLD in the children treated with conventional ventilation, but the neurodevelopmental outcomes were similar. In a later study, Rais-Bahrami et al.[157] compared the neurodevelopmental outcome at 5 years of age of survivors who were treated with ECMO and those patients they defined as near-miss ECMO. The near-miss ECMO group consisted of infants transported to their hospital because of failure to respond to medical management, with the intention of initiating ECMO, but who recovered without the use of bypass. They found similar rates of handicapping conditions in both groups as well.

The major medical morbidity of ECMO survivors in the first year is related to respiratory illness.[158] Of all survivors, 62% had a history of taking, or were receiving, medications for a respiratory illness, and 25% were rehospitalized for respiratory problems during the first year. In addition, 26% had evidence of growth failure and 6% were seen for a nonstatic neurologic problem. The most consistent abnormal growth parameter was microcephaly, and all children with microcephaly had associated respiratory and/or neurologic illness.[158,159] Dodge et al.,[160] however, reported only a 25% incidence of respiratory problems at 2 years, using the need for long-term respiratory medications or a tracheostomy as their criteria for respiratory morbidity. The majority of ECMO survivors have shown abnormal pulmonary mechanics at 6 months of age with increased airway resistance,[161] but lung function was slightly better compared to that of infants treated with conventional management for similar diagnoses.[162] Certain variables during the acute course may interact with the underlying diagnosis to affect the overall outcome. Kornhauser et al.[163] found that the major risk for BPD after ECMO was the duration of mechanical ventilation. Infants at highest risk were those who had received more than 96 hours of mechanical ventilation before beginning ECMO. In a comparison of patients treated with ECMO and a cohort of infants treated with conventional or high-frequency ventilation, Vaucher et al.[164] demonstrated a 50% reduction in the incidence of CLD in the ECMO-treated children. Hamutacu et al[165] reported the outcome of ECMO-treated children at a mean age of 11 years. They found that greater than 50% had cough and wheezing during exercise with evidence of airway obstruction, hyperinflation, and hypoxia at rest compared with control patients. These children also had qualitative and quantitative differences in their ventilatory response to exercise, with 25% having decreased O_2 saturation during exercise, reflecting decreased aerobic fitness.

Children with RDS and MAS often have more medical complications, longer medical courses before being placed on ECMO, and more mechanical pulmonary complications that may all affect the overall long-term outcome.[166] CLD can result from both the pulmonary effects of meconium itself and the ventilator-induced lung injury. In addition, the extrapulmonary effects of prolonged severe hypoxia, particularly on the brain, contribute to the long-term neurologic outcome. Before the use of ECMO for MAS, survivors were found to have a higher prevalence of asthmatic symptoms and abnormal bronchial reactivity than the general population. Similarly, Swaminathan et al.[167] documented evidence of hyperinflation, increased closing volume, airway obstruction, and airway hyperreactivity. The current worldwide survival rate for more than 5000 neonates with MAS receiving ECMO support is 94%.[168] This is the highest survival rate for any neonatal condition that meets eligibility criteria for ECMO. In their follow-up study of ECMO survivors, Bernbaum et al.[169] reported a 33% incidence of BPD in ECMO-treated MAS patients at discharge, but by follow-up at 1 year the majority of patients had significant clinical improvement in respiratory status. The majority of their MAS patients also had some form of feeding dysfunction requiring supplemental tube feedings at discharge, but by 1 year of age their entire MAS population was being fed normally.

The most complex group of patients to survive with ECMO support consists of those with congenital diaphragmatic hernia (CDH). These infants have the highest initial mortality rate, prolonged initial hospitalizations, other congenital anomalies, require the longest periods of ECMO and ventilatory support, and later have a high incidence of gastroesophageal reflux, feeding problems, and failure to thrive.[169-171] The overall incidence of BPD in ECMO patients at discharge was 40% in the survivors studied by Bernbaum et al.[169] However, they documented BPD in 63% of those with CDH as compared to less than half of the

patients in the other diagnostic categories. At follow-up at age 1 year, 50% of the CDH population continued to have requirements for supplemental oxygen, diuretics, or bronchodilators as compared to only 17% of the MAS population. Schwartz et al.[172] found evidence that pulmonary hypertension persists or recurs well beyond the neonatal period in a significant portion of ECMO-treated children with CDH. Thirty-eight percent of the children, who were studied at a mean age of 3.8 ± 2.2 years, met echocardiographic criteria for pulmonary hypertension, although only a very small number had any clinical symptoms of this disorder. Most of those patients with pulmonary hypertension had wheezing and some degree of exercise intolerance. Significant nonpulmonary morbidities of this population include adverse gastrointestinal, nutritional, musculoskeletal, and neurosensory problems, whether the infants have been treated with ECMO or not.[173-175] Children with CDH often have foregut dysmotility leading to significant gastroesophageal reflux (GER), delayed gastric emptying, and feeding difficulties.[173] Jaillard et al[175] reported that 20% of patients with CDH and 40% of CDH ECMO survivors had growth retardation with weight less than 5th percentile at 2 years because of catabolic stress in the neonatal period, oral aversion, GER, and persistent pulmonary morbidity. Infants with large diaphragmatic hernias or treated with ECMO are at greatest risk for neurodevelopmental delay.[174] Sensorineural hearing loss has been described and approximately half of infants with initially normal hearing assessments develop hearing loss later in infancy.[174]

Neurodevelopmental Outcome

The overall survival rate for infants treated with ECMO is 82%, and the vast majority of the survivors have a normal neurologic examination, fall within the normal range for developmental measures, and have intelligence scores in the average range. Bernbaum et al.[169] and Glass et al.[159] reported mean Bayley[124] scores of ECMO survivors within the normal range at 1-year follow-up. However, this masks a large minority with poor outcomes, associated either with ongoing cardiopulmonary or neurologic problems.[155] Children who are considered handicapped or who have one or more major disabilities have been reported in up to 10% to 36% of ECMO survivors.[158,160,176-178] The handicapping sequelae included spastic cerebral palsy, sensorineural hearing loss (SNHL), and cognitive deficiencies at school age. Studies reporting on later intellectual scores for ECMO survivors found that 10% to 30% of children had IQ scores greater than 1.5 to 2 SD below the mean normal range, and up to 35% of those children with seemingly normal outcomes qualified for special services at school age.[155] In follow-up studies of ECMO survivors at 5 years of age, Glass et al.[177] described a general lowering of IQ, a significant difference on multiple neuropsychological measures, and three times the incidence of behavior problems in ECMO survivors compared to normal full-term controls. This same group reported that the probability of disability at age 5 years was associated with the severity of brain lesions identified by routine cranial ultrasonography and computed tomography.[179] The severity of neonatal neuroimaging was inversely associated with decreased intellectual status, greater neuropsychological deficits across all domains, and poorer preacademic skills.

Some studies have reported a higher incidence of right-sided cerebral lesions after ECMO and attribute the lateralized brain abnormalities to the ligation of the right common carotid artery (RCCA).[180,181] However, Graziani et al.[182] did not find that post-ECMO neuroimaging or clinical evaluations indicated a selective or greater injury to the right cerebral hemisphere and believed that the long-term consequences of RCCA ligation have not been determined. Reconstruction of the RCCA immediately after decannulation has been done successfully.[183] Follow-up studies comparing patients with reconstruction to those whose RCCA was permanently ligated found significantly fewer brain scan abnormalities and less cerebral palsy (CP) in the reconstructed patients but similar scores on developmental and IQ testing.[184] The long-term consequences of RCCA ligation and the risks and benefits of RCCA reconstruction remain unknown.

Sensorineural hearing loss (SNHL) has been identified as a significant complication in survivors of PPHN[185-187] and is the most common single neurosensory morbidity in ECMO survivors.[160] The incidence ranges between 3% and 21% of children.[147,177,178] Although some children may be diagnosed early with auditory brainstem response screening, SNHL may present later as an isolated high frequency loss with progressive deterioration and therefore remain undetected for several years.[188] The exact mechanism for the SNHL remains unknown, but it may be associated with various aggressive therapies commonly employed in this population before the initiation of ECMO. Hyperventilation has been associated with hearing loss, whereas permissive hypercapnia might be protective.[185] In addition, the risk for SNHL was associated with profound hypocarbia before initiation of ECMO therapy.[189] Future research and a large population study are needed to determine the relationship of SNHL to the primary diagnosis and mode of treatment.

In their study published in 1996, Gringlas et al.[190] concluded that the primary diagnoses associated with the requirement for ECMO were not predictive of later developmental outcome. Nield et al.[191] reported no difference in functional status or neurologic sequelae at 3.5 years among children in different diagnostic categories. Robertson et al.[192] noted no differences in neurodevelopmental disabilities, and mean Bayley MDI and PDI scores at 2 years of age were within the normal range for a group of ECMO-treated patients compared with infants, who met ECMO criteria but were treated with conventional ventilation because of lower oxygenation indices after transfer.

The risk factors for poor neurodevelopmental outcome might be related to the increased severity of the underlying illness and the various treatment modalities used before ECMO rather than either the specific respiratory diagnosis or the ECMO therapy itself. Hofkosh et al.[178] and Kornhauser et al.[163] both distinguished survivors with BPD as having worse developmental outcomes. These findings were further substantiated by the published results of Vaucher et al.[164] Their data showed that infants treated with ECMO were as likely to have normal neurologic examinations as those managed with alternative treatment

TABLE 32-1 Predictors of Neurodevelopmental Outcome at 12 to 30 Months

Outcome	Risk Factor	OR	95% CI	P Value
Neuromotor outcome				
Suspect or abnormal	CLD	2.60	0.97-0.99	0.005
	PPHN	4.40	1.16-16.49	0.01
	Neuroimaging abnormality*	5.10	1.55-17.09	0.01
Cerebral palsy	Neuroimaging abnormality*	10.30	1.56-67.83	0.001
	Gestational age	0.60	0.37-0.96	0.03
Developmental outcome				
MDI <84	Male gender	2.20	0.99-4.86	0.05
PDI <84	Neuroimaging abnormality*	6.30	1.72-23.32	0.006
	CLD	2.21	1.13-4.34	0.02
	Qualifying PaO_2	1.06	1.00-1.10	0.05
Adverse outcome†	Neuroimaging abnormality*	6.43	1.89-21.89	0.003
	CLD	2.38	1.23-4.59	0.01

From Vaucher YE, Dudell GG, Bejar R, et al: J Pediatr 128:115, 1996.
*Moderate or severe.
†Neuromotor, neurosensory, or developmental.
95% *CI*, 95% Confidence interval; *CLD*, chronic lung disease; *MDI*, mental developmental index; *OR*, odds ratio; *PaO_2*, partial arterial oxygen tension; *PDI*, motor developmental index, *PPHN*, persistent pulmonary hypertension of the newborn.

strategies; chronic lung disease and moderate-to-severe neonatal neuroimaging abnormalities rather than treatment with ECMO were the major determinants of neurodevelopmental outcome.

Major disabilities were more common in infants with CLD, and CLD increased the risk of neurodevelopmental delay at 12 to 30 months after adjusting for other variables such as respiratory diagnosis and treatment modality (Table 32-1). Kumar et al.[193] found that longer duration of ventilation and use of supplemental oxygen were significantly associated with abnormal neurodevelopmental outcome. ECMO survivors with CDH were noted to have increased neurologic sequelae and lower cognitive scores.[194,195]

However, this higher incidence of neurologic sequelae in the CDH population might be due to the increased severity of illness, as reflected in lower Apgar scores, decreased initial and best pO_2, and the need for surgical patch closure of either the diaphragm or abdomen.[175,196] Graziani et al.[189] studied the outcome of 181 ECMO survivors to determine the neonatal clinical correlates of severe cardiorespiratory failure treated with ECMO and the neurodevelopmental sequelae. Their results indicated that there were no differences in outcome among the primary diagnostic groups requiring ECMO (Table 32-2). The risk for cerebral palsy was increased in infants who had hypotension (systolic blood pressure below 39 mm Hg) or required cardiopulmonary resuscitation before ECMO (Table 32-3).

Inhaled nitric oxide (iNO) has been used increasingly as an alternative to ECMO, particularly for children with PPHN. Early reports[197,198] found no differences between iNO-treated infants and either placebo or ECMO-treated patients for any long-term outcome. However, neurodevelopmental sequelae occurred at a somewhat higher rate in the study with less severe entry criteria, using the

TABLE 32-2 Primary Diagnosis, Gestational Age, Birth Weight, and Outcome in 181 Survivors of Neonatal Venoarterial (*n* = 152) or Venovenous (*n* = 29) Extracorporeal Membrane Oxygenation

	OUTCOMES			
	NORMAL		SUSPECT§	ABNORMAL‖
Neonatal Factors*	12-46 months† (*n* = 96)	4.8-6 yr‡ (*n* = 34)	4.8-6 yr (*n* = 17)	16 months-8 yr (*n* = 34)
Primary diagnosis				
MAS/PPHN	63	23	9	20
Diaphragmatic hernia	12	4	0	2
RDS/HMD	8	5	7	6
Sepsis/pneumonia	13	2	1	6
Gestational age, weeks (mean [SD])	39.4 (±2)	40.1 (±2)	39.6 (±2)	39.2 (±2)
Birth weight, kg (mean [SD])	3.31 (±0.6)	3.33 (±0.5)	3.20 (±0.5)	3.18 (±0.5)

From Graziani LJ, Gringlas M, Baumgart S: Clin Perinatol 24:664, 1997.
*No significant differences in primary diagnosis, gestational age, or birth weight among the four groups: Chi-squared test.
†Presumed normal because of young age. No definite evidence of mental retardation (MR), cerebral palsy (CP), or sensorineural hearing loss (SNHL).
‡Wechsler Preschool and Primary Scales of Intelligence—Revised (WPPSI-R) full scale IQ ≥85; normal neurologic examination, and normal hearing thresholds for both ears at school age.
§WPPSI-R full-scale IQ between 71 and 84, without CP and SNHL at school age.
‖CP (*n* = 17); SNHL without CP or MR (*n* = 12); MR without CP or SNHL (*n* = 5).
MAS/PPHN, Meconium aspiration syndrome/persistent pulmonary hypertension of the newborn; *RDS/HMD*, respiratory distress syndrome/hyaline membrane disease; *SD*, standard deviation.

TABLE 32-3 **Cerebral Palsy (n = 17) Compared with Normal School-Age Outcome (n = 34) in 51 Venoarterial ECMO Survivors: Neonatal Clinical Features**

Clinical Features	Normal* (n = 34)	Cerebral Palsy† (n = 17)	P Value‡
Lowest pH Pre-ECMO	7.16 ± 0.19	7.19 ± 0.23	NS
Lowest PaO_2 Pre-ECMO	29.9 ± 8.5	31.6 ± 23.5	NS
Lowest $PaCO_2$ Pre-ECMO	22.9 ± 9.6	18.5 ± 7.7	NS
Oxygenation index§	63.7 ± 46.9	92.7 ± 64.5	<0.02
Lowest systolic blood pressure‖	46.2 ± 9.5	40.9 ± 11.3	<0.01
CPR before ECMO (n [%])	0 (0)	8 (47)	<0.0001

From Graziani LJ, Gringlas M, Baumgart S: Clin Perinatol 24: 665, 1997. Adapted from Graziani LJ, Baumgart S, Desai S, et al: J Child Neurol 12: 415-422, 1997.
Data represent mean ± standard deviation (SD), except for cardiopulmonary resuscitation (CPR). Gestational age, birth weight, Apgar scores, age at start of extracorporeal membrane oxygenation (ECMO), duration of ECMO, and highest neonatal indirect bilirubin level did not differ significantly between the two groups.
*Normal neurologic examination full-scale WPPSI-R IQ scores >84, and normal bilateral hearing at age 4.8-6.0 years.
†Spastic form of cerebral palsy (CP) at age 15 months to 8 years, confirmed by repeated examinations.
‡Chi-square or Kruskal-Wallis tests of significance. *NS*, Not significant.
§Last oxygenation index before ECMO. Normal, n = 15; cerebral palsy, n = 6.
‖In mm Hg, before or during ECMO.
CPR, Vigorous cardiopulmonary resuscitation prior to ECMO exclusive of the immediate resuscitation at birth. Percentage calculated from the total number of survivors in each column.
Pao_2, Partial pressure of oxygen; *$PaCO_2$*, partial pressure of carbon dioxide (lowest value [mm Hg] in postductal arterial blood before ECMO).

oxygenation index (OI) as a marker of the severity of the physiologic features of the PPHN.[197-199] The OI may not be a predictor of long-term outcome among survivors. This was confirmed in a more recent study by Ichiba et al.[200] in which no significant correlation was found between OI before iNO and long-term outcome. Mortality and long-term neurodevelopmental outcome were associated with the response to iNO therapy rather than the severity of the PPHN.

Conclusion

The development of techniques for the mechanical ventilation of infants with respiratory failure should be considered one of the major advances in medical therapy in the past several decades. As improvements in assisted ventilation and other supportive technologies allow for the survival of smaller and more severely ill newborns, comprehensive long-term follow-up of these babies remains essential, both for the documentation and critical evaluation of evolving patient care and for the detection of any potentially handicapping conditions in children who have survived neonatal intensive care. The interactions between lung growth and repair of lung injury and brain growth and early brain injury in growing children remain speculative at best. The discovery of abnormal outcomes in groups of patients may lead to improvements in clinical practice. The early detection of abnormalities in an individual child permits anticipatory guidance for the family and the child, as well as the provision of appropriate early intervention services to minimize the impact of any impairment. Only through careful follow-up can care be improved for patients, both present and future.

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Appendixes

1. Modes of Ventilation (with Advantages and Disadvantages)
2. Lung Volumes in the Infant
3. Changes in Respiratory System Dimensions with Growth
4. Effect of Age on Lung Size
5. Lung Volume in Full-Term and Premature Newborns
6. Allen's Test
7. Procedure for Obtaining Capillary Blood Gases
8. A. Arterial Blood Gas Values in Normal Full-Term Infants
   B. Arterial Blood Gas Values in Normal Premature Infants
9. Blood Gas Values in Cord Blood and in Arterial Blood at Different Ages During the Neonatal Period
   A. Oxygen Tension
   B. Carbon Dioxide Tension
   C. pH
   D. Base Excess
10. Hemoglobin-Oxygen Dissociation Curves
11. Siggaard-Andersen Alignment Nomogram
12. Neutral Thermal Environmental Temperatures
13. A. Fetal-Infant Growth Chart for Preterm Infants
    B. Maturational Assessment of Gestational Age
14. Heart Rates in Premature and Full-Term Neonates
15. Systolic and Diastolic Blood Pressure in Newborn Infants
16. Mean Blood Pressure and Pulse Pressure in Newborn Infants
17. Blood Chemistries
    A. Normal Blood Chemistry Values, Term Infants
    B. Normal Blood Chemistry Values, Low-Birthweight Infants, Capillary Blood, First Day
    C. Blood Chemistry Values in Premature Infants During the First 7 Weeks of Life (birthweight, 1500-1750 g)
18. Hematologic Values in Newborn Infants.
    A. Normal Hematologic Values during the First 14 Days of Life
    B. Changes in Hemoglobin and Reticulocyte Count in Term and Preterm Infants
19. Leukocyte Values and Neutrophil Counts in Term and Premature Infants
    A. Leukocyte Values in Term and Premature Infants.
    B. Total Neutrophil Count Reference Range in the First 60 Hours of Life
20. Platelets
    A. Venous Platelet Counts in Normal Low-Birthweight Infants
    B. Platelet Counts in Full-Term Infants
21. Coagulation Factors and Test Values in Term and Premature Infants
22. Cerebrospinal Fluid Values in Term and Premature Infants
23. Daily Maintenance, Fluid, Mineral, and Glucose Requirements for Term Neonates
24. Neonatal/Pediatric Transport: Transport Log

Modes of Ventilation (With Advantages and Disadvantages)

Mode Classification	Principle of Operation	Advantages	Disadvantages
Time-cycled, pressure limited	PIP set during inspiration flow of gas delivered to achieve pressure desired; flow down after PIP attained until inspiratory phase completed		
Volume control (not actually a mode but indicates what is constant during the ventilated breath delivery and should be used as a prefix for each "mode," e.g., VC-SIMV)	Volume constant, pressure variable		High PIPs with decreasing lung compliance and/or airway resistance
Synchronized or patient-triggered ventilation (PTV)	Inspiratory phase initiated by patient's own inspiratory effort Methods of triggering: 1. Impedance (thorax-Sechrist SAVI). 2. Motion (Infrasonic's Star-sync 3. Pressure: senses decrease in baseline pressure with patient inspiratory effort 4. Flow: senses decrease in baseline flow; secondary to patient's inspiratory effort 5. Volume: triggers inspiration in response to preset volume loss	Improves patient-ventilator synchrony Flow triggering has become the standard on all current ventilators Flow triggering has been shown to decrease the amount of work needed to trigger Volume triggering versus flow triggering: decreased "noise" from circuit condensate decreases potential of false triggering	Auto-cycling if too sensitive or variable leak around ETT Patient "locked out" if not sensitive enough Volume triggering versus flow triggering: delay from the signal processing may produce phase lag Volume triggering (Drager Babylog) has not been adequately evaluated Breath stacking
IMV	Preset mandated breaths are delivered at a set frequency independent of the patient's spontaneous breaths		Potential for air leak
SIMV	A version of IMV in which the ventilator sets up a timing window around the scheduled delivery of a mandatory breath in an attempt to deliver the mandated breath in conjunction with the patient's inspiratory effort; if no effort is detected during the timing window, the ventilator will deliver the scheduled mandated breath	Primarily used as weaning strategy due to range of ventilator breaths Improves patient-ventilator synchrony Prevents breath stacking and potential for air leak/gas trapping/volutrauma	Same as for *Synchronized or patient-triggered ventilation*
Pressure control (not actually a mode but indicates what is constant during the ventilated breath delivery and should be used as a prefix for each "mode," e.g., PC – SIMV + PS)	Pressure constant, volume variable: flow variable (decelerating waveform) Constant PIP (square pressure waveform)	Better gas distribution Rapid pressurization helps overcome airway resistance	Variable volumes in face of changing lung compliance or lung resistance with potential for hypo- or hyperinflation
Pressure-regulated volume control (patient or machine-triggered, pressure limited, and time cycled with tidal volume as the conditional variable used to change the pressure limit)	Variable flow rate (decelerating waveform) but targets specific tidal volume A dual-control mode	Good if you need high PIP Combines guaranteed tidal volume with pressure-limited features	An assist-control mode; therefore there is the potential for hyperventilation if the patient is not well-sedated or paralyzed and becomes tachypneic

Continued

Appendix 1

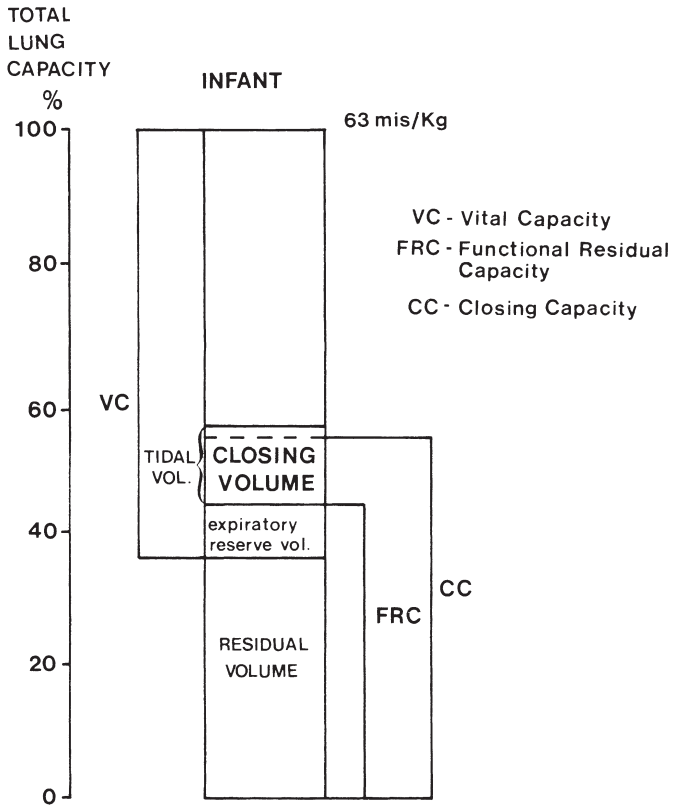
Modes of Ventilation (With Advantages and Disadvantages)—cont'd

Mode Classification	Principle of Operation	Advantages	Disadvantages
	Inspiration is pressure controlled within a breath, but the pressure limit is automatically adjusted up or down (based on the calculated value for respiratory system compliance derived from a "test" breath) to achieve a preset tidal volume A form of pressure-limited, time-cycled ventilation that uses tidal volume as a feedback control for continuously adjusting the pressure limit	Limits PIP (within a given range), avoiding lung overinflation while maintaining the advantage of volume control (delivering a consistent minute ventilation even in the face of changing lung mechanics)	Not a "weaning" mode
Pressure support (pressure controlled patient-triggered, pressure limited, patient cycled)	Spontaneous breathing mode in which a patient's inspiratory effort is assisted by the ventilator up to a preset inspiratory pressure Inspiration is terminated when inspiratory flow reaches either a minimum level or a percentage of the initial flow; the patient determines his or own rate, inspiratory time, and tidal volume A secondary safety termination typically includes time; this prevents prolonged inspiratory times in the presence of air leaks where flow criteria may not be met	Weaning Decreases WOB by overcoming resistance of ETT	If used just to overcome resistance of the ETT, there is no further decrease in WOB when pressures of >10 cm H_2O are applied
Proportional assist ventilation (PAV): Evita ventilator by Drager, whose term for this is "proportional pressure support" (pressure controlled, patient triggered, pressure limited, and flow cycled)	A spontaneous mode that is a form of pressure control in which pressure will vary continuously throughout inspiration and is proportional to the volume and flow signals (flow and volume are controlled by parameters based on patient effort; the greater the patient effort, the faster the flow and the higher the tidal volume)	Potentially the most "comfortable" form of ventilation	Experimental Not approved for infant ventilation
Volume-assured pressure support (VAPS): pressure controlled, patient or time triggered, pressure limited, and flow cycled	A dual-control mode in which adjustments are made within the breath to achieve a target volume; ventilation starts inspiration in pressure control; if the target volume has not been delivered by the time inspiratory flow decays to a preset inspiratory flow, the ventilator switches to volume control	Limits PIP (within a given range), which avoids lung overdistension while maintaining the advantage of volume control (delivering a constant minute ventilation even if changes in lung mechanics occur)	
CPAP (pressure controlled, patient triggered, patient cycled, unsupported spontaneous breathing)	Mode of operation (debated as to whether truly a "mode," because no tidal volume is generated by the ventilator) in which a preset pressure is maintained while the patient is allowed to breathe spontaneously; patient determines his or her own rate and tidal volume	Increases mean airway pressure and therefore oxygenation Possibly decreases WOB if optimizes FRC and ventilation/perfusion matching	

CPAP, Continuous positive airway pressure; *ETT,* endotracheal tube; *FRC,* functional residual capacity; *IMV*, intermittent mandatory ventilation; *PIP*, peak inspiratory pressure; *PS,* pressure support; *SIMV,* synchronized intermittent mandatory ventilation; *VC,* volume-controlled; *WOB,* work of breathing.

Appendix 2

Lung Volumes in the Infant



From Smith CA, Nelson NM: The Physiology of the Newborn Infant. 4th ed. Springfield, IL, Charles C Thomas, Publisher, 1976.

Appendix 3

Changes in Respiratory System Dimensions with Growth*

	Newborn to 1 Month	Infant
Chest diameter (cm)		
Transverse	10	14
Anteroposterior	7.5	9
Trachea, length (mm)	40/57	42/67
Diameter (mm)	4	5
CSA (mm^2)	26	34
Mainstem bronchi		
Diameter (mm)	4	4
CSA, right/left (mm^2)	—	20/13
Bronchioles, diameter (mm)	0.3	0.4
CSA (mm^2)	0.07	0.12
Terminal bronchioles		
Diameter (mm)	0.2	0.3
Internal diameter (mm)	0.1	0.12
CSA	0.03	0.07
Alveoli, diameter (mm)	0.05	0.06-0.07
Surface area (m^2)	2.8	6.5
Body length (cm)	50	—
Weight (kg)	3.4	—
Surface area (m^2)	0.21	0.3
Lung weight (g)	50	70
Dead space (mL)	7-8	—

From Scarpelli EM (ed): Pulmonary Physiology of the Fetus, Newborn, and Child. Philadelphia, Lea & Febiger, 1975. Reprinted by permission.
*Values from Engel S (autopsy data) and Fearon S, Whalen JS (living subjects); (autopsy/living).
CSA, Cross-sectional area.

Appendix 4

Effect of Age on Lung Size*

Age	No. of Cases Studied	Alveoli (10^6)	Respiratory Airways (10^6)	Air-tissue Interface (m^2)	Body Surface Area (m^2)	Generations of Respiratory Airways
Birth	1	24	1.5	2.8	0.21	—
3 months	3	77	2.5	7.2	0.29	21
7 months	1	112	3.7	8.4	0.38	—
13 months	1	129	4.5	12.2	0.45	22
22 months	1	160	7.1	14.2	0.50	—
4 years	1	257	7.9	22.2	0.67	—
8 years	1	280	14.0	32.0	0.92	23
Adult		296	14.0	75.0	1.90	23
Approximate fold-increase, birth to adult	—	10	10	21	9	—

From Thibeault DW, Gregory GA (eds): Neonatal Pulmonary Care. Menlo Park, CA, Addison-Wesley Publishing Co., 217-236, 1979, and Scarpelli EM (ed): Pulmonary of the Fetus, Newborn, and Child. Philadelphia, Lea & Febiger, 1975.
*Values from Dunnill MS.

Appendix 5

Lung Volume in Full-Term and Premature Newborns

Reference	Method	Weight (kg)	Age	Lung Volume
Berglund and Karlberg	Helium	2.0-5.0	0.5-7 days	27 mL/kg
Klaus et al.	Plethysmography	2.3-4.1	11-20 min	23 mL/kg
			30-40 min	29 mL/kg
			25-48 hr	28 mL/kg
			>96 hr	39 mL/kg
Nelson et al.	Plethysmography	1.3-4.0	16 hr-71 days	40.6 mL/kg
	N_2 washout	1.3-4.0	16 h-71 days	31.3 mL/kg
Kraus and Auld	Plethysmography	>1.75	<24 hr	2 mL/cm
	Helium	>1.75	<24 hr	1.3 mL/kg
	Plethysmography	>1.75	3-6 days	1.8 mL/kg
	Helium	>1.75	3-6 days	1.4 mL/kg
	Plethysmography	<1.75	<24 hr	1.7 mL/kg
	Helium	<1.75	<24 hr	0.9 mL/kg
	Plethysmography	<1.75	12-19 days	0.9 mL/kg
	Helium	<1.75	12-19 days	0.8 mL/kg
				30.4 mL/kg
Lacourt and Polgar	Plethysmography	0.68-2.65 (premature)	1-72 days	1.12 mL/cm
				32.4 mL/kg
	Plethysmography	1.5-3.6 (full·term)	1-18 days	1.72 mL/kg
Ronchetti et al.	Plethysmography	1.38-2.6	4-28 days	37.5 mL/kg
	Helium	1.38-2.6	4-28 days	29.5 mL/kg

From Thibeault DW, Gregory GA (eds): Neonatal Pulmonary Care. Menlo Park, CA, Addison-Wesley Publishing Co., 1979, and Scarpelli EM (ed.): Pulmonary Physiology of the Fetus, Newborn, and Child. Philadelphia, Lea & Feblger, 1975.

Appendix 6

Allen's Test

Gently squeeze the hand to partially empty it of blood. Apply pressure to both the ulnar and radial arteries. Then remove pressure from the hand and the ulnar artery. If the entire hand flushes and fills with blood, the ulnar artery can supply the hand with blood and the radial artery can be safely punctured or cannulated.

Appendix 7

Procedure for Obtaining Capillary Blood Gases

Equipment needed:

- 75-µL capillary tube (heparinized)
- Monocet lancet (3-mm)
- Alcohol sponge
- Metal stirrer and magnet
- Sealing wax

Procedure for obtaining capillary blood gases:

- Wash hands.
- Warm infant's foot for 3 minutes with water at body temperature or slightly warmer. Use thermometer. Water temperature should not exceed 39° C (101-104° F).
- Cleanse heel with alcohol sponge.
- Puncture with Monocet lancet.
- Wipe away first drop of blood.
- Collect blood in sample tube by holding tube below level of puncture and allow blood to flow freely into tube. Avoid squeezing heel to fill tube because this introduces serum and venous blood and renders the sample inaccurate. Avoid introducing air into the tube.
- Hold an alcohol sponge against the puncture site to stop flow.
- Place metal stirrer in tube.
- Slide the magnet along the tube to move the stirrer and mix the blood.
- Seal the ends of the tube.
- Send to the laboratory for analysis.

Appendix 8

A, Arterial Blood Gas Values in Normal Full-Term Infants*

		Umbilical Vein	Umbilical Artery	5-10 min	20 min	30 min	60 min	5 hr	24 hr	2 days	3 days	4 days	5 days	6 days	7 days
pH	$\bar{X}$	7.320	7.242	7.207	7.263	7.297	7.332	7.339	7.369	7.365	7.364	7.370	7.371	7.369	7.371
	SD	0.055	0.059	0.051	0.040	0.044	0.031	0.028	0.032	0.028	0.027	0.027	0.031	0.023	0.026
P_{CO_2} (mm Hg)	$\bar{X}$	37.8	49.1	46.1	40.1	37.7	36.1	35.2	33.4	33.1	33.1	34.3	34.8	34.8	35.9
	SD	5.6	5.8	7.0	6.0	5.7	4.2	3.6	3.1	3.3	3.4	3.8	3.5	3.6	3.1
P_{O_2} (mm Hg)	$\bar{X}$	27.4	15:9	49.6	50.7	54.1	63.3	73.7	72.7	73.8	75.6	73.3	72.1	69.8	73.1
	SD	5.7	3.8	9.9	11.3	11.5	11.3	12.0	9.5	7.7	11.5	9.3	10.5	9.5	9.7
Standard bicarbonate	$\bar{X}$	20.0	18.7	16.7	17.5	18.2	19.2	19.4	20.2	19.8	19.7	20.4	20.6	20.6	21.8
(mEq/L)	SD	1.4	1.8	1.6	1.3	1.5	1.2	1.2	1.3	1.4	1.4	1.7	1.7	1.9	1.3

From Bancalari E: Pulmonary function testing and other diagnostic laboratory procedures. J Peds 110(3):448-456, 1987 Thibeault DW, Gregory GA (eds): Neonatal Pulmonary Care. Reading, MA, Addison-Wesley Publishing Co., 1979, p. 123, Table 7-4. Used by permission.

*Values from Koch and Wendel. Blood obtained through umbilical artery line. PO, and Pco, measured with Clark and Severinghaus electrodes.

SD, Standard deviation; $\bar{X}$, sample mean.

B, Arterial Blood Gas Values in Normal Premature Infants*

		3-5 hr	6-12 hr	13-24 hr	25-48 hr	3-4 days	5-10 days	11-40 days
pH	$\bar{X}$	7.329	7.425	7.464	7.434	7.425	7.378	7.425
	SD	0.038	0.072	0.064	0.054	0.044	0.043	0.033
P_{CO_2} (mm Hg)	$\bar{X}$	47.3	28.2	27.2	31.3	31.7	36.4	32.9
	SD	8.5	6.9	8.4	6.7	6.7	4.2	4.0
P_{O_2} (mm Hg)	$\bar{X}$	59.5	69.7	67.0	72.5	77.8	80.3	77.8
	SD	7.7	11.8	15.2	20.9	16.4	12.0	9.6
Base excess (mEq/L)	$\bar{X}$	–3.7	–4.7	–3.0	–2.3	–2.9	–3.5	–2.1
	SD	1.5	3.1	3.3	3.0	2.3	2.3	2.2

From Bancalari E: Pulmonary function testing and other diagnostic laboratory procedures. *In* Thibeault DW, Gregory GA (eds): Neonatal Pulmonary Care, Reading, MA, Addison-Wesley Publishing Co., 1979, p 123, Table 7-5. Used by permission.

*Values from Orzalesi et al. Mean birthweight, 1.76 kg; gestational age, 34.5 wk. Blood obtained from radial, temporal, or umbilical artery. P_{O_2} measured with Clark electrode, and P_{CO_2} calculated with use of the Siggaard-Andersen nomogram.

SD, Standard deviation; $\bar{X}$, sample mean.

Appendix 9

Blood Gas Values in Cord Blood and in Arterial Blood at Different Ages During the Neonatal Period

A. OXYGEN TENSION

		UV	UA	5-10 min	20 min	30 min	60 min	5 hr	24 hr	2 days	3 days	4 days	5 days	6 days	7 days
P_{O_2} (mm Hg)	$\bar{X}$	15.9	27.4	49.6	50.7	54.1	63.3	73.7	72.7	73.8	75.6	73.3	72.1	69.8	73.1
	SD	3.8	5.7	9.9	11.3	11.5	11.3	12.0	9.5	7.7	11.5	9.3	10.9	9.5	9.7
	Range	7	15	33	31	31	38	55	54	62	56	60	56	55	57
		23	40	75	85	85	83	106	95	91	102	93	102	96	94

From Koch G, Wendel H: Adjustment of arterial blood gases and acid-base balance in the normal newborn infant during the first week of life. Biol Neonat 12:136-161, 1968. By permission of S. Karger, A.G. Basel.
SD, Standard deviation; *UA*, umbilical artery; *UV*, umbilical vein; $\bar{X}$, sample mean.

B. CARBON DIOXIDE TENSION

		UV	UA	5-10 min	20 min	30 min	60 min	5 hr	24 hr	2 days	3 days	4 days	5 days	6 days	7 days
P_{CO_2} (mm Hg)	$\bar{X}$	49.1	37.8	46.1	40.1	37.7	36.1	35.2	33.4	33.1	33 .1	34.3	34.8	34.8	35.9
	SD	5.8	5.6	7.0	6.0	5.7	4.2	3.6	3.1	3.3	3.4	3.8	3.5	3.6	3.1
	Range	35	26	35	31	28	28	29	27	26	26	27	28	28	30
		60	52	65	58	54	45	45	40	43	40	43	41	42	42

From Koch G, Wendel H: Adjustment of arterial blood gases and acid base balance in the normal newborn infant during the first week of life. Biol Neonat 12:136-161, 1968. By permission of S. Karger, A.G. Basel.
SD, Standard deviation; *UA*, umbilical artery; *UV*, umbilical vein; $\bar{X}$, sample mean.

C. pH

		UV	UA	5-10 min	20 min	30 min	60 min	5 hr	24 hr	2 days	3 days	4 days	5 days	6 days	7 days
pH	$\bar{X}$	7.320	7.242	7.207	7.263	7.297	7.332	7.339	7.369	7.365	7.364	7.370	7.371	7.369	7.37
	SD	0.055	0.059	0.051	0.040	0.044	0.031	0.028	0.032	0.028	0.027	0.027	0.031	0.032	0.02
	Range	7.178	7.111	7.091	7.180	7.206	7.261	7.256	7.290	7.314	7.304	7.320	7.296	7.321	7.32
		7.414	7.375	7.302	7.330	7.380	7.394	7.389	7.448	7.438	7.419	7.440	7.430	7.423	7.43

From Koch G, Wendel H: Adjustment of arterial blood gases and acid base balance in the normal newborn infant during the first week of life. Biol Neonate 12:136-161, 1968. By permission of S. Karger, A.G. Basel.
SD, Standard deviation; *UA*, umbilical artery; *UV*, umbilical vein; $\bar{X}$, sample mean.

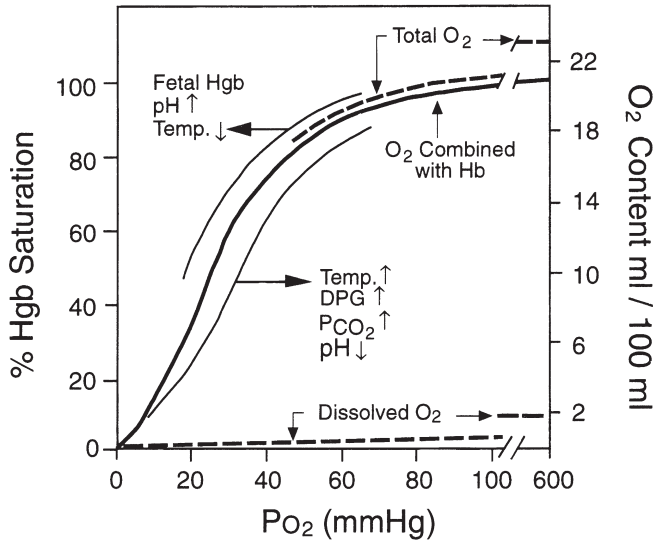
D. BASE EXCESS

		UV	UA	5-10 min	20 min	30 min	60 min	5 hr	24 hr	2 days	3 days	4 days	5 days	6 days	7 days
BE	$\bar{X}$	–5.5	–7.2	–9.8	–8.8	–7.8	–6.5	–6.3	–5.2	–5.8	–5.9	–5.0	–4.7	–4.7	–3.2
	SD	1.2	1.7	2.3	1.9	1.7	1.3	1.3	1.1	1.2	1.2	1.1	1.1	1.1	0.6

Calculated from data in Koch G, Wendel H: Adjustment of arterial blood gases and acid base balance in the normal newborn infant during the first week of life. Biol Neonate 12:136-161, 1968. By permission of S. Karger, A.G. Basel.
SD, Standard deviation; *UA*, umbilical artery; *UV*, umbilical vein; $\bar{X}$, sample mean.

Appendix 10

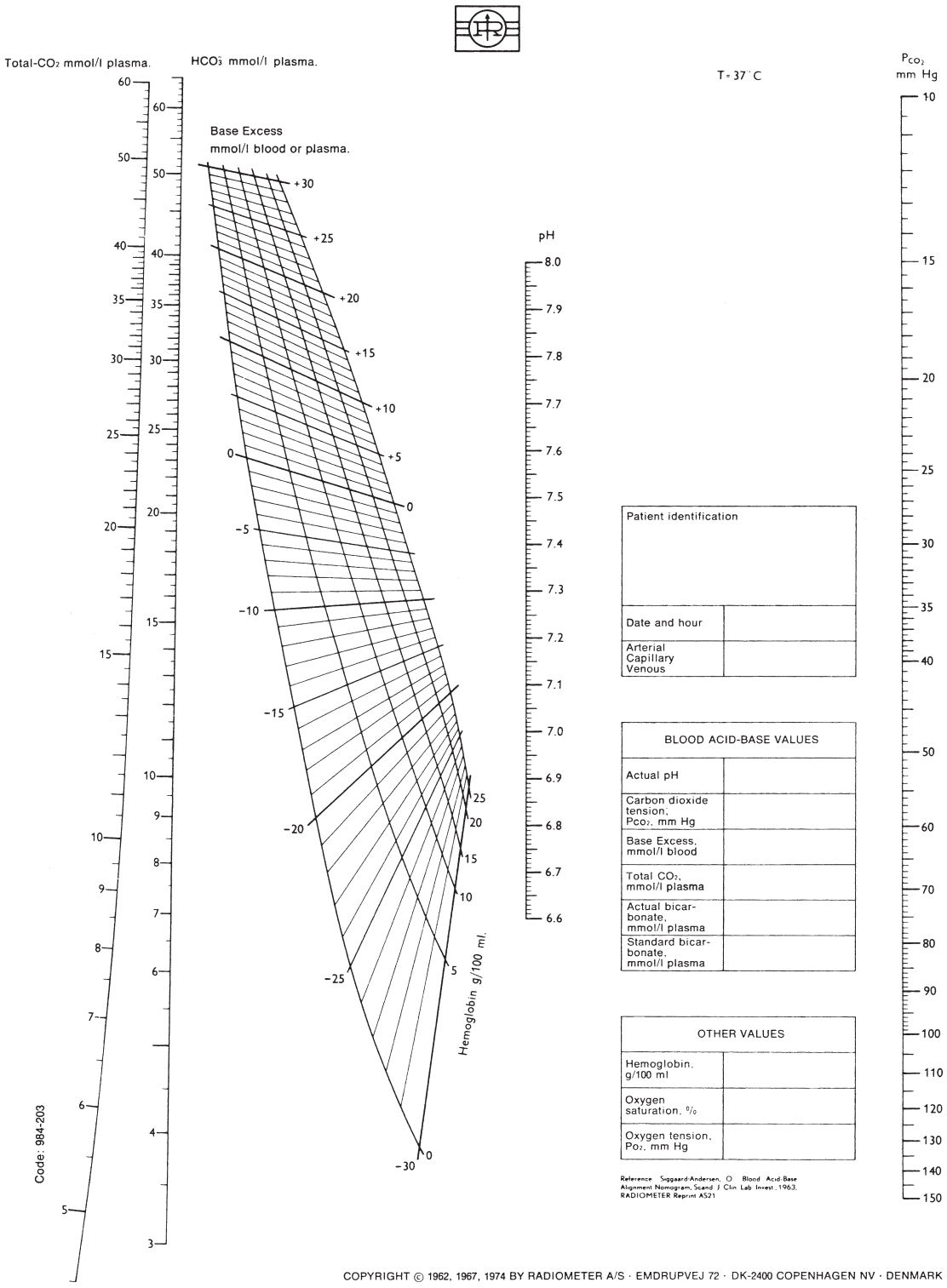
Hemoglobin-Oxygen Dissociation Curves



Nonlinear or S-shaped oxyhemoglibin curve and the linear or straight-line dissolved oxygen (O_2) relationships between the O_2 saturation (SaO_2) and the O_2 tension (Po_2). Total blood O_2 content is shown with division into a portion combined with hemoglobin and a portion physically dissolved at various levels of Po_2. Also shown are the major factors that change the O_2 affinity for hemoglobin and, thus, shift the oxyhemoglobin dissociation curve either to the left or to the right (see also Appendix 11). Modified from West JB: Respiratory Physiology—the Essentials. 2nd ed. Baltimore, Williams & Wilkins, 1979, pp 71, 73.

Appendix 11

Siggaard-Andersen Alignment Nomogram



Patient identification	
Date and hour	
Arterial Capillary Venous	

BLOOD ACID-BASE VALUES	
Actual pH	
Carbon dioxide tension, P_{CO_2}, mm Hg	
Base Excess, mmol/l blood	
Total CO_2, mmol/l plasma	
Actual bicarbonate, mmol/l plasma	
Standard bicarbonate, mmol/l plasma	

OTHER VALUES	
Hemoglobin, g/100 ml	
Oxygen saturation, %	
Oxygen tension, P_{O_2}, mm Hg	

Reference: Siggaard-Andersen, O.: Blood Acid-Base Alignment Nomogram, Scand J Clin Lab Invest., 1963. RADIOMETER Reprint AS21

Appendix 12

Neutral Thermal Environmental Temperatures*

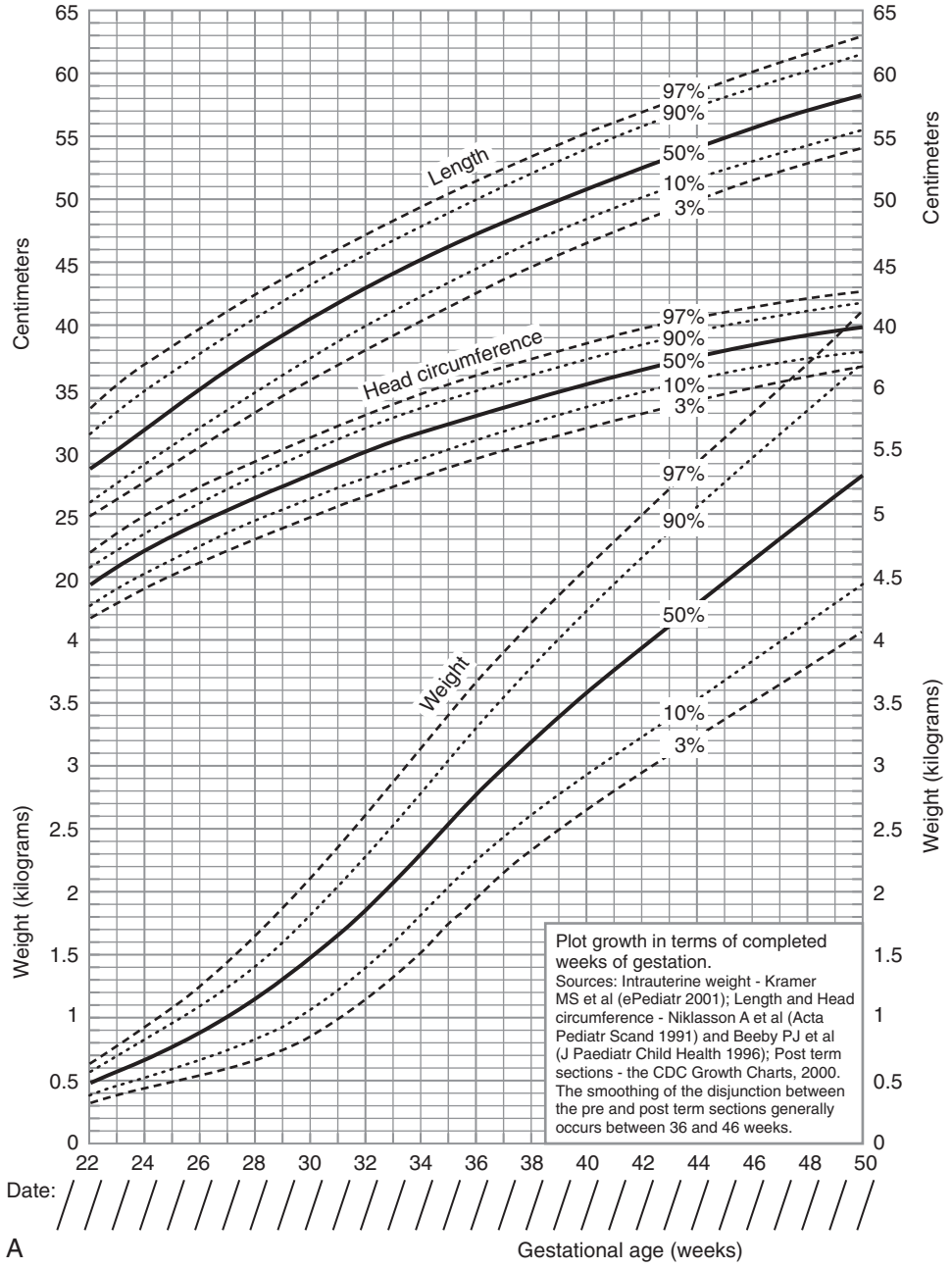
Age and Weight	Range of Temperature (°C)	Age and Weight	Range of Temperature (°C)
0-6 hr		72-96 hr	
<1200 g	34.0-35.4	<1200 g	34.0-35.0
1200-1500 g	33.9-34.4	1200-1500 g	33.0-34.0
1501-2500 g	32.8-33.8	1501-2500 g	31.1-33.2
>2500 g (and >36 wk)	32.0-33.8	>2500 g (and >36 wk)	29.8-32.8
6-12 hr		4-12 days	
<1200 g	34.0-35.4	<1500 g	33.0-34.0
1200-1500 g	33.5-34.4	1501-2500 g	31.0-33.2
1501-2500 g	32.2-33.8	>2500 g (and >36 wk)	
>2500 g (and >36 wk)	31.4-33.8	4-5 days	29.5-32.6
12-24 hr		5-6 days	29.4-32.3
<1200 g	34.0-35.4	6-8 days	29.0-32.2
1200-1500 g	33.3-34.3	8-10 days	29.0-31.8
1501-2500 g	31.8-33.8	10-12 days	29.0-31.4
24-36 hr <1 9		<1500 g	32.6-34.0
<1200 g	34.0-35.0	1501-2500 g	31.0-32.2
1200-1500 g	33.1-34.2	>2500 g (and >36 wk)	29.0-30.8
1501-2500 g	31.6-33.6	2-3 wk	
>2500 g (and >36 wk)	30.7-33.5	<1500 g	32.0-34.0
36-48 hr		1501-2500 g	30.5-33.0
<1200 g	34.0-35.0	3-4 wk	
1200-1500 g	33.0-34.1	<1500 g	31.6-33.6
1501-2500 g	31.4-33.5	1501-2500 g	30.0-32.7
>2500 g (and >36 wk)	30.5-33.3	4-5 wk	
48-72 hr		<1500 g	31.2-33.0
<1200 g	34.0-35.0	1501-2500 g	29.5-32.2
1200-1500 g	33.0-34.0	5-6 wk	
1501-2500 g	31.2-33.4	<1500 g	30.6-32.3
>2500 g (and >36 wk)	30.1-33.2	1501-2500 g	29.0-31.8

Adapted from Scopes J, Ahmed I: Minimal rates of oxygen consumption in sick and premature newborn infants. Arch Dis Child 41:417, 1966. For their table, Scopes and Ahmed maintained the walls of the incubator at a temperature 1° to 2° C warmer than that of the ambient air temperatures.

*Generally, the smaller infants in each weight group require a temperature in the higher portion of the temperature range. Within each time range, the younger the infant, the higher the temperature required.

Appendix 13A

Fetal-infant Growth Chart for Preterm Infants



A

Appendix 13B

MATURATIONAL ASSESSMENT OF GESTATIONAL AGE (New Ballard Score)

NAME _____ **SEX** _____

HOSPITAL NO. _____ **BIRTH WEIGHT** _____

RACE _____ **LENGTH** _____

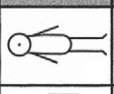
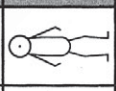
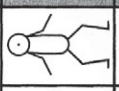
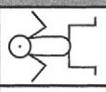
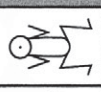
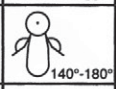
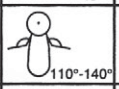
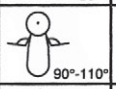
DATE/TIME OF BIRTH _____ **HEAD CIRC.** _____

DATE/TIME OF EXAM _____ **EXAMINER** _____

AGE WHEN EXAMINED _____

APGAR SCORE: 1 MINUTE _____ **5 MINUTES** _____ **10 MINUTES** _____

NEUROMUSCULAR MATURITY

NEUROMUSCULAR MATURITY SIGN	SCORE							RECORD SCORE HERE
	-1	0	1	2	3	4	5	
POSTURE								
SQUARE WINDOW (Wrist)	 >90°	 90°	 60°	 45°	 30°	 0°		
ARM RECOIL		 180°	 140°-180°	 110°-140°	 90°-110°	 <90°		
POPLITEAL ANGLE	 180°	 160°	 140°	 120°	 100°	 90°	 <90°	
SCARF SIGN								
HEEL TO EAR								
							TOTAL NEUROMUSCULAR MATURITY SCORE	

PHYSICAL MATURITY

PHYSICAL MATURITY SIGN	SCORE							RECORD SCORE HERE
	-1	0	1	2	3	4	5	
SKIN	sticky friable transparent	gelatinous red translucent	smooth pink visible veins	superficial peeling &/or rash, few veins	cracking pale areas rare veins	parchment deep cracking no vessels	leathery cracked wrinkled	
LANUGO	none	sparse	abundant	thinning	bald areas	mostly bald		
PLANTAR SURFACE	heel-toe 40-50 mm:-1 <40 mm:-2	>50 mm no crease	faint red marks	anterior transverse crease only	creases ant. 2/3	creases over entire sole		
BREAST	imperceptible	barely perceptible	flat areola no bud	stippled areola 1-2 mm bud	raised areola 3-4 mm bud	full areola 5-10 mm bud		
EYE/EAR	lids fused loosely: -1 tightly: -2	lids open pinna flat stays folded	sl. curved pinna; soft; slow recoil	well-curved pinna; soft but ready recoil	formed & firm instant recoil	thick cartilage ear stiff		
GENITALS (Male)	scrotum flat, smooth	scrotum empty faint rugae	testes in upper canal rare rugae	testes descending few rugae	testes down good rugae	testes pendulous deep rugae		
GENITALS (Female)	clitoris prominent & labia flat	prominent clitoris & small labia minora	prominent clitoris & enlarging minora	majora & minora equally prominent	majora large minora small	majora cover clitoris & minora		
							TOTAL PHYSICAL MATURITY SCORE	

SCORE

Neuromuscular_____

Physical _____

Total_____

MATURITY RATING

score	weeks
-10	20
-5	22
0	24
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

GESTATIONAL AGE (weeks)

By dates_____

By ultrasound_____

By exam_____

Reference
Ballard JL, Khoury JC, Wedig K, et al: New Ballard Score, expanded to include extremely premature infants. *J Pediatr* 1991; 119:417-423. Reprinted by permission of Dr Ballard and Mosby - Year Book, Inc.

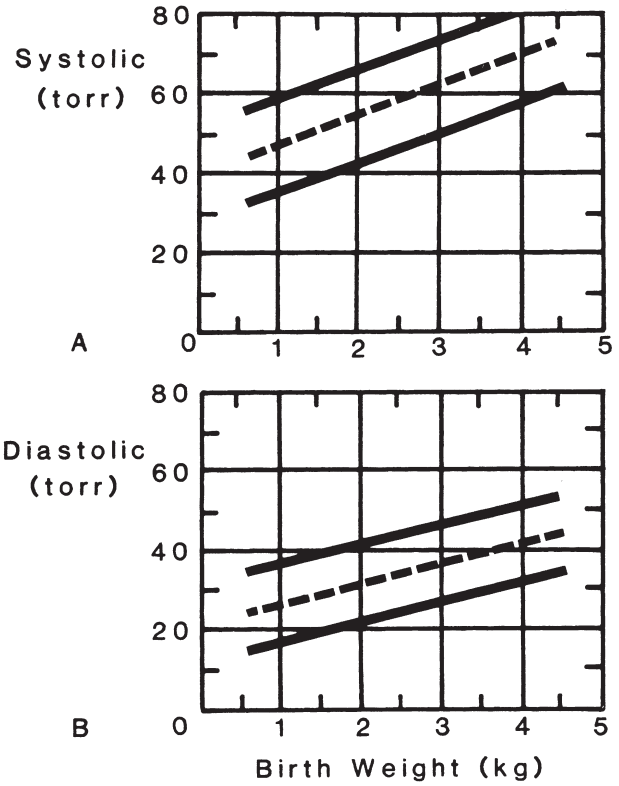
Appendix 14

Heart Rates in Premature and Full-Term Neonates

	1-7 DAYS			1-4 WEEKS		
	Minimum	**Mean**	**Maximum**	**Minimum**	**Mean**	**Maximum**
Premature neonates (<1500 g)	125	145	168	110	161	192
Premature neonates (1500-2500 g)	100	147	195	123	157	190
Full-term neonates	100	133	175	115	163	190

Appendix 15

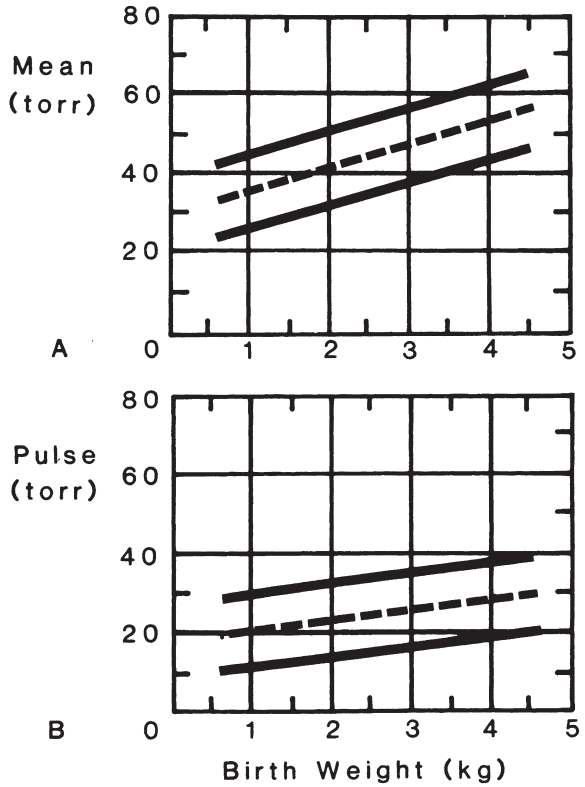
Systolic and Diastolic Blood Pressure in Newborn Infants



Systolic blood pressure (A) and diastolic blood pressure (B) in the first 12 hours of life as a function of birthweight. From Versmold HT, Kitterman JA, Phibbs RH, et al: Aortic blood pressure during the first 12 hours of life in infants with birth weight 610 to 4,220 grams. Pediatrics 67:607-613, 1981. Reproduced by permission of *Pediatrics,* copyright 1981.

Appendix 16

Mean Blood Pressure and Pulse Pressure in Newborn Infants



Mean blood pressure (A) and pulse pressure (B) in the first 12 hours of life as a function of birthweight. From Versmold HT, Kitterman JA, Phibbs RH, et al: Aortic blood pressure during the first 12 hours of life in infants with birth weight 610 to 4,220 grams. Pediatrics 67:607-613, 1981. Reproduced by permission of *Pediatrics,* copyright 1981.

Appendix 17

Blood Chemistries

A. NORMAL BLOOD CHEMISTRY VALUES, TERM INFANTS

Determination	Sample Source	Cord*	1-12 hr	12-24 hr	24-48 hr	48-72 hr
Sodium (mEq/L)†	Capillary	147 (126-166)	143 (124-156)	145 (132-159)	148 (134-160)	149 (139-162)
Potassium (mEq/L)		7.8 (5.6-12)	6.4 (5.3-7.3)	6.3 (5.3-8.9)	6.0 (5,2-7.3)	5.9 (5.0-7.7)
Chloride (mEq/L)		103 (98-110)	100.7 (90-111)	103 (87-114)	102 (92-114)	103 (93-112)
Calcium (mg/100 mL)		9.3 (8.2-11.1)	8.4 (7.3-9.2)	7.8 (6.9-9.4)	8.0 (6.1-9.9)	7.9 (5.9-9.7)
Phosphorus (mg/100 mL)		5.6 (3.7-8.1)	6.1 (3.5-8.6)	5.7 (2 .9-8.1)	5.9 (3.0-8.7)	5.8 (2.8-7.6)
Blood urea (mg/100 mL)		29 (21-40)	27 (8-34)	33 (9-63)	32 (13-77)	31 (13-68)
Total protein (g/100 mL)		6.1 (4.8-7.3)	6.6 (5.6-8.5)	6.6 (5.8-8.2)	6.9 (5.9-8.2)	7.2 (6.0-8.5)
Blood sugar (mg/100 mL)		73 (45-96)	63 (40-97)	63 (42-104)	56 (30-91)	59 (40-90)
Lactic acid (mg/100 mL)		19.5 (11-30)	14.6 (11-24)	14.0 (10-23)	14.3 (9-22)	13.5 (7-21)
Lactate (mm/L)‡		2.0-3.0	2.0			

*First number refers to the mean; second set of numbers refers to the range.
†Acharya PT, Payne WW: Arch Dis Child 40:430, 1965.
‡Daniel SS, Adamsons K Jr, James LS: Pediatrics 37:942, 1966. Reprinted by permission of Pediatrics, Copyright 1966.

B. NORMAL BLOOD CHEMISTRY VALUES, LOW-BIRTHWEIGHT INFANTS, CAPILLARY BLOOD, FIRST DAY

Determination	<1000 g	1001-1500 g	1501-2000 g	2001-2500 g
Sodium (mEq/L)	138	133	135	134
Potassium (mEq/L)	6.4	6.0	5.4	5.6
Chloride (mEq/L)	100	101	105	104
Total CO_2 (mEq/L)	19	20	20	20
Urea (mg/100 mL)	22	21	16	16
Total serum protein (g/100 mL)	4.8	4.8	5.2	5.3

From Pincus JB, Gittleman IF, Saito M, et al: Pediatrics 18:39, 1956. Reprinted by permission of Pediatrics, Copyright 1956.

C. BLOOD CHEMISTRY VALUES IN PREMATURE INFANTS DURING THE FIRST 7 WEEKS OF LIFE (BIRTHWEIGHT, 1500-1750 g)

	AGE 1 wk			AGE 3 wk			AGE 5 wk			AGE 7 wk		
Constituent	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
Sodium (mEq/L)	139.6	±3.2	133-146	136.3	±2.9	129-142	136.8	±2.5	133-148	137.2	±1.8	133-142
Potassium (mEq/L)	5.6	±0.5	4.6-6.7	5.8	±0.6	4.5-7.1	5.5	±0.6	4.5-6.6	5.7	±0.5	4.6-7.1
Chloride (mEq/L)	108.2	±3.7	100-117	108.3	±3.9	102-116	107.0	±3.5	100-115	107.0	±3.3	101-115
Carbon dioxide (mmol/L)	20.3	±2.8	13.8-27.1	18.4	±3.5	12.4-26.2	20.4	±3.4	12.5-26.1	20.6	±3.1	13.7-26.9
Calcium (mg/100 mL)	9.2	±1.1	6.1-11.6	9.6	±0.5	8.1-11.0	9.4	±0.5	8.6-10.5	9.5	±0.7	8.6-10.8
Phosphorus (mg/100 mL)	7.6	±1.1	5.4-10.9	7.5	±0.7	6.2-8.7	7.0	±0.6	5.6-7.9	6.8	±0.8	4.2-8.2
Blood urea nitrogen (mg/100 mL)	9.3	±5.2	3.1-25.5	13.3	±7.8	2.1-31.4	13.3	±7.1	2.0-26.5	13.4	±6.7	2.5-30.5
Total protein (g/100 mL)	5.49	±0.42	4.40-6.26	5.38	±0.48	4.28-6.70	4.98	±0.50	4.14-6.90	4.93	±0.61	4.02-5.86
Albumin (g/100 mL)	3.85	±0.30	3.28-4.50	3.92	±0.42	3.16-5.26	3.73	±0.34	3:20-4.34	3.89	±0.53	3.40-4.60
Globulin (g/100 mL)	1.58	±0.33	0.88-2.20	1.44	±0.63	0.62-2.90	1.17	±0.49	0.48-1.48	1.12	±0.33	0.5-2.60
Hemoglobin (g/100 mL)	17.8	±2.7	11.4-24.8	14.7	±2.1	9.0-19.4	11.5	±2.0	7.2-18.6	10.0	±1.3	7.5-13.9

Adapted from Thomas J, Reichelderfer T: Clin chem. 14:272, 1968.

Appendix 18

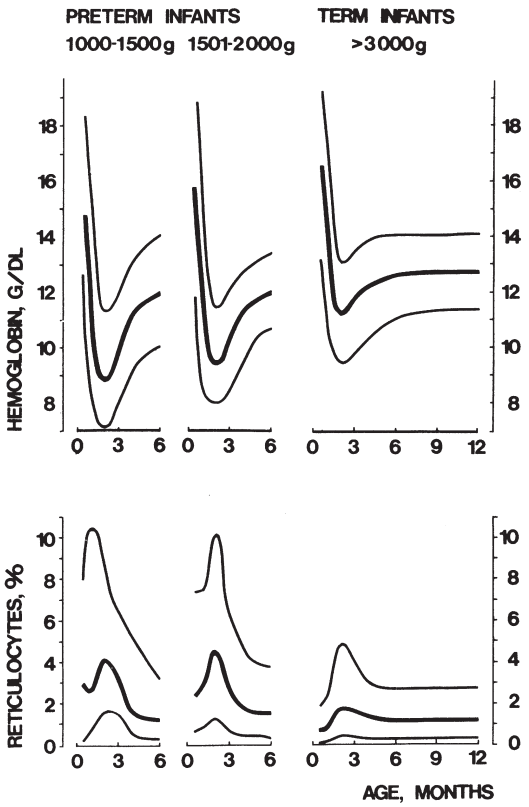
Hematologic Values in Newborn Infants

A. NORMAL HEMATOLOGIC VALUES DURING THE FIRST 14 DAYS OF LIFE

Value	GESTATIONAL AGE (wk) 28	34	Full-term Cord Blood	Day 1	Day 3	Day 7	Day 14
Hemoglobin (g/dL)	14.5	15.0	16.8	18.4	17.8	17.0	16.8
Hematocrit (%)	45	47	53	58	55	54	52
Red blood cells (mm^3)	4.0	4.4	5.25	5.8	5.6	5.2	5.1
MCV (μm^3)	120	118	107	108	99	98	96
MCH (pg)	40	38	34	35	33	32.5	31.5
MCHC (%)	31	32	31.7	32.5	33	33	33
Reticulocytes (%)	5-10	3-10	3-7	3-7	1-3	0-1	0-1
Platelets (1000 s/mm^3)			290	192	213	248	252

From Klaus MH, Fanaroff AA: Care of the High Risk Neonate, 4th ed. Philadelphia, Saunders, 1993, p. 486.
MCH, Mean corpuscular hemoglobin; *MCHC*, mean corpuscular hemoglobin concentration; *MCV*, mean corpuscular volume; *pg,* picogram.

B. CHANGES IN HEMOGLOBIN AND RETICULOCYTE COUNT IN TERM AND PRETERM INFANTS



Changes in hemoglobin and reticulocyte count in two groups of preterm infants and a group of term infants (Reproduced, with permission, from Dallman PR: Anemia of prematurity. Annu Rev Med 32:143, 1981. Copyright 1981, by Annual Review, Inc.)

Appendix 19

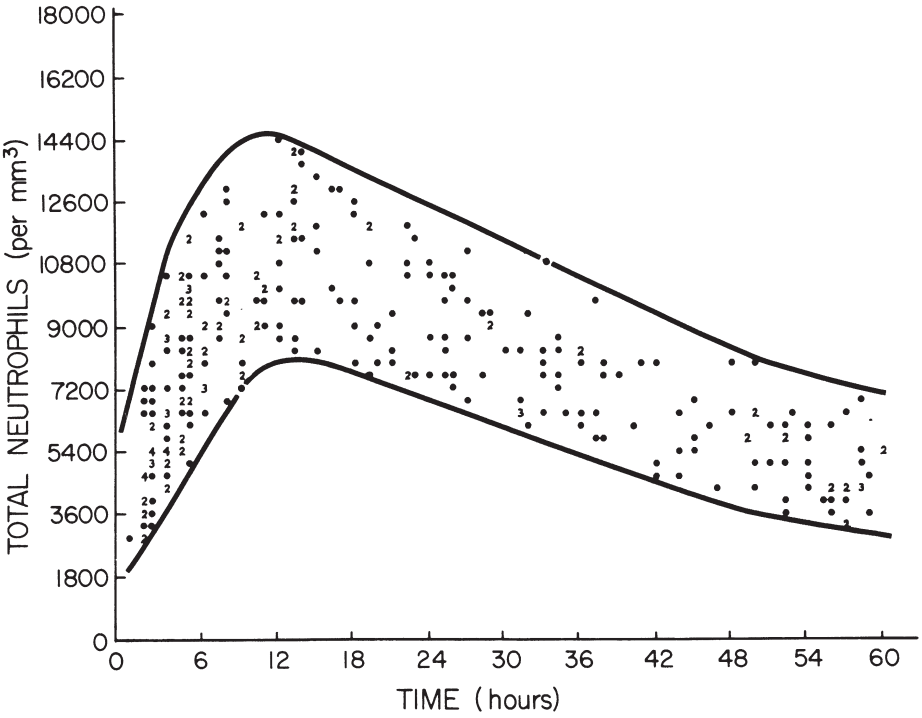
Leukocyte Values and Neutrophil Counts in Term and Premature Infants

A. LEUKOCYTE VALUES IN TERM AND PREMATURE INFANTS (10^3 CELLS/μL)

Age (hr)	Total White Cell Count	Neutrophils	Bands/Metas	Lymphocytes	Monocytes	Eosinophils
Term Infants						
0	10.0-26.0	5.0-13.0	0.4-1.8	3.5-8.5	0.7-1.5	0.2-2.0
12	13.5-31.0	9.0-18.0	0.4-2 .0	3.0-7.0	1.0-2.0	0.2-2.0
72	5.0-14.5	2.0-7.0	0.2-0.4	2.0-5.0	0.5-1.0	0.2-1.0
144	6.0-14.5	2.0-6.0	0.2-0.5	3.0-6.0	0.7-1.2	0.2-0.8
Premature Infants						
0	5.0-19.0	2.0-9.0	0.2-2.4	2.5-6.0	0.3-1.0	0.1-0.7
12	5.0-21.0	3.0-11.0	0.2-2.4	1.5-5.0	0.3-1.3	0.1-1.1
72	5.0-14.0	3.0-7.0	0.2-0.6	1.5-4.0	0.3-1.2	0.2-1.1
144	5.5-17.5	2.0-7.0	0.2-0.5	2.5-7.5	0.5-1.5	0.3-1.2

From Oski F, Naiman J: Hematologic Problems in the Newborn. Philadelphia, Saunders, 1982.

B. TOTAL NEUTROPHIL COUNT REFERENCE RANGE IN THE FIRST 60 HOURS OF LIFE



From Monroe BL, Weinberg AG, Rosenfeld CR, et al: The neonatal blood count in health and disease: I. Reference values for neutrophilic cells. J Pediatr 95:91, 1979.

Appendix 20

Platelets

A. VENOUS PLATELET COUNTS IN NORMAL LOW-BIRTHWEIGHT INFANTS

Day	No. of Infants	Mean (mm^3)	Range (1000 s)
0	60	203,000	80-356
3	47	207,000	61-335
5	14	233,000	100-502
7	52	319,000	124-678
10	40	399,000	172-680
14	50	386,000	147-670
21	47	388,000	201-720
28	40	384,000	212-625

From Appleyard WJ, Brinton A: Biol Neonat 17:30, 1971.

B. PLATELET COUNTS IN FULL-TERM INFANTS

Day	Mean	Range
Cord	200,000	100,000-280,000
1	192,000	100,000-260,000
3	213,000	80,000-320,000
7	248,000	100,000-300,000
14	252,000	

From Fanaroff AA, Martin RJ (eds): Behman's Neonatal-Perinatal Medicine, 3rd ed. St. Louis, C.V. Mosby, 1983.

Appendix 21

Coagulation Factors and Test Values in Term and Premature Infants

	Normal	Term Infant (Cord Blood)	Premature Infant (Cord Blood)
Fibrinogen (mg %)	200-400	200-250	200-250
Factor II (%)	50-150	40	25
Factor V (%)	75-125	90	60-75
Factor VII (%)	75-125	50	35
Factor VIII (%)	50-150	100	80-100
Factor IX (%)	50-150	25-40	25-40
Factor X (%)	50-150	50-60	25-40
Factor XI (%)	75-125	30-40	—
Factor XII (%)	75-125	50-100	50-100
Factor XIII (titer)	1:16	1:8	1:8
Partial thromboplastin time (sec)	30-50	70	80-90
Prothrombin time (sec)	10-12	12-18	14-20
Thrombin time (sec)	10-12	12-16	13-20

From Avery GB: Neonatology. 2nd ed. Philadelphia, J.B. Lippincott Co., 1981, p. 570.

Appendix 22

Cerebrospinal Fluid Values in Term and Premature Infants

	Term	Pre-term
WBC Count (cells/mm^3)		
No. of infants	87	30
Mean	8.2	9.0
Median	5	6
Standard deviation (SD)	7.1	8.2
Range	0-32	0-29
±2 SD	0-22.4	0-25.4
Percentage PMN	61.3%	57.2%
Protein (mg/dL)		
No. of infants	35	17
Mean	90	115
Range	20-170	65-150
Glucose (mg/dL)		
No. of infants	51	23
Mean	52	50
Range	34-119	24-63
CSF/Blood Glucose (%)		
Mean	81	74
Range	44-248	55-105

From Sarff L, Platt L, McCracken G: J Pediatr 88:473, 1976.
CSF, Cerebrospinal fluid; *PMN*, polymorphonuclear cells; *WBC*, white blood cell.

Appendix 23

Daily Maintenance, Fluid, Mineral, and Glucose Requirements for Term Neonates

Component	Amount
Water	100 mL/kg for each kg <10 50 mL/kg for each kg 11-20 20 mL/kg for each kg >20
Sodium	2-3 mEq/kg
Potassium	2-3 mEq/kg
Chloride	3-5 mEq/kg Calcium chloride is 27% Ca^{2+}
Calcium	20-40 mg/kg Calcium gluconate is 9% Ca^{2+}
Magnesium	15-25 mg/kg
Phosphorus	20-40 mg/kg
Glucose	2.4-4.8 g/kg

Appendix 24

Neonatal/Pediatric Transport: Transport Log

CHILDREN'S HOSPITAL OF THE KING'S DAUGHTERS, INC.
601 Children's Lane, Norfolk, VA 23507-1910

Neonatal/Pediatric Transport
TRANSPORT LOG

Date _____ pg 1 of _____ Referral Zip Code _____
Dispatch # _____ Call/Dispatch Time _____/_____
Mileage-Begin _____ End _____ ❑ Primary ❑ Backup
Fixed Wing/Helicopter Statute miles: Ambulance #: KD Addressograph or MRN, Patient name, DOB

Signature	Initials	Time		Time	Hospital
			Enroute		
			At scene		
			Transport		
			At Destination		

Patient Name _____ Diagnosis _____
Age _____ DOB _____ Weight _____ lb/kg Allergies ❑ None ❑ Latex ❑ Drug _____ Other _____
Communicable disease exposure? ❑ No ❑ Yes _____ Immunizations ❑ UTD ❑ NUTD _____
Referring MD Receiving MD PCP

Neonatal transports ONLY: Mom's age _____ G ____ PARA _____ Ab _____ EDC _____ Bld Type _____ Race _____
Prenatal Care _____ Preg. complications _____ Antibiotics? ❑ Yes ❑ No Why? _____
Serologies HIV _____ Rubella _____ βStrep _____ VDRL/RPR _____ Chlamydia _____ HBsAg _____ GC _____
Ob-Gyn _____ Sub Abuse? Cigarettes _____ ETOH _____ Other _____
Complications of previous preg./del _____
Parent's language _____ Social Hx: Siblings (age/sex) _____ Room#/Contact# for Mom _____
Siblings in good health? _____ Primary caregiver _____ Household composition _____
ROM date/time _____ ❑ AROM ❑ SROM Del ❑ Vaginal ❑ C-section Why? _____ Del date/time _____
EGA _____ Apgars 1 ___ 5 ___ 10 ___ Vit. K _____ Erythromycin Oint _____ HEP B _____ T4/PKU _____ Brm kit given ___

History of present condition _____

Medications given at referral hospital _____

Time	Medications/Procedures	Time	Patient Response

Total Output	Urine	Stool	Gastric	Other

Time	Procedure
	Oximeter attached Alarms-Hi Low
	Cardiac monitor attached Alarms-Hi Low
	Patient secured to ❑ Stretcher ❑ Pedimate ❑ Car Seat ❑ Incubator-Air temp
	ID band checked by / ❑ ID confirmed by parent/guardian ❑ X-rays ❑ Consent ❑ Copied Chart
	Family/patient received ❑ CHKD map ❑ Unit Info ❑ Photograph ❑ Time w/Pt. ❑ Orientation to CHKD/Transport
	Patient secured in ambulance
	Report called to
	ETA called to admitting unit

Call Clear Date _____ Time _____ Attendant In-Charge _____ Date _____

CHKD Form 0851 MR 8/04 White-CHKD Medical Record Yellow-CHKD Transport Team Pink-Hospital/MD

Appendix 24

Neonatal/Pediatric Transport: Transport Log—cont'd

CHILDREN'S HOSPITAL OF THE KING'S DAUGHTERS, INC.
601 Children's Lane, Norfolk, VA 23507-1910

Neonatal/Pediatric Transport
TRANSPORT LOG

Page ____ of ____

Isolation: ❑ Airborne ❑ Contact ❑ Droplet ❑ Bag/Mask ____ Pop Off ____
Pain Scale: ❑ FLACC ❑ FACES ❑ 0–10 ETT size/position Addressograph or MRN, Patient Name, DOB

Vital Signs	TIME															
	T															
	Heater															
	HR															
	RR															
	S BP															
	D BP															
	M BP															
	Pain															
Respiratory	SpO_2															
	FIO_2															
	Via															
	$ETCO_2$															
	NO/NO_2															
	PIP/VT															
	PEEP/CPAP															
	RATE															
	FLOW															
	IT															
	Alarms															
	HT															
	HHN															
	Other															
Labs	AVC															
	pH															
	PCO_2															
	PO_2															
	HCO_3															
	B.E.															
	Sat															
	Glu															
IV	1															
	2															
	3															
	4															
	Other															

t-trach V-Ventilator IT-inspiratory Time M BP-Mean BP S BP-Systolic BP D BP-Diastolic BP M-Mask H-Oxyhood
NC-Nasal Cannula Mom-To Mom's Room PPV-Positive Pressure Ventilation PRB-Partial Rebreather Amb-Secured in Ambulance
P-Chemical Mattress HT-Humidifier Temp

ASSESSMENT CODES: √ within normal guidelines *abnormal findings → no change from previous assessment /area not assessed

TIME																
NEURO																
RESP																
CV																
GI																
GU																
SKIN																
Musc.																
IV SITES																

Attendant in-charge _____ Date _____
CHKD Form 0853 MR 08/04

White-CHKD Medical Record Yellow-CHKD Transport Team Pink-Hospital/MD

Appendix 24

Neonatal/Pediatric Transport: Transport Log—cont'd

CHILDREN'S HOSPITAL OF THE KING'S DAUGHTERS, INC.
601 Children's Lane, Norfolk, VA 23507-1910

Neonatal/Pediatric Transport
TRANSPORT LOG

Page ____ of ____

Addressograph or MRN, Patient Name, DOB
SEX: ❑ MALE ❑ FEMALE ❑ OTHER RACE _____

Initial Systems Assessment Date: _____ Time _____

Neuro:
❑ Alert Oriented _____
❑ Normal per baseline
Responds to ❑ touch ❑ voice ❑ pain ❑ unresponsibe ❑ inconsolable
AF ❑ flat ❑ bulging ❑ sunken ❑ pulsatile
Other _____

Resp:
Rate: ❑ regular ❑ irregular ❑ other _____
BrS: ❑ clear ❑ equal ❑ unequal ❑ bilateral
Aeration: ❑ good ❑ fair ❑ poor ❑ equal

Adventitious Sounds _____
❑ rales
❑ rhonchi
❑ wheezes ❑ insp ❑ exp
location _____
❑ stridor _____

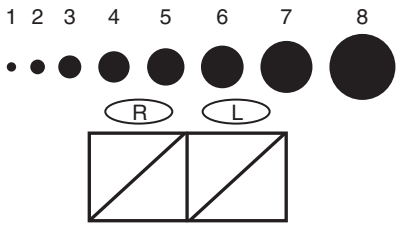
Audible sounds: ❑ grunting ❑ wheezing ❑ stridor ❑ congestion ❑ cough _____

Retractions: ❑ mild ❑ moderate ❑ severe
❑ supraclavicular ❑ suprasternal
❑ intercostol ❑ substernal ❑ subcostal
❑ accessory muscles ❑ nasal flaring
Initial SpO_2: _____

Airway Adjunct: FiO_2: _____ via:
❑ nasal cannula ❑ hood ❑ NCPAP
❑ partial rebreather ❑ face mask
❑ ETT/ ❑ Trach size: _____ ❑ cuffed
❑ uncuffed position: _____

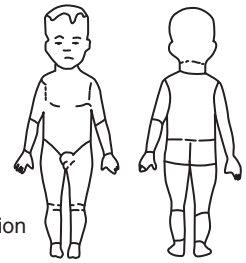
Ventilator Settings: FIO_2 _____ PIP/TV _____
PEEP/CPAP ____ Rate/MV ____ IT ____
Pressure Support ____ $ETCO_2$ _____
Other _____

Pupils: **(Size/Reaction)**



B Brisk NR No Reaction
S Sluggish NT Not Testable

Skin:
Picture Legend
1. IV Site(s)
2. Incision/ Lacerations
3. Staples/Suture
4. Hematoma/ Ecchymosis
5. Redness/Abrasion
6. Stoma
7. Other: _____



❑ warm ❑ dry ❑ other
Mucous Memb ❑ moist ❑ sticky ❑ dry
Skin turgor _____
Other _____

Musc:
❑ MAE _____
Tone ❑ normal ❑ weak ❑ flaccid
Other _____

GU:
Last Void _____
❑ Foley Size _____
Other _____

GI:
❑ NPO
Abdomen ❑ soft ❑ firm ❑ distended ❑ tender to touch

BS ❑ present ❑ hyperactive ❑ active ❑ hypoactive ❑ absent

Tubes and Drains ❑ tube placement √
Type/Size _____
❑ straight drain ❑ I.C.S. ❑ LIS
Other _____

Cardiac:
Monitor _____
Rhythm ❑ regular ❑ irregular ❑ other
Murmur ❑ present ❑ absent _____

Appearance ❑ pink ❑ cyanotic ❑ pale ❑ mottled ❑ diaphoretic ❑ cool ❑ clammy

Pulses Peripheral
UE ❑ absent-0 ❑ thready-1 ❑ regular-2 ❑ bounding-3 to 4 ❑ irregular
LE ❑ absent-0 ❑ thready-1 ❑ regular-2 ❑ bounding-3 to 4 ❑ irregular

Carotid ❑ absent-0 ❑ thready-1 ❑ regular-2 ❑ bounding-3 to 4 ❑ irregular

Femoral ❑ absent-0 ❑ thready-1 ❑ regular-2 ❑ bounding-3 to 4 ❑ irregular

Liver Edge ❑ palpable ❑ non-palpable _____

Capillary Refill
peripheral ❑ <2 sec ❑ >2 sec
sternal ❑ <2 sec ❑ >2 sec
Other _____

X-ray results

IV Time	#	Site	Size	Type of Fluid	Rate
	1				
	2				
	3				
	4				
Other					

Nursing Diagnosis:
❑ Potential Alteration in Neuro Status
❑ Potential Alteration Respiratory Status
❑ Potential Alteration CV Status
❑ Potential Alteration in Parent/Child Bonding
❑ Potential for Infection
❑ Potential Alteration in Fluid/Electrolyte Balance
❑ Potential Alteration in Skin Integrity
❑ _____

Time	Narrative Notes

Attendant In-Charge _____ Date _____

CHKD Form 0852MR 08/04

White - CHKD Medical Record Yellow - CHKD Transport Team Pink - Hospital/MD

Neonatal/Pediatric Transport: Transport Log—cont'd

CHILDREN'S HOSPITAL OF THE KING'S DAUGHTERS, INC.
601 Children's Lane, Norfolk, VA 23507-1910

Neonatal/Pediatric Transport
TRANSPORT LOG

Page ____ of ____

Patient Label or MRN, Acct#, Patient Name, DOB, Date of Service

Time	Narrative Notes:

Attendant In Charge: ____ Date __________________
CHKD Form 0854 MR 08/04

White-CHKD Medial Record Yellow-CHKD Transport Team Pink-Hospial/MD

Neonatal/Pediatric Transport: Transport Log—cont'd

CHILDREN'S HOSPITAL OF THE KING'S DAUGHTERS, INC.
601 Children's Lane, Norfolk, VA 23507-1910

Neonatal/Pediatric Transport
ORDERS FOR TRANSPORT ONLY

Page ____ of ____ Addressograph

▲ Routine order for this type of patient. MD signature at the end of this order set activates the order. To omit the order, the ordering MD must cross through and initial the order to be omitted.

❑ Box must be checked by the ordering MD to activate the order.

DATE _____ TIME _____

▲ Pulse Oximeter

▲ Transport to: ❑ CHKD ❑ Other: _____
❑ NICU ❑ PICU ❑ ED ❑ Nursery ❑ Floor/Other: _____

▲ CHKD Transport via: ❑ Ground ❑ Fixed Wing/Rotor Wing ❑ Tail # _____

❑ NPO

❑ OGT ❑ NGT ❑ LCS ❑ Straight Drain

❑ Foley Catheter to straight drain

❑ Outpatient Transport From: _____ To: _____

❑ Cardiac Respiratory Monitor

Airway Adjuncts: FIO_2: _____ via: ❑ Nasal Cannula ❑ Hood ❑ Partial Non-rebreather ❑ Face Mask
❑ Trach ❑ Other: _____ Keep sats ≥ _____

Ventilator via: ❑ ETT ❑ Trach ❑ Nasal Settings: FIO_2 _____ PIP/TV _____ PEEP/CPAP _____
Rate/IMV _____ I.t. _____ $ETCO_2$ range _____–_____ Keep sats ≥ _____ Other:_____

IVF: ❑ Saline Lock
❑ Maintenance IVF _____@_____ cc/hr
❑ Other: _____
❑ Other: _____

Labs: ❑ via ISTAT® ❑ A/V/C/ Blood Gas ❑ Glucose _____ ❑ Electrolytes _____ ❑ Blood Culture
❑ CBC ❑ Other: _____

X-rays: ❑ Chest AP ❑ Abdomen AP ❑ Other: _____ Reason for X-ray: _____

Medications:_____
_____
_____
_____
_____
_____

Other: _____
_____
_____

V.O./T.O. R and A Dr. _____/_____RN MD Signature: _____

Date/Time	Order and Signature

CHKD Form 0751 MR Rev 8/04

White - Medical Record Yellow - Transport Pink - Pharmacy

Neonatal/Pediatric Transport: Transport Log—cont'd

CHILDREN'S HOSPITAL OF THE KING'S DAUGHTERS, INC.
601 Children's Lane, Norfolk, VA 23507-1910

Transport
CONSENT TO TRANSPORTATION AND TREATMENT

CHKD Addressograph or Patient Name, Patient DOB

1. On the advice of the attending physician, _____, I, the legal guardian or parent of _____, hereby authorize transport of this patient to Children's Hospital of The King's Daughters (CHKD) or _____ for further observation and treatment.
2. I hereby authorize transportation via:
   - ❑ The Mobile Intensive Care Unit operated by Children's Hospital of The King's Daughters;
   - ❑ CHKD NICU Personnel;
   - ❑ _____

   I further authorize the Children's Hospital personnel to initiate all necessary treatment and diagnostic procedures while the patient is in their care en route.
3. I hereby agree to be financially responsible for care rendered to this patient during transport.
4. The laws of Virginia authorize health care providers to test patients for HIV antibodies when the health care provider is exposed to the body fluids of the patient. In the event of exposure, I understand that I will be deemed to have consented to testing, and consent to release test results to the health care worker who may have been exposed. Prior to testing, I will be informed and given an opportunity to ask questions.
5. I hereby acknowledge that the Organized Health Care Arrangement Notice of Privacy Practices for CHKD has been provided to me.

CONDITION OF ADMISSIONS TO CHKD

6. I, the undersigned, request admission to the CHKD for either myself or my child/ward and hereby authorize the Hospital, its employees, and Dr. _____ (and whomever he may designate as his assistants, including residents) to treat me or my child/ward in ways they determine to be therapeutically necessary. I understand that this treatment may include tests, examinations, administration of drugs, and medical or surgical procedures.
7. I hereby irrevocably authorize my insurance company Medicaid or Medicare, CHAMPUS or other provider of my health benefits to pay any of my benefits directly to Children's Hospital of The King's Daughters or to my physicians in payment for the services rendered on my account or on the account of my child/ward. I agree to pay the Hospital and the physicians for any charges not paid by my health care benefits.
8. I have received information about the use of a password during my child/ward's inpatient hospitalization. I have provided the following password for that use: _____.
9. I hereby authorize transport from CHKD to _____ when the patient's condition is such that continuing care and treatment may be effectively provided at the above facility.

I certify that this form has been fully explained to me and that I understand its contents. Furthermore, I permit a copy of this authorizing document to be used in place of the original. I certify that I am the patient, patient's parent or legal guardian and have the authority to grant this consent. I certify that all statements are true and correct. I understand that false statements or documents, or concealment of material fact may be prosecuted under federal or state laws.

_____ Date

_____ Patient or Parent/Legal Guardian

_____ Witness

_____ Relationship to Patient/Legal Authority

_____ Witness (for telephone consents)

FINANCIAL AGREEMENT

The undersigned patient and/or responsible party(ies) agree that in consideration of services rendered to the patient, each of them jointly and severally, will pay and guarantee payment of the hospital and physician bills in accordance with the regular terms and charges of the hospital and physician. Any portion of the bill not covered by insurance will be payable at discharge unless other arrangements are made with the Patient Accounts Department. It is further agreed that in the event of nonpayent that the hospital and physician shall have the right to proceed against the responsible party(ies) without making demands of, or taking any action proceeding against the other as a prerequisite. The undersigned agree to pay all costs of collection including agency fees and attorney fees in the amount of THIRTY-THREE AND ONE-THIRD PERCENT (33.3%) of the amount owed.

_____ Date

_____ Guarantor

_____ Witness

Appendix 25

Neonatal ICU Flow Sheet

CHILDREN'S HOSPITAL OF THE KING'S DAUGHTERS, INC.
601 Children's Lane, Norfolk, VA 23507-1910

NEONATAL ICU FLOW SHEET

DATE:	DAY OF ADMISSION

VITAL SIGNS																	APNEA/BRADYCARDIA							
		TEMP																						
TIME	INITIALS	PATIENT	SKIN	ENVIRONMENT	HEATING	% HUMIDITY	HR	RR	SYSTOLIC	DIASTOLIC	MEAN	SITE	WAVE/CAL	O_2 SAT %	OXIMETER SITE	PAIN	TIME/INIT	HR	APNEA	DURATION	FEEDING?	COLOR Δ?	O_2 SAT %	STIM

Yes or √ = Yes No or Ø = No N/A = Not Applicable	**BP/PULSE OX SITES:** L = Line C = Cuff RA = R arm RL = R leg LA = L arm LL = L leg
WAVE FORM: N = Normal D = Dampened F = Flat	**OXIMETER SITE:** *Refer to patient care note Δ indicates change in Probe Site
ACTION: M = Medication *see notes	**STIM (STIMULATION):** G = Gentle Stimulation B = Manual Bag Ventilation M = Moderate Stimulation MB = Manual Breath Button V = Vigorous Stimulation ↑ O_2 = Increase O_2

SIGNATURE	INITIALS	SHIFT

Appendix 25

Neonatal ICU Flow Sheet—cont'd

Neonatal ICU Flowsheet

Date:	RESPIRATORY PROCEDURES	TIME/INIT
Ventilator: Mode:		
ETT: Size:		
Position:		
Suction Catheter Length:		
Trach Tube Lot #/Size:		
Trach Suction Catheter Length:		
# and Size of Trach Tubes @ Bedside:		

Assisted ventilation										Blood gases									Breath sounds				Sputum				
TIME	INITIALS	FiO_2/Via	PIP/Amp	PEEP/CPAP	V_T	MAP	Rate/Hz	Flow/SP	I.t.	A/V/C	pH	PCO_2	pO_2	HCO_3	B.E.	Sat	O_2Sat%		Before sxn r/l	After sxn r/l	Aeration	Mechanics	Color	Amount	Viscosity	Odor	CPT/HHN

FiO_2 DELIVERY:	FD = Flow Driver	D = Diminished	SPUTUM COLOR:	Mo = Moderate
M = Mask	TC = Trach Collar	CR = Crackles	W = White	Co = Copious
H = Oxyhood	NO = Nitric Oxide	MECHANICS:	G = Green	VISCOSITY:
D = Dräger	NO_2 = Nitric Dioxide	G = Grunting	C = Colorless	Th = Thin
IS = Infant Star	V_T = Tidal Volume	F = Flaring	Y = Yellow	Te = Tenacious
E = Evita	SP = Servo Pressure	R = Retraction	R = Red	ODOR:
J = HFJV	BREATH SOUNDS:	AERATION:	B = Brown	P = Present
O = HFOV	Cl = Clear	P = Poor	AMOUNT:	A = Absent
LTV = LTV vent	C = Coarse	Mo = Moderate	N = None	
NC = Nasal Cannula	W = Wheeze	G = Good	Sc = Scant	
HFNC = High Flow NC	R = Rales			

Neonatal ICU Flow Sheet—cont'd

Neonatal ICU Flowsheet Date _____

TIME	IV STARTS/LINE INSERTIONS/SITE	TIME	IV STARTS/LINE INSERTIONS/SITE

	PUMP		IV SOLUTIONS/ PARENTERAL NUTRITION	TUBING CHANGE	SITE	LUMEN	LINE TYPE	LINE DAY
	L	S						
1								
2								
3								
4								
5								
6								
7								
8								

TIME	INITIALS	SITE √	1	2	3	4	5	6	7	8	9	TIME	INITIALS	PLACEMENT √	POSITION	ABD GIRTH	ROUTE	RES / D/R	AMT	FDG TYPE	BrM √
0700																					
0800																					
0900																					
1000																					
1100																					
1200																					
1300																					
1400																					
1500																					
1600																					
1700																					
1800																					
12 HR.																					
1900																					
2000																					
2100																					
2200																					
2300																					
2400																					
0100																					
0200																					
0300																					
0400																					
0500																					
0600																					
12 HR.																					
24 HR.																					

L = Large Volume Infusion Pump S = Syringe Pump	**Route Codes:** G = Gastrostomy D = Duodenal	CUM = Cumulative NG = Naso Gastric	Res = Residual OG = Oral Gastric	D = Discard PO = By Mouth	R = Refed

Neonatal ICU Flow Sheet—cont'd

Neonatal ICU Flowsheet Date _____

INTAKE TOTALS				
	PARENTERAL			ENTERAL
SHIFT	FLUID	LIPID	BLOOD	
07–19				
19–06				
24 HOUR TOTAL				

OUTPUT TOTALS				
SHIFT	URINE	cc/kg/ HOUR	STOOL	GASTRIC
0700–1859				
1900–0659				
24 HOUR TOTAL				

AGE/GROWTH PARAMETER			
DATE	TIME	PARAMETER	VALUE
		Admission weight	
		Current weight	
		Previous weight	
N/A	N/A	Difference	
		FOC	
		Length	
		Admission Gestational Age	
		Current Gestational Age	

		OUTPUT											
		URINE	GASTRIC				STOOL		CHEST TUBES				
			Emesis	In	Out				1	Out	2	Out	
TIME	INITIAL	AMT	AMT	AMT	AMT	ASSESS	AMT	ASSESS	Tube Lgth	Drainage	Tube Lgth	Drainage	
07													
08													
09													
10													
11													
12													
13													
14													
15													
16													
17													
18													
12hr													
19													
20													
21													
22													
23													
24													
01													
02													
03													
04													
05													
06													
12hr													

ASSESS CODES: BR = Brown Y = Yellow M = Meconium S = Seedy	Blk = Black Bld = Bloody W = Watery H = Hard SO = Soft	F = Formed GN = Green CG = Coffee Ground	**STOOL CODES:** Sm = Small Mo = Moderate Lg = Large	Yes or √ = Yes No or Ø = No N/A = Not Applicable	↑ = Up ↓ = Down Lgth = Length

Neonatal ICU Flow Sheet—cont'd

Neonatal ICU Flowsheet Date _____

Time						
Initials						
HEMATOLOGY						
WBC						
RBC						
HGB						
HCT						
Platelets						
Retic						
DIFFERENTIAL						
Polys						
Bands						
Eos						
Baso						
Lymphs						
Mono						
Meta						
NRBC						
TPN LABS						
Alb						
Phos						
TRIG						
Mg++						
AST						
ALT						
Alk Phos						
GGT						

TIME	DIAGNOSTIC TESTING	INITIALS

Time						
Inititals						
Blood chemistry/miscellaneous						
Glu						
iGlu						
BUN						
Na+						
Cl						
CO_2						
Cr						
T. Bili						
D. Bili						
Ca						
CRP						
Lactate						

CRITICAL VALUES REFERENCE ***Expected Response Time = 30 min.***	
Bilirubin	>25 mg/dL
Blood Cx	Positive
Calcium	<6.5 mg/dL or >13 mg/dL
CSF Culture	Positive
CSF Gm Stain	Positive
Total CO_2	<10 mEq/L
PCO_2	<20 or >80 mmHg
Glucose	<40 mg/dL or >400 mg/dL
Hemoglobin	<5 gm/dL or >25 gm/dL
pH	<7.15 or >7.60
Potassium	<2.8 mEq/L or >6.5 mEq/L
PT	>75 seconds
Sodium	<125 mEq/L or >160 mEq/L
WBC	<2.0 x 10^3 cells/mm^3

Appendix 25

Neonatal ICU Flow Sheet—cont'd

Neonatal ICU Flowsheet Date _____ Patient Label or MRN, Acct#, Patient Name, DOB, Date of Service

DAILY ROUTINE	INITIALS A	INITIALS B	DAILY ROUTINE	INITIALS A	INITIALS B	DAILY ROUTINE	INITIALS A	INITIALS B
Bath			Isolation: state type N-Neutropenia, C-contact, D-droplet, A-airborne			Side Rails		
Oral Care			Monitor Alarms Heart Rate High ____ Low ____			Developmental Positioning		
Catheter/Tube Care			Monitor Alarms Resp/Apnea High ____ Low ____			Position Change ____ hr and prn		
Phototherapy Flux			Monitor Alarms Pulse Oximeter High ____ Low ____			Phototherapy: state type W = White B = Blue S = Spot B = Blanket		
Code Med Sheet			Monitor Alarms BP High ____ Low ____			Review POC		

ASSESSMENT																
√ = within normal guidelines * = abnormal assessment or change from previous → = no change from previous / = the area was not assessed																
Time																
Neuro																
Resp																
CV																
GI																
GU																
Skin																
Musc																
Lines																
Pain																
Fall Risk																
Initials																

FAMILY INTERACTION								
TIME	INITIALS	PERSON	CALLED	VISIT	HELD	FED	BATHED	CONSULTS

M = Mother
F = Father
GM = Grandmother
GF = Grandfather
KC = Kangaroo Care
PT/OT/ST = Physical/ Occupational/Speech Therapy
SW = Social Work
CH = Chaplain
Ch Life = Child Life

Psych/Social Data _____
_____
_____

Neonatal ICU Flow Sheet—cont'd

Neonatal ICU Flowsheet Date _____ Patient Label or MRN, Acct#, Patient Name, DOB, Date of Service

STAGE I	STAGE II	STAGE III	STAGE IV
Possible painful IV site No erythema Edema <1 inch in any direction	Possible painful IV site Edema 1–6 inches in any direction Possible discoloration Good pulse below infiltration site Good capillary refill below infiltration site	Mild to moderate pain Edema >6 inches any direction Blanching Skin cool to touch Good pulse below infiltration site Good capillary refill below infiltration site	Moderate to severe pain Edema >6 inches any direction Blanching Skin cool to touch Decreased or absent pulse* Capillary refill greater than 4 sec* Skin breakdown or necrosis* ***Any one of these last 3 present constitutes a Stage IV infiltrate** **EXTRAVASATION OF A VESICANT IS ALWAYS RATED AS A STATE IV INFILTRATE.*** Vesicant Solution: Solutions capable of causing tissue injury or destruction dependent on the pH and osmolarity of the solution. Vesicant solutions include but are not limited to TPN, Intralipids, Vancomycin, and Gentamicin.
Initial documentation required in nursing narrative notes: Cannula type and size, medication infusing at time of infiltration, method of infusion, measurement of swelling of affected extremity, pain assessment, amount of residual fluid aspirated.	**Initial documentation required in nursing narrative notes:** 1. Cannula type and size, medication infusing at time of infiltration, method of infusion, measurement of swelling of affected extremity, pain assessment, amount of residual fluid aspirated. 2. Name of Physician/NP/PA notified and time Hyaluronidase injected (if ordered). 3. Follow up assessment 15 min, 30 min, then q shift until signs/symptoms resolved.		

Use the following codes to document in the appropriate section:
Document pain score as number or s = sleeping, document Length and Width in inches, Capillary Refill in seconds C = cold compress H = hot compress. Otherwise use Y or √ = yes, N or Ø = No

SITE **Date/time of infiltrate**	DATE/TIME/INITIALS	Pain Score @ site	Length of swelling	Width of swelling	Blanching	Skin cool to touch	Pulse present below site	Capillary refill below site	Skin breakdown	Able to move extremity	Cold or Hot compress in use
15 min post											
30 min post											
Shift change											
Shift change											

OUTCOME of IV Infiltration/Extravasation: No further follow up needed ____ Plastics consulted for follow up ____

NEONATAL INFANT PAIN SCALE			
Category	***Behavior***	***Operational Definition***	***Score***
Facial Expression	Relaxed muscles	Restful face, neutral expression	0
	Grimace	Tight facial muscles, furrowed brow/chin/jaw (negative facial)	1
Cry	No cry	Quiet, not crying	0
	Whimper	Mild moaning, intermittent	1
	Vigorous	Load scream, crying, shrill, continuous, silent cry if intubated	2
Breathing Patterns	Relaxed	Usual pattern and rate for this infant	0
	Change in breathing	Indrawing, faster than usual, gagging, breath holding	1
Arms	Relaxed/restrained	No muscular rigidity, occasional random movement of arms	0
	Flexed/extended	Tense straight arms, rigid and/or rapid flexion and extension	1
Legs	Relaxed/restrained	No muscular rigidity, occasional random leg movement	0
	Flex/extended	Tense straight legs rigid and/or rapid flexion and extension (bicycling)	1
State of Arousal	Sleeping/awake	Quiet, peaceful, sleeping	0
	Fussy	Alert, restless, thrashing	1
TOTAL PAIN SCORE and TRANSFER TO VS ON PAGE 1			

Nursing Diagnoses from Plan of Care:

1. _____ 2. _____

3. _____ 4. _____

Neonatal ICU Flow Sheet—cont'd

Neonatal ICU Flowsheet Date __________________ Patient Label or MRN, Acct#, Patient Name, DOB, Date of Service

TIME	FOCUS	PATIENT CARE NOTES

SIGNATURE	INITIALS	SHIFT	SIGNATURE	INITIALS	SHIFT

Appendix 26

A. Neonatal Resuscitation Record

Patient Name _____ Date _____

Est. Wt. _____ grams Sex _____ Est. Gest. Age _____

Time of Birth _____ AM/PM

Time Resuscitation Procedures Initiated:

Time Resuscitation Procedures Completed:

Perinatal History:

Min	Heart Rate	Muscle Tone	Reflex Irritabillty	Color	Resp. Effort	Total
A 1						
P 5						
G 10						
A 15						
R 20						
S 25						

Amniotic Fluid: ❑ Clear ❑ Meconium Stained

PROCEDURES	START	END	BY WHOM	
UVC or UAC				UA/UV size: 3.5 5 8
Intubation				ETT Size: 2.5 3.0 3.5 4.0
Intubation w/Ventilation				
Intubation/Suctioning Only				
Cardiac Compressions				
Positive Pressure Ventilation				
Free Flow Oxygen @ _____ L/min				
Suction				
O/G Tube In: ❑ Yes ❑ No				

DRUGS	TIME/AMT	TIME/AMT	ROUTE
Epinephrine 1:10000 0.1 - 0.3 mL/kg			
Volume Expander: 5% Albumin 10 mL/kg Normal saline Ringer's Lactate			
Sodium Bicarbonate 0.5 mEq/mL 2 mEq/kg (4.2% solution)			
Naloxone Hydrochloride 0.4 mg/mL or 0.1 mg/kg 1.0 mg/mL			
Blood Products			
Others			

FLUSH SOLUTIONS

_____ Normal saline + 1 unit heparin/cc

_____ 1/2 Normal saline + 1 unit heparin/cc

_____ Other

BASE I.V. SOLUTION	LABS
_____ D_5W	_____ Glucose
_____ $D_{10}W$	

Condition at Completion of Resuscitation: ❑ Good ❑ Fair ❑ Guarded ❑ Expired

Transferred to: ❑ Newborn Nursery ❑ NICU

Comments: _____

Resuscitation Personnel Signatures:

M.D. _____

NNP _____

R.N. _____

Recording R.N. _____

R.T. _____

B. Evaluation of Code Performance

EVALUATION OF CODE PERFORMANCE
Quality Assurance Document

✦✧DO NOT COPY✧✦

MR #

Location of Code: _____ Date: _____/_____/_____

Occurrence Time: _____

Announcement Time: _____

Admitting Diagnosis/Chief Complaint: _____

Events Leading to Arrest: _____

_____

Was palpable pulse present at onset of medical emergency? ❍ Yes ❍ No

Attending Physician: _____ Attending Physician Present? ❍ Yes ❍ No

Type of Emergency

❍ Respiratory Compromise
❍ Cardiac Compromise
❍ Other medical emergency Specify: _____

Patient Outcome

❍ Remained in Department
❍ Expired
❍ Transferred to _____

Code Team Members/Emergency Medical Response Participants **☆ All no answers require a comment throughout the remainder of the form**			
	YES	No ☆	
Did Code Team/Emergency Medical Response Team Members Arrive?			
Did the appropriate team members fill roles?			

Emergency Medical Response Duties	**Appropriate Action Taken**			***Comments***
	YES	No☆	N/A	
Operator/Announced Overhead/Activated Pagers Correctly/Department Announcement				
Team Directed and Organized				
Defibrillated/Cardioverted *Please check:* ❍ CV Tech ❍ Attending MD ❍ Resident ❍ PICU/RN ❍ Sync. Cardioverted ❍ Defibrillated ❍ Called "All Clear" ❍ Paddles ❍ Delivered energy lubricated/proper placement				
CPR not interrupted >5 seconds				
Pulse transmitted with chest compressions				
Proper chest rise and fall with ventilations				
Notifies attending physician				

B. Evaluation of Code Performance—cont'd

Emergency Medical Response Duties	Appropriate Action Taken			*Comments*
	YES	NO☆	N/A	
Family Notified				
Needed Supplies available				
Equipment functioning properly				
Beepers/overhead speaker system/stairwell doors functioned appropriately				
Standard precautions followed				
Overall Team Effort				
All members participated in code evaluation				
Members transported patient as necessary				

Ensure the following documentation is completed:

- Complete QCC and forward to manager for signature
- Attach pink copy of Cardiac Arrest Record, if applicable, to completed evaluation form and forward to CPES for Resuscitation

Any other comments from team members to enhance response:

_____

_____

_____

_____

_____ _____

Evaluation completed by Date

_____ _____

Evaluation form reviewed by Date

Date_____ Time event recognized _____ Age_____ Weight (kg)_____ Signatures:

Was Code Team activated? ❑ Yes ❑ No

Type of event: ❑ Respiratory ❑ Respiratory leading to cardiac ❑ Cardiac Physician in Charge:_____

Monitors on patient at onset of event: ❑ ECG ❑ Pulse oximeter ❑ Apnea ❑ None

Patient conscious at onset? ❑ Yes ❑ No Pulse present at onset? ❑ Yes ❑ No Recording Nurse:_____

Airway/Ventilation

Breathing: ❑Spontaneous ❑Apnea ❑Agonal ❑Assisted

Type of ventilation: ❑ Mouth/Mouth ❑Mouth/Mask ❑BVM ❑ETT ❑Trach ❑Other_____

Time of first assisted ventilation_____

Intubation: Time_____ Size_____

By whom:_____

Number of visualizations/attempts:_____

Confirmation:❑Auscultation ❑$ETCO_2$ ❑Other

Circulation

Initial Rhythm_____

Rhythm when compressions started_____

Patient Defibrillated? ❑Yes ❑No

Number of IV attempts_____

Type of Isolation _____

Outcome

Event Ended @_____

Status: ❑Alive ❑Expired

Reason Resuscitation Ended:

❑Restored circulation ❑Restored ventilation

❑Unresponsive to ALS ❑Medical Futility

❑Restriction by family ❑Advance Directive

TIME	HR	RR	BP	O_2 Sat	INTERVENTION (CPR, Medications – Dose & Route, Defib/Cardiovert, Intubation, Vasoactive Drips)	PATIENT ASSESSMENT/RESPONSE

CHKD Form#0668 MR 5/02 FDB: Code Committee Addressograph

Children's Hospital of The King's Daughters, Inc.
601 Children's Lane, Norfolk, VA 23507-1910

Medical Emergency Response Documentation Form
Page _____ of _____

White-Medical Record Yellow-Pharmacy Pink-Reviewer

Date_____ Physician in Charge Signature:_____ Recording Nurse Signature:_____

Time	HR	RR	BP	O_2 Sat	INTERVENTION (CPR, Medications – Dose & Route, Defib/Cardiovert, Intubation, Vasoactive Drips)	Patient Assessment/Response

CHKD Form # 0669 MR 5/02 FDB: Code Committee Addressograph

Children's Hospital of The King's Daughters, Inc.
601 Children's Lane, Norfolk, VA 23507-1910

Medical Emergency Response Documentation- SUPPLEMENTAL FORM
Page _____ of _____

White-Medical Record Yellow-Pharmacy Pink-Reviewer

B. Evaluation of Code Performance—cont'd

Signature______________________________
Print Name______________________________
☐ Performed artificial ventilation – Type ____________________
☐ Performed chest compressions
☐ Performed venipuncture - _______ attempts ☐ Performed intraosseous
☐ Medication administration ☐ Performed cardioversion/defibrillation
☐ Performed intubation ☐ Other procedure –Type____________________

Signature______________________________
Print Name______________________________
☐ Performed artificial ventilation – Type ____________________
☐ Performed chest compressions
☐ Performed venipuncture - _______ attempts ☐ Performed intraosseous
☐ Medication administration ☐ Performed cardioversion/defibrillation
☐ Performed intubation ☐ Other procedure –Type____________________

Signature______________________________
Print Name______________________________
☐ Performed artificial ventilation – Type ____________________
☐ Performed chest compressions
☐ Performed venipuncture - _______ attempts ☐ Performed intraosseous
☐ Medication administration ☐ Performed cardioversion/defibrillation
☐ Performed intubation ☐ Other procedure –Type____________________

Signature______________________________
Print Name______________________________
☐ Performed artificial ventilation – Type ____________________
☐ Performed chest compressions
☐ Performed venipuncture - _______ attempts ☐ Performed intraosseous
☐ Medication administration ☐ Performed cardioversion/defibrillation
☐ Performed intubation ☐ Other procedure –Type____________________

Signature______________________________
Print Name______________________________
☐ Performed artificial ventilation – Type ____________________
☐ Performed chest compressions
☐ Performed venipuncture - _______ attempts ☐ Performed intraosseous
☐ Medication administration ☐ Performed cardioversion/defibrillation
☐ Performed intubation ☐ Other procedure –Type____________________

Signature______________________________
Print Name______________________________
☐ Performed artificial ventilation – Type ____________________
☐ Performed chest compressions
☐ Performed venipuncture - _______ attempts ☐ Performed intraosseous
☐ Medication administration ☐ Performed cardioversion/defibrillation
☐ Performed intubation ☐ Other procedure –Type____________________

Signature______________________________
Print Name______________________________
☐ Performed artificial ventilation – Type ____________________
☐ Performed chest compressions
☐ Performed venipuncture - _______ attempts ☐ Performed intraosseous
☐ Medication administration ☐ Performed cardioversion/defibrillation
☐ Performed intubation ☐ Other procedure –Type____________________

Signature______________________________
Print Name______________________________
☐ Performed artificial ventilation – Type ____________________
☐ Performed chest compressions
☐ Performed venipuncture - _______ attempts ☐ Performed intraosseous
☐ Medication administration ☐ Performed cardioversion/defibrillation
☐ Performed intubation ☐ Other procedure –Type____________________

Signature______________________________
Print Name______________________________
☐ Performed artificial ventilation – Type ____________________
☐ Performed chest compressions
☐ Performed venipuncture - _______ attempts ☐ Performed intraosseous
☐ Medication administration ☐ Performed cardioversion/defibrillation
☐ Performed intubation ☐ Other procedure –Type____________________

Signature______________________________
Print Name______________________________
☐ Performed artificial ventilation – Type ____________________
☐ Performed chest compressions
☐ Performed venipuncture - _______ attempts ☐ Performed intraosseous
☐ Medication administration ☐ Performed cardioversion/defibrillation
☐ Performed intubation ☐ Other procedure –Type____________________

CHKD Form # 0670 MR 5./02 FDB: Code Committee

Addressograph

Children's Hospital of The King's Daughters, Inc.
601 Children's Lane, Norfolk, VA 23507-1910

Medical Emergency Response Documentation Form-SIGNATURES

White- Medical Record Yellow- Reviewer

B. Evaluation of Code Performance—cont'd

Children's Hospital Of The King's Daughters, Inc.
601 Children's Lane
Norfolk, VA 23507-1911

QUALITY CARE CONTROL REPORT

(2) LOCATION	(3) STATUS	(4) SEX	(6) VARIANCE TIME
	☐ OTHER DEPART. ☐ INPATIENT ☐ OUTPATIENT ☐ VISITOR ☐ _____ OTHER	☐ MALE ☐ FEMALE	_____ A.M. _____ P.M.
		(5) AGE	(7) VARIANCE DATE
		_____	___/___/___

(ADDRESSOGRAPH)

(8) EVENT THAT OCCURRED

- ☐ Diagnosis/Diagnostic Test
- ☐ TX/Monitoring
- ☐ Medication Event
- ☐ Product/Equipment Related
- ☐ Fall/Found on Floor
- ☐ Communication Events/ Issues
- ☐ Injury Related
- ☐ Property Related
- ☐ Other Specific Risk Issues
- ☐ Administrative Events
- ☐ Other _____

* Refer to back of form.

(9) ADMITTING DIAGNOSIS

(10) OUTCOME/SEVERITY (USE BEST JUDGEMENT ✓ ONE)

- ☐ No injury or inconsequential injury or effect
- ☐ Consequential (possible temporary injury or effect)
- ☐ Serious (possible minor permanent injury or effect)
- ☐ Severe (possible major permanent injury or effect)
- ☐ Death
- ☐ Not Applicable (e.g.; property loss; AMA/walkout)

_____ Equipment Number

(11) PHYSICIAN NOTIFIED?

☐ NO
☐ YES _____ NAME ___/___/___ DATE

DID M.D. SEE PATIENT?

☐ NO
☐ YES _____ NAME ___/___/___ DATE

X-RAYS TAKEN?

☐ NO
☐ YES

DOES PHYSICIAN WANT TO BE NOTIFIED OF FOLLOW-UP?

☐ NO ☐ YES

(12) BRIEFLY DESCRIBE VARIANCE (GIVE FACTS; BE BRIEF) INCLUDE INJURY/DAMAGE/LOSS, IF ANY.

(13) STATUS BEFORE FALL (MED VARIANCE)

CALL BELL ☐ Yes ☐ No SIDE RAILS ☐ Yes ☐ No

PATIENT STATUS _____

MEDICATION
VARIANCE CATEGORY _____

(14) WAS PATIENT/SUBJECT AWARE OF VARIANCE? ☐ YES ☐ NO **GIVE PATIENT/SUBJECT RESPONSE/REACTION TO VARIANCE –**

(15) COMPLETED BY (USE FOR BOXES 1 THRU 14)

X _____ SIGNATURE ___/___/___ DATE

(16) OUTCOME SCREENS - TO BE COMPLETED BY HEAD NURSE / SUPERVISOR AND INCLUDE ALL MAROON BOXES ABOVE.

INPATIENT & OUTPATIENT

- ☐ DOA OR ED Death following inpatient, ED, or OPD visit - this facility past 7 days
- ☐ Return visit for **complications** following inpatient, ED, or OPD visit
- ☐ Unscheduled return visit following inpatient, ED, or OPD visit **(no complications)**
- ☐ Fracture/Burn (2˚ or 3˚) /Tissue Necrosis with ulceration, not present on admission
- ☐ Cardiac/respiratory arrest (Exclude "No Code" patients)
- ☐ Unplanned transfer, general care to Intensive Care or to another hospital
- ☐ Admission for possible adverse result of ED/OPD management
- ☐ Readmission within 7 days of discharge
- ☐ Neurological deficit not present on admission

INFECTION CONTROL PRACTITIONER

- ☐ Severe Post-Op or other nosocomial infection
- ☐ Consent policy and procedure variance
- ☐ Foreign Body, possibly retained
- ☐ Unscheduled return to OR, same admission
- ☐ Procedure injury: removal or repair of organ or body part injured during therapeutic or diagnostic procedure
- ☐ Surgery injury: removal or repair of organ or body part injured during surgery
- ☐ Cancellation of surgery after induction of anesthesia

(17) COMPLETED BY (USE FOR OUTCOME SCREENS/ONGOING MONITORS)

X _____ SIGNATURE ___/___/___ DATE

(18) QUALITY ASSURANCE (MARK BOX 12 IF BOXES 18 OR 19 ARE COMPLETED)

_____ CONTROL NUMBER

CONCERN ☐ YES ☐ NO

HOSPITAL/FACILITY – RETAINED INFORMATION

X _____ PI SIGNATURE ___/___/___ DATE

CHARTING OCCURRENCES

THIS REPORT DOES NOT REPLACE ADEQUATE CHARTING. IT IS A PERFORMANCE IMPROVEMENT TOOL, NOT A PATIENT RECORD. CHART VARIANCES CONSISTENTLY WITH HOSPITAL POLICIES.

RUSH
THIS REPORT TO
PERFORMANCE IMPROVEMENT
IN **24 HOURS**

FOLLOW UP _____

(19)

SUPERVISOR X _____ SIGNATURE ___/___/___ DATE

QUALITY REVIEW COORDINATOR X _____ SIGNATURE ___/___/___ DATE

B. Evaluation of Code Performance—cont'd

REPORTABLE EVENT

(QUALITY/MANAGEMENT TOOL/FOR INTERNAL PURPOSES ONLY)

DIAGNOSIS/DIAGNOSTIC TEST

Test Performance Related
Test Selection Related
Test Interpretation Related
Omitted Test/Assessment
Tested Incorrect Patient
Test Results Related
Performance of Unordered Test
Other Diagnostic Event:

TX/MONITORING

Foreign Body Related
Treatment of Incorrect Body Part
Treated Incorrect Patient
Treatment Order Related
Performance of Unordered Treatment
Infection/Contamination/Exposure
Body Part Injury: Adjacent to Treatment Site
Intubation/Extubation Related
Omitted Treatment
Treatment Performance Related
Patient Monitoring Related
Invasive Line Site Event (including epidurals)
Intravenous Line Event (peripheral)
Discharge Instruction Event (exclude Meds)
Readiness for Discharge/Release (event)
Unplanned Return to the ED within 72 hours for Related Symptoms
UTI Post Admission w/Indwelling Urinary Cath.
Treatment Refused
Other Treatment Event:

MEDICATION EVENT

TYPE OF EVENT (CIRCLE ROUTE OF MED ALSO)

Time of Administration Related
Dispensing Event
Dose/Rate Related
MD Order Related
Incorrect Patient
Unordered (not ordered)
Incorrect Medication Given
Route of Administration Related
Omitted
Transcription Event
Other Medication Event:

ADVERSE REACTION (CIRCLE ROUTE ALSO)

Adverse Drug Reaction
Adverse Blood Reaction
Other Adverse Reactions:

ROUTE OF MED (CIRCLE TYPE OF EVENT ALSO)

PO
Injectable
IV/IV Med/IV Admixture
Topical
Inhalant
Transdermal
Transfusion
Other Route:

MED INSTRUCTION

Discharge Instruction - Medication(s) Related

PRODUCT/EQUIPMENT RELATED

Equipment Selection Event
Product/Equipment Failure
Product/Equipment Malfunction
Unavailable Product/Equipment
User Related Product/Equipment
Equipment Design Issue
Other Product/Equipment Event:
Medical Equip. Related
Respiratory Equip. Related

FALL/FOUND ON FLOOR

CATEGORY OF FALL (CIRCLE TYPE OF FALL ALSO)

Witnessed Fall
Unwitnessed Fall/Found on Floor

TYPE OF FALL (CIRCLE CATEGORY OF FALL ALSO)

Ambulation Related Fall/Fall on Treadmill
Bathroom Related Fall
Bed Related Fall
Chair/Commode Related Fall
Transfer Related Fall
Table/Stretcher Related Fall
Tripped with Fall Occurring
Slipped on Slick Surface/Fell
Other Fall Event:

COMMUNICATION EVENTS/ISSUES

Abandonment/MD Non-attendance Allegation
AMA (left after being told needed to stay)
Informed Consent Issue
Confidentiality Related
Security Related
Patient Rights Issue

WALKOUTS

Left After Being Seen But Before Being Told of the Need to Stay
Walkout (left prior to being seen)
Elopement
Other Communication Event/Issue: NOC

INJURY RELATED

Struck/Injured Against An Object
Struck/Injured Against Another Person
Struck/Injured by Another Person
Struck/Injured by A Moving Object
Self-Inflicted Injury with Survival (exclude patients w/ ICD9 codes of 436,331.0, or 294.1)
Suicide
Food Related
Injury: Caught Between
Assault: Sexual
Assault: Other
Medical Immobilization
Patient Positioning Related
Injury Occurred While Moving Patient
Seclusion Related
Child/Vulnerable Issue
Other Injury Event:

PROPERTY RELATED

Property Damaged/Lost
(9026.02/9026.01)

OTHER RISK ISSUES

Complaint: (9024.01)
Behavioral Event: (9025.01)
Other Risk Issue Event: (9028.01)

OTHER SPECIFIC EVENTS

DOA w/In 7 Days of Previous Care Given Same Facility
ED Death w/In 7 Days of Previous Care Given Same Facility
Unscheduled Return Visit After Previous Care Given Same Facility (no complications)
Fracture
Burn
Necrosis
Skin Tear
Decubitus (newly acquired)
Unplanned Transfer to ICU
Unplanned Transfer to Another Facility
Admission Related to OPD Complication
Readmission w/In 30 Days for Same/Related Diagnosis
Unscheduled Return to OR, Same Admission
Cancellation of surgery Post Anesthesia induction

ADMINISTRATIVE EVENTS

Timeliness of Diagnosis Related
Determination of Diagnosis Related
Timeliness of Treatment or Admission Related
EMTALA/COBRA Related
Credentialing: Staff Privileges
Credentialing: Peer Review
Ostensible Agency/Vicarious Liability
Libel/Slander/Defamation
Billing Issue
Contract Issue
Other Regulatory Issue
Deposition Request
Medical Record Request

B. Evaluation of Code Performance—cont'd

FOLLOW-UP OF QCC/MEDICATION ERROR

Name _____

MR # _____

Dept. _____

Departments involved _____ _____

_____ _____

Describe occurrence _____

_____

Did you have sufficient knowledge/information to administer the medication/IV solution/treatment as prescribed? NA ___ Yes ___ No ___ (if no comment) medication/IV error employee # _____

_____

_____

Did anything contribute to the error? _____

_____

Treatment required: ___ No treatment required ___ Medical &/or Diagnostic Intervention
___ Nursing/Physician intervention ___ Nursing intervention only
___ Surgical Intervention ___ Transferred to higher level of care ___ N/A

How could this incident have been prevented? _____

_____

Outcome/significance of this occurrence:

___ Minor temporary ___ Major temporary ___ Unknown ___ None
___ Major permanent ___ Death ___ Minor permanent

Patient's/visitor's current status: ___ Good ___ Fair ___ Serious
___ Discharged ___ Transferred to: _____

Are there residual effects from occurrence? Yes ___ No ___

If yes, describe _____

_____

_____ _____
Signature Employee number

Actions: As **Department Manager**, what actions have you taken/will take to prevent a recurrence?

___ Discuss with employee ___ Inservice ___ Review at Staff Meeting
___ Employee counseling ___ Discuss with Medical Director ___ Other

Additional information: _____

_____

Manager's Signature _____

B. Evaluation of Code Performance—cont'd

Children's Hospital Of The King's Daughters, Inc.
601 Children's Lane
Norfolk, VA 23507-1911

QUALITY CARE CONTROL REPORT

(2) LOCATION	(3) STATUS	(4) SEX	(6) VARIANCE TIME
	☐ OTHER DEPART. ☐ INPATIENT ☐ OUTPATIENT ☐ VISITOR ☐ _____ OTHER	☐ MALE ☐ FEMALE	_____ A.M. _____ P.M.
		(5) AGE	(7) VARIANCE DATE
		_____	___/___/___

(ADDRESSOGRAPH)

(8) EVENT THAT OCCURRED

- ☐ Diagnosis/Diagnostic Test
- ☐ TX/Monitoring
- ☐ Medication Event
- ☐ Product/Equipment Related
- ☐ Fall/Found on Floor
- ☐ Communication Events/ Issues
- ☐ Injury Related
- ☐ Property Related
- ☐ Other Specific Risk Issues
- ☐ Administrative Events
- ☐ Other _____

* Refer to back of form.

(9) ADMITTING DIAGNOSIS

(10) OUTCOME/SEVERITY (USE BEST JUDGEMENT ✓ ONE)

- ☐ No injury or inconsequential injury or effect
- ☐ Consequential (possible temporary injury or effect)
- ☐ Serious (possible minor permanent injury or effect)
- ☐ Severe (possible major permanent injury or effect)
- ☐ Death
- ☐ Not Applicable (e.g.; property loss; AMA/walkout)

_____ Equipment Number

(11) PHYSICIAN NOTIFIED?

☐ NO
☐ YES _____ NAME ___/___/___ DATE

DID M.D. SEE PATIENT?

☐ NO
☐ YES _____ NAME ___/___/___ DATE

X-RAYS TAKEN?

☐ NO
☐ YES

DOES PHYSICIAN WANT TO BE NOTIFIED OF FOLLOW-UP?

☐ NO ☐ YES

(12) BRIEFLY DESCRIBE VARIANCE (GIVE FACTS; BE BRIEF) INCLUDE INJURY/DAMAGE/LOSS, IF ANY.

(13) STATUS BEFORE FALL (MED VARIANCE)

CALL BELL ☐ Yes ☐ No SIDE RAILS ☐ Yes ☐ No

PATIENT STATUS _____

MEDICATION
VARIANCE CATEGORY _____

(14) WAS PATIENT/SUBJECT AWARE OF VARIANCE? ☐ YES ☐ NO GIVE PATIENT/SUBJECT RESPONSE/REACTION TO VARIANCE –

(15) COMPLETED BY (USE FOR BOXES 1 THRU 14)

X _____ SIGNATURE ___/___/___ DATE

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- ☐ Return visit for **complications** following inpatient, ED, or OPD visit
- ☐ Unscheduled return visit following inpatient, ED, or OPD visit **(no complications)**
- ☐ Fracture/Burn (2˚ or 3˚) /Tissue Necrosis with ulceration, not present on admission
- ☐ Cardiac/respiratory arrest (Exclude "No Code" patients)
- ☐ Unplanned transfer, general care to Intensive Care or to another hospital
- ☐ Admission for possible adverse result of ED/OPD management
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INFECTION CONTROL PRACTITIONER

- ☐ Severe Post-Op or other nosocomial infection
- ☐ Consent policy and procedure variance
- ☐ Foreign Body, possibly retained
- ☐ Unscheduled return to OR, same admission
- ☐ Procedure injury: removal or repair of organ or body part injured during therapeutic or diagnostic procedure
- ☐ Surgery injury: removal or repair of organ or body part injured during surgery
- ☐ Cancellation of surgery after induction of anesthesia

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X _____ SIGNATURE ___/___/___ DATE

(18) QUALITY ASSURANCE (MARK BOX 12 IF BOXES 18 OR 19 ARE COMPLETED)

_____ CONTROL NUMBER

CONCERN ☐ YES ☐ NO

HOSPITAL/FACILITY – RETAINED INFORMATION

X _____ PI SIGNATURE ___/___/___ DATE

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RUSH
THIS REPORT TO
PERFORMANCE IMPROVEMENT
IN **24 HOURS**

FOLLOW UP _____

(19)

SUPERVISOR X _____ SIGNATURE ___/___/___ DATE

QUALITY REVIEW COORDINATOR X _____ SIGNATURE ___/___/___ DATE

Appendix 27

Delivery Room Care of the Neonate: Neonatal Resuscitation

Both routine assessment and resuscitation of the newborn at delivery should be provided in accordance with the principles of the American Heart Association and the American Academy of Pediatrics (AAP) Neonatal Resuscitation Program. Although the guidelines for neonatal resuscitation focus on delivery room resuscitation, most of the principles are applicable throughout the neonatal period and early infancy. Each hospital should have policies and procedures addressing the care and resuscitation of the newborn, including the qualifications of physicians and staff who provide this care. A program should be in place that ensures the competency of these individuals as well as their periodic credentialing. At every delivery, there should be at least one person whose primary responsibility is the newborn and who is capable of initiating resuscitation including positive-pressure ventilation and chest compressions. Either that person or someone else who is immediately available should have the skills required to perform a complete resuscitation, including endotracheal intubation and the use of medications. Approximately 10% of infants require some assistance at birth, and approximately 1% require extensive assistance.

Recognition and immediate resuscitation of a distressed neonate requires an organized plan of action and the immediate availability of qualified personnel and equipment. Responsibility for identification and resuscitation of a distressed neonate should be assigned to a qualified individual, who may be a physician, certified nurse midwife, advanced practice neonatal nurse, labor and delivery nurse, nurse-anesthetist, nursery nurse, physician assistant or respiratory therapist. The provision of services and equipment for resuscitation should be planned jointly by the medical and nursing directors of the departments involved in resuscitation of the newborn, usually the departments of obstetrics, anesthesia, and pediatrics. A physician, usually a pediatrician, should be designated to assume primary responsibility for initiating, supervising, and reviewing the plan for management of newborns requiring resuscitation in the delivery room. The following issues should be considered in this plan:

- A list should be developed of maternal and fetal complications that require the presence in the delivery room of someone qualified in all aspects of newborn resuscitation
- Individuals qualified to perform neonatal resuscitation should demonstrate the following capabilities:
  - Ability to rapidly and accurately evaluate the newborn condition
  - Knowledge of the pathogenesis of risk factors predisposing for the need for resuscitation (eg, hypoxia, drugs, hypovolemia, trauma, anomalies, infections, and preterm birth), as well as specific indications for resusciation
  - Skills in airway management, including bag and mask ventilation, laryngoscopy, endotracheal intubation and suctioning of the airway, chest compressions, emergency administration of drugs and fluids, and maintenance of thermal stability. Recognition and decompression of a tension pneumothorax by needle aspiration also is a desirable skill.
  - Skill in placing an umbilical venous catheter. This is especially important because most medications needed for resuscitation should be given by this route.
- Procedures should be developed to ensure the readiness of equipment and personnel and to provide for periodic review and evaluation of the effectiveness of the system.
- Contingency plans should be created for multiple births and other unusual circumstances.
- Guidelines should be developed for documentation of the resuscitation, including interventions, medications, and the time of each intervention.
- Procedures should be developed for transfer of responsibility for care.

From the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists: *Guidelines for Perinatal Care,* 5th edition. Washington, DC, 2007, AAP and ACOG, pp. 205-206.

Appendix 28

Clinical Considerations in the Use of Oxygen

The hazards associated with nonindicated administration of supplemental oxygen to preterm neonates have been recognized for many years. Studies conducted in the 1950s indicated that prolonged oxygen therapy without clinical indication was associated with increased rates of retinopathy of prematurity, formerly called retrolental fibroplasia. The ensuing blanket restriction of ambient oxygen therapy resulted in a marked decrease in retinopathy of prematurity at the cost of an increase in morbidity and mortality. Current practice includes the prudent use of supplemental oxygen as needed, based on an objective determination of oxygen requirements.

When supplemental oxygen therapy is considered, the potential risks, in terms of both hypoxia and hyperoxia, should be weighed. Clinical judgment of physical signs alone as a guide to the amount of supplemental oxygen needed is acceptable for short periods, emergencies, or abrupt clinical changes. However, ongoing use of supplemental oxygen should be guided by an objective assessment of patient oxygenation.

ADMINISTRATION AND MONITORING

In an emergency, high concentrations of supplemental oxygen may be administered by a face mask, nasal prongs, or endotracheal tube. When a neonate requires oxygen therapy beyond the emergency period, the oxygen should be warmed and humidified and the concentration or flow should be monitored and regulated. Supplemental oxygen can be delivered via an endotracheal tube, oxygen hood, nasal prong, or incubator. Oxygen analyzers should be calibrated in accordance with manufacturers' recommendations. Orders for oxygen therapy should include desired ambient concentration, flow, or both. The concentration

or flow rate of oxygen should be checked routinely. Alternatively, orders should be written to adjust fraction of inspired oxygen (FIO_2) or flow within a stated range to maintain oxygen saturation within specific limits. There should be an institutional guideline for ordering, delivering, and documenting oxygen therapy and monitoring.

An important development in the care of neonates who require oxygen therapy is the ability to monitor oxygenation continuously with noninvasive techniques. The pulse oximeter measures oxyhemoglobin saturation and the transcutaneous oxygen analyzer provides an indirect measurement of PaO_2. Because neither technique measures PaO_2 directly, they should be used as adjuncts to, rather than substitutes for, arterial blood gas sampling, especially in neonates with moderate to severe respiratory distress.

Periodic or continuous measurement of PaO_2 in samples from an umbilical or peripheral artery catheter is the most reliable method of assessing the effectiveness of oxygen therapy. If an indwelling arterial catheter is not in place, peripheral artery puncture can be used, but this is painful and repeated sampling from these sites is not always possible. Oxygenation is not accurately estimated in arterialized capillary samples. However, arterialized capillary sampling provides fairly reliable estimates of arterial pH and $PaCO_2$. The combined use of continuous, transcutaneous oxygen saturation monitoring and intermittent percutaneous arterial blood gases to guide oxygen therapy is an attractive pragmatic strategy when invasive arterial catheters are not in place.

In neonates whose condition is unstable, noninvasive measurements should be correlated with PaO_2 as often as every 8 to 24 hours. More frequent analyses of arterial blood gas may be indicated for the assessment of pH and PaO_2. In neonates whose condition is stable, correlation with arterial blood gas samples may be performed less when clinically indicated.

The use of either pulse oximetry or transcutaneous oxygen measurement may shorten the time required to determine optimum inspired oxygen concentration and ventilator settings in the acute care setting. Both measurements are particularly useful in monitoring oxygen therapy in neonates who are recovering from respiratory distress or who require long-term supplemental oxygen. Pulse oximetry is particularly advantageous for long-term monitoring of oxygen therapy because transcutaneous oxygen measurements underestimate oxygenation in older neonates with bronchopulmonary dysplasia (BPD) and may cause burns. Pulse oximetry is widely available.

In consideration of the current, but incomplete, understanding of the effects of oxygen administration, the following recommendations are offered:

- Supplemental oxygen should be used for specific indications, such as cyanosis, low PaO_2, or low oxygen saturation.
- The continuous use of supplemental oxygen, other than for resuscitation, should be monitored by assessments of PaO_2, oxygen saturation, or both.
- Oxygenation monitoring should be available whenever oxygen is continuously administered to newborns.
- For neonates who require oxygen therapy for acute care, measurements of blood pH and $PaCO_2$ should accompany measurements of PaO_2. In addition, a record of blood gas measurements, noninvasive measurements of oxygenation, details of the oxygen delivery system (eg, ventilator, continuous positive airway pressure, nasal cannula, hood, mask, settings), and ambient oxygen concentrations (FIO_2, liter of flow per minute, or both) should be maintained.
- The optimal range for oxygen saturation and PaO_2 that balances tissue metabolism, growth and development, and toxicity has not been elucidated fully for preterm infants receiving supplemental oxygen. Oxygen saturation values between 85-95% and PaO_2 values between 50 mm Hg and 80 mm Hg are examples of ranges pragmatically determined by some clinicians to guide oxygen therapy in preterm infants. Additional research to determine the "optimal" oxygenation ranges for oxygen saturation and PaO_2 is needed. Of note, even with careful monitoring, oxygen saturation and PaO_2 may fluctuate outside specified ranges, particularly in neonates with cardiopulmonary disease.
- Regular and periodic (every 1-4 hours) measurement and recording of the concentration of oxygen delivered to the neonate receiving supplemental oxygen is recommended.
- Except for an emergency situation, air-oxygen mixtures should be warmed and humidified before being administered to newborns.

From the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists: *Guidelines for Perinatal Care*, 6th edition, Washington, DC, 2007, AAP and ACOG, pp. 260–262.

Appendix 29

Executive Summary: Final COBRA Regulations

On June 22, 1994, the Health Care Financing Administration (HCFA) published final regulations to implement the Emergency Treatment and Labor Act, commonly referred to as COBRA, a law designed to prevent patient dumping.

Since 1985, COBRA has required that all persons presenting for treatment to a hospital emergency department receive a medical screening examination by qualified personnel to determine whether an emergency medical condition exists. A patient with an emergent medical condition may not be discharged or transferred to another medical facility from *anywhere* in the hospital unless any emergent condition has been stabilized to the extent possible and the physician has certified that the medical benefits of the transfer outweigh any risks. An informed consent to the transfer or discharge must also be obtained.

In large part, the final regulations merely clarify the initial legislation. However, there are a few significant additions, which are summarized below.

1. Hospitals will be required to report suspected COBRA violations to HCFA.
2. A patient who arrives on hospital property has presented to the emergency department, thus an ambulance cannot be diverted once on campus. If the ambulance is owned by the hospital, the patient is

on hospital property regardless of the ambulance's location.
3. The definition of *emergency condition* is expanded to include psychiatric disturbances and symptoms of substance abuse. It has always included potential for loss of life, limb, organ, or bodily function, active labor, and severe pain.
4. A hospital is required to maintain a list of physicians on-call to provide stabilizing treatment. If an on-call physician fails to respond and this prompts transfer to another facility for stabilization and treatment of an emergent medical condition, the transferring doctor *must* write the on-call physician's name and number in the medical chart, essentially documenting this as a violation of COBRA.
5. The emergency department must maintain a log of all patients showing ultimate disposition (e.g., patient refused treatment, admission, transfer, or discharge).
6. A tertiary care facility and its associated physicians may not refuse to accept an *appropriate* transfer if capacity and capability exists.

Appendix 30

OSHA Guidelines for Occupational Exposure

A, UNIVERSAL PRECAUTIONS FOR USE WITH ALL PATIENTS (ADAPTED FROM THE CENTERS FOR DISEASE CONTROL AND PROTECTION [CDC])

1. Wash hands after contact with body substances (e.g., urine, sputum, blood) before invasive procedures, and before eating or preparing food.
2. Wear gloves for direct hand contact with patient body substances (e.g., blood, urine, sputum), mucous membranes, non-intact skin, and when performing dressing changes.
3. Wear a paper isolation gown or plastic apron if soiling with any body substance is likely.
4. When performing procedures that may result in splashing of patient body fluids (e.g., tracheal suctioning, wound irrigation, endoscopy), wear a paper isolation gown or plastic apron, mask, and clear plastic goggles for eye and mouth protection.
5. Needles used shall not be bent, broken, recapped, or otherwise manipulated by hand. ONE-HANDED RECAPPING by the blood gas technician is, however, acceptable.
6. Dispose of needles and sharps in plastic needle/sharps containers provided for that purpose.
7. If exposure to blood or body fluids occurs, remove the body substance by washing hands, face, arms, or other body area affected. IMMEDIATELY report the exposure to your supervisor.
8. Treat all patient specimens as potentially infective.
9. Clean up spills of blood/body fluids with a hospital-grade disinfectant, used at manufacturer's recommended dilution. For large spills, notify environmental services immediately. They have the special equipment and information needed to handle such spills.
10. Although saliva has NOT been implicated in the transmission of HIV, minimize the need for mouth-to-mouth resuscitation by using one-way valve mouthpieces, resuscitation bags, or other ventilation devices in CPR situations.

CLINICAL NOTES

- The collection of arterial blood gases has been singled out by the CDC as a procedure wherein recapping of needles is often a medical necessity. However, never recap by holding the cap in one hand and pushing the needle into the cap. When you must recap, lay the cap down on a flat surface and insert the needle into the cap, picking it up off the surface without touching the cap with your other hand. Once you have done this, you can point the needle to the ceiling and secure the cap onto the hub, touching only the base of the cap.
- As an alternative to the above, you can place the cap into the plastic shroud that the 3-mL syringes come in. The shroud can be held or left standing on a flat surface, providing a holder for the cap and allowing the needle to be recapped safely.
- Always wear the equipment that is needed to avoid contact of any kind with blood or other body fluids (e.g., gloves when handling contaminated circuits).
- Wash hands between patients even if using gloves. Never reuse gloves from patient to patient. Always wash hands even after removal of gloves.
- Use the face shields (masks with plastic eye protection built in) when faced with any possibility of splashing or splattering body fluid into your face in other circumstances. The regular surgical masks offer less protection from penetration by fluids.
- Be sure to use the special white masks (3M PN #1814 Healthware Particulate Respirator) when giving pentamidine or working with active tuberculosis (TB) patients. Use eye protection in addition when there is any threat of splashing into your face.
- Normal prescription eyewear serves as protective equipment only if fitted with side shields.
- Procedures should always be performed in such a manner as to minimize the splashing or spraying of blood and body fluids.

From Oakes, DF (ed): Neonatal/Pediatric Respiratory Care: A Critical Care Pocket Guide. Old Town, ME, Health Educator Publications, 1996, pp. 9-7, 9-8, and 9-9.

Appendix 30

OSHA Guidelines for Occupational Exposure—cont'd

B, SPECIFIC GUIDELINES

(Check hospital policy for variations)

	Entry into ICU	Between Patient Contact	After Touching Hair, Face, Clothing, or Equipment	Handling Infected Patients or Equipments	After Touching Contaminated Patients or Equipment	Aseptic Techniques (Minor Proc.; ABG Sticks, IV or A-Lines, etc.)	Sterile Techniques (Major Proc., Surgery, Deliveries)	Procedures with Chance of Exposure to Body Fluids (SX, etc.)
Hands								
Wash hands vigorously for 10 sec with soap and water, dry with paper towels.		X	X					
Scrub hands and arms to elbow with antiseptic for 2-5 min., clean nails, scrub again, rinse with hands up, dry with paper towels.	X				X	X		
Scrub hands and arms to elbow with antiseptic for 4-5 min., clean nails, scrub again, rinse with two sterile towels (hands first)							X	
Gloves								
Wear nonsterile gloves		X		X		X		
Wear sterile gloves							X	X
Clothing								
Clean scrubs/uniforms (daily) or clean cover gown over street clothes (e.g., parents)	X							X
Cover gown over scrubs/uniform				X		X		
Sterile gown							X	
Mask—eye shield							X	X

From Oakes DF (ed): Neonatal/Pediatric Respiratory Care: A Critical Care Pocket Guide. Old Town, ME, Health Education Publications, 1994, pp. 9-7, 9-8, and 9-9.

Appendix 31

FDA Safety Alert: Hazards of Heated-Wire Breathing Circuits

The U.S. Food and Drug Administration has learned of instances in which improperly used heated-wire breathing circuits have overheated, softened, or melted, causing diminished gas delivery, fires, and burns to patients and caregivers.

To prevent such occurrences, it is important to take the following precautions:

1. Use only those heated-wire breathing circuits labeled for use with the specific humidifier being used. When in doubt about whether the breathing circuit is electrically compatible with the humidifier, *don't use it* without first consulting your biomedical engineering support group or the breathing circuit manufacturer.
2. Make sure the heated-wire breathing circuit has a recommended minute volume compatible with the ventilator settings.
3. Don't cover heated-wire breathing circuits with sheets, blankets, towels, clothing, or other materials.
4. Don't rest the circuits on other surfaces, such as the patient's body, bed rails, blankets, or medical equipment. Instead, use a boom arm or tube-tree to support the breathing circuit.

Appendix 32

Effective FIO_2 Conversion Tables for Infants on Nasal Cannula

1. The tables below are based on those used in the STOP-ROP trials.* The data were derived from equations #3 and #4 in the paper by Benaron and Benitz, "Maximizing the stability of oxygen delivered by nasal cannula" (Arch Pediatr Adoles Med 148:294–300, 1994).

*The STOP-ROP Multicenter Study Group: Supplemental therapeutic oxygen for prethreshold retinopathy of prematurity (STOP-ROP): A randomized, controlled trial. I: Primary outcomes. Pediatrics 105:295–310, 2000.

2. These tables include assumptions made by Benaron and Benitz (that nasal flow is constant over the entire inspiratory cycle and that the upper airway does not act as a reservoir) plus the following assumptions made by the STOP-ROP investigators: Inspiration time = 0.3 seconds; tidal volume = 5 mL/kg; and that either inspiration is entirely nasal or that cannula flow is sufficiently low that on each inspiration the infant exhales all output from the cannula.
3. Example: *What is the effective FIO_2 in a 2.0-kg infant on 100% cannula at a flow of 0.15 L/min?*
   Answer: Use 2.0 and 0.15 L/min in Table 1 to get a factor of 8. Then use Table 2 and the factor of 8 and 100% oxygen to yield an effective FIO_2 of 27%. Thus the effective oxygen concentration is less than 30% and the infant is eligible for the physiologic evaluation.

TABLE 1 Factor as a Function of Flow and Weight*†

		WEIGHT (kg)								
Flow (L/min)	**Flow (L/min)**	**0.7**	**1.0**	**1.25**	**1.5**	**2**	**2.5**	**3**	**3.5**	**4**
0.01		1	1	1	1	1	0	0	0	0
0.03	1/32	4	3	2	2	2	1	1	1	1
0.06	1/16	9	6	5	4	3	2	2	2	2
0.125	1/8	18	12	10	8	6	4	4	4	4
0.15		21	15	12	10	8	6	5	4	4
0.25	1/4	36	52	20	17	13	10	8	7	6
0.5	1/2	71	50	40	33	25	20	17	14	13
0.75	3/4	100	75	60	50	38	30	25	21	19
1.0	1.0	100	100	80	67	50	40	33	29	25
1.25		100	100	100	83	63	50	42	36	31
1.5		100	100	100	100	75	60	50	43	38
2.0		100	100	100	100	100	80	67	57	50

*Factor = 100 × min (1 U min/kg) (See Table 2).
†NOTE: If your patient's exact values are not included in the table, round up or down to find the value closest to that of your patient. If the value is exactly halfway between the two values, round up.

Appendix 32

Effective FIO_2 Conversion Tables for Infants on Nasal Cannula—cont'd

TABLE 2 Effective FIO_2 (×100) as a Function of Factor and Concentration*

	CONCENTRATION (%)						
Factor	**21**	**22**	**25**	**30**	**40**	**50**	**100**
0	21	21	21	21	21	21	21
1	21	21	21	21	21	21	22
2	21	21	21	21	21	22	23
3	21	21	21	21	22	22	23
4	21	21	21	21	22	22	24
5	21	21	21	21	22	22	25
6	21	21	21	22	22	23	26
7	21	21	21	22	22	23	27
8	21	21	21	22	23	23	27
9	21	21	21	22	23	24	28
10	21	21	21	22	23	24	29
11	21	21	21	22	23	24	30
12	21	21	21	22	23	24	30
13	21	21	22	22	23	25	31
14	21	21	22	22	24	25	32
15	21	21	22	22	23	25	33
17	21	21	22	23	24	26	34
18	21	21	22	23	24	26	35
19	21	21	22	23	25	27	36
20	21	21	22	23	25	27	37
21	21	21	22	23	25	27	38
22	21	21	22	23	25	27	36
23	21	21	22	23	25	28	39
25	21	21	22	23	25	28	41
27	21	21	22	23	25	29	42
28	21	21	22	24	26	29	43
29	21	21	22	24	27	29	44
30	21	21	22	24	27	30	45
31	21	21	22	24	27	31	47
33	21	21	22	24	27	31	47
36	21	21	22	24	28	31	49
38	21	21	23	24	28	32	51
40	21	21	23	25	29	33	53
42	21	21	23	25	29	33	53
43	21	21	23	25	29	33	55
44	21	21	23	25	29	34	56
50	21	21	23	25	30	35	60
55	21	22	23	26	31	37	64
57	21	22	23	26	32	38	66
60	21	22	23	26	32	38	68
63	21	22	24	27	33	39	71
67	21	22	24	27	34	40	74
71	21	22	24	27	34	42	77
75	21	22	24	28	35	43	80
80	21	22	24	28	36	44	84
83	21	22	24	28	37	45	87
86	21	22	24	29	37	46	89
100	21	22	25	30	40	50	100

*Shaded area signifies FIO_2 > 3.0 (i.e., O_2 concentration >30%).

Appendix 33

Drugs

PHARMACOPEIA FOR THE NEWBORN PERIOD

Dosages and comments about these drugs are based on experience, consensus among neonatologists, and the limited evidence available from studies in neonates. Other styles of treatment are often acceptable and may be superior to those listed. Newer recommendations about extended interval dosing of gentamicin for premature newborns less than 35 weeks of gestation have not been included because of limited safety data to date.

ADMINISTRATION ROUTES

ET—endotracheal
IM—intramuscularly
IT—intrathecally or intratracheally
IV—intravenously
PO—by mouth
PR—by rectum
SC—subcutaneously
TOP—topical

Drug	Route and Dose	Contraindications and Cautions
Acetaminophen	Loading dose: PO: 24 mg/kg; PR: 30 mg/kg Maintenance: PO: 12 mg/kg; PR: 20 mg/kg; preterm <32 wk: q12h; 32 wk: q8h; term: q6h	Divide suppositories lengthwise as drug may not be evenly distributed throughout the suppository; high doses, especially with glutathione deficiency from poor nutrition, may cause hepatic necrosis
Acetazolamide	IV, PO: 5 mg/kg/dose q6-8h; increase as needed to 25 mg/kg/dose (*temporarily effective*), max dose 55 mg/kg/day	Hyperchloremic metabolic acidosis, hypokalemia, drowsiness, paresthesias
Acyclovir	IV, PO: 15 mg/kg/dose q8h IV over 1 hr for neonatal skin, eye, or mouth infections; 20 mg/kg/dose q8h IV over 1 hr for neonatal CNS or disseminated infection	Transient renal dysfunction; lengthen dose interval with renal failure
Adenosine	Initial: 50 mcg/kg/dose IV as rapidly as possible (1-2 sec) followed by saline flush of the line Increase dose by 50 mcg/kg/dose IV and repeat every 1-2 min if there is no response and no AV block	Contraindicated in heart transplant patients; higher dosages needed in patients receiving methylxanthines; antidote for severe bradycardia is aminophylline 5-6 mg/kg over 5 min
Albumin, 5%	IV: 0.5-1 g/kg slowly	Hypovolemia, heart failure; monitor blood pressure
Albuterol	Aerosol: 0.5-1 mg/dose q2-6h PO: 0.1-0.3 mg/kg/dose q6-8h	Tachycardia, arrhythmias, tremor, irritability
Amikacin	IM, IV: Postnatal age 0-4 wk, <1200 g: 7.5 mg/kg/dose q18-24h; ≤1 week, 1200-2000 g: 7.5 mg/kg/dose q12-18h; and 2000 g 10 mg/kg/dose q12h; >1week, 1200-2000 g: 7.5 mg/kg/dose q8-12h; and >2000 g: 10 mg/kg/dose q8h	Nephrotoxicity; ototoxicity; blood level monitoring recommended (desirable levels: peak, 10-25 mcg/mL; trough, 3-5 mcg/mL)
Aminophylline	*See* Theophylline *Day 1*: 0.5-1.0 mg/kg/dose infused over 4-6 hr	*See* Theophylline
Amiodarone	Loading dose: 5 mg/kg IV over 30-60 min, preferably by central venous catheter Maintenance: Infusion: 5-15 mcg/kg/min; PO: 5-10 mg/kg/dose q12h	Phlebitis, hypotension, bradycardia, liver enzyme elevations, increased and decreased thyroid function, photosensitivity, optic neuritis, pulmonary fibrosis in adults
Amoxicillin	PO: 15 mg/kg/dose q12h; *urinary tract prophylaxis*: often dosed at 5 mg/kg/dose q day	Diarrhea, nausea, vomiting
Amoxicillin–clavulanic acid	PO: 15 mg/kg/dose q12h based on amoxicillin component	Diarrhea, nausea, vomiting
Amphotericin	*Day 1*: 0.5-1.0 mg/kg/dose infused over 4-6 hr (may start at the maximum dose on day 1 if tolerated); *do not use filters with pore size <1 μm*; 1.5 mg/kg/dose q24h may be used with resistant infections; total dosage: 30-35 mg/kg over 6 wk	Decreased renal potassium reabsorption, anemia, thrombocytopenia, fever, chills, nausea, vomiting
Amphotericin B liposome	IV: 1-5 mg/kg/dose q24h over 2 hr; usually start with 1 mg/kg/day and increase to higher dose for more serious infections (e.g., osteomyelitis, meningitis)	Decreased renal potassium reabsorption, anemia, thrombocytopenia, fever, chills, nausea, vomiting
Ampicillin	IV: 50-100 mg/kg/dose; if <7 days and <2 kg: q12h; if ≥7 days or >2 kg: q8h Highest dose for meningitis Maintain q12h for 4 wk for <1200 g	Diarrhea, rash, urticaria are rare in infants; candida skin infections

Appendix 33

Drugs—cont'd

Drug	Route and Dose	Contraindications and Cautions
Amrinone	Initial: 0.75 mg/kg over 2-3 min; maintenance: 3-5 mcg/kg/min	Fluid balance, electrolytes, renal function
Ascorbic acid	*See* Vitamin C (ascorbic acid)	
Atropine	IV, IM, ET, SC: 0.01-0.03 mg/kg, repeat q4-6h prn; minimum dose of 0.1 mg	Hyperthermia, tachycardia, urinary retention
Bacitracin	TOP: as ointment (500 units/g), q4-8h	
Beractant	IT: *for prophylactic treatment*: give 4 mL/kg as soon as possible; may repeat at 6-hr intervals to a maximum of 4 doses in 48 hr	May give additional doses if infant still has respiratory distress and needs >30% F_{IO_2} to keep PAO_2 >50 mm Hg
	IT: *for rescue treatment*: give 4 mL/kg as soon as respiratory distress syndrome is diagnosed; may repeat at 6-hr intervals to a maximum of 4 doses in 48 hr	Administer each dose as 4 doses of 1 mL/kg each, giving each dose over 2-3 sec and turning newborn to a different position after each dose
Bethanechol	PO: 0.1-0.2 mg/kg/dose q6-8h or 3 mg/m^2/dose q8h 20 min before feeding	Diarrhea, jitteriness, tremors, sleeplessness, bronchoconstriction, increased tracheobronchial secretions
Bumetanide	IV, PO: 0.02-0.2 mg/kg/dose q8-12h	Loop diuretic that also acts on proximal tubule; 40 times as potent as furosemide; less ototoxicity than furosemide; hypokalemia, hyponatremia, metabolic alkalosis
Caffeine	PO, IV: loading dose: 10 mg/kg; maintenance dose: 2.5 mg/kg/dose q24h (*doses are for the nonsalt form of drug—caffeine base*)	Restlessness, emesis, tachycardia; therapeutic plasma concentration 5-20 mcg/mL free base
Calcium chloride 10% (27 mg elemental Ca^{2+}/mL)	IV: 0.2 mL (9 mg Ca^{2+})/kg/dose for acute hypocalcemia; repeat q10 min	Bradycardia if injected too quickly; necrosis from extravascular leakage
Calcium glubionate 6.47% (23 mg elemental Ca^{2+}/mL)	PO: *treatment*: 500-1000 mg/kg/day q3-4h; *supplement*: 150 mg/kg/day q3-4h	High osmotic load of syrup may cause diarrhea
Calcium gluconate 10% (9.3 mg elemental Ca^{2+}/mL)	IV: 1 mL (9 mg Ca^2)/kg/dose for acute hypocalcemia; repeat q10 min	Bradycardia if injected too quickly; necrosis from extravascular leakage
	PO: 3-9 mL/kg/day in 2-4 divided doses (28-84 mg Ca^{2+}/kg/day) for chronic use	
Calcium lactate 13% (130 mg elemental Ca^{2+}/g powder)	PO: 0.5 g/kg/day in divided doses q6-8h	Same as for calcium gluconate; gastrointestinal irritation
Calfactant (Infasurf)	Initial: IT: 3 mL/kg divided into 2 aliquots repeated up to 3 times q12h	Do not shake or filter; ventilate for at least 30 sec after dose until infant is stable
Captopril	PO: 0.01-0.05 mg/kg/dose q6-24h; increase dose up to 0.5 mg/kg/dose to control blood pressure	High initial doses may cause hypotension and renal insufficiency
Carnitine	IV: 10 mg/kg/day added to parenteral solution when not eating	Monitor serum carnitine concentrations
Cefotaxime	IV: 50 mg/kg/dose; <7 days: q12h; >7 days: q8h	Adjust dose for renal impairment
Ceftazidime	IV: 30 mg/kg/dose over 30 min; preterm <30 wk up to 4 wk age: q12h; >4 wk: q8h; 30-36 wk up to 2 wk age: q12h; >2 wk: q8h; 37-44 wk up to 1 wk age: q12h; >1 wk: q8h	Phlebitis; cleared by glomerular filtration; increase dosing interval with renal dysfunction
Cefuroxime	IV, IM: 25-50 mg/kg/dose; <7 days: q12h; >7 days: q8h	Rare hypersensitivity reactions in infants; may cross-react with penicillins in older children causing rashes, eosinophilia, granulocytopenia
Cephalothin	IV, IM: 20 mg/kg/dose; preterm <7 days: q12h (until 4 wk for <1200 g); >7 days q8h; term <7 days: q8h; 7 days: q6h	Phlebitis, additive nephrotoxicity with gentamicin
Chloral hydrate	PO, PR: sedative: 10-30 mg/kg/day divided q6-8h; hypnotic: 50-100 mg/kg as single dose	Tolerance, physical dependence, and addiction may develop with seizures Irritant to skin and mucous membranes; gastritis Metabolism is slower in infants than in adults; metabolite half-life = 27.8 hr in term infants to 39 hr in preterm infants Repeated doses may accumulate metabolites, causing hypotension and renal failure
Chlorothiazide	PO: 5-15 mg/kg/dose q12-24h	Hypokalemia; hyponatremia decreases calcium excretion; hyperglycemia
Cimetidine	PO, IV: 2.5-5 mg/kg/dose q6h according to gastric pH ≥5	Decreases drug clearance by hepatic cytochrome P450

Continued

Appendix 33

Drugs—cont'd

Drug	Route and Dose	Contraindications and Cautions
Citric acid/sodium citrate	Dose according to degree of metabolic acidosis; each mL is equivalent to 1 mEq HCO_3 and contains 1 mEq sodium	Adds sodium and potassium and must be used carefully with renal dysfunction, hyperkalemia, or hypernatremia
Clindamycin	PO, IV: 5 mg/kg/dose; preterm <1 wk: q12h; preterm >1 week or term <1 wk: q8h; term >1 wk: q6h; maintenance: q12h till 4 wk for <1200 g	Pseudomembranous colitis is rare in newborns; limited experience in newborns, hepatic metabolism
Colfosceril palmitate	IT: *for prophylactic treatment*: give 5 mL/kg as soon as possible; may repeat second and third doses 12 and 24 hr later to those infants remaining on ventilators IT: *for rescue treatment*: give 5 mL/kg as soon as respiratory distress syndrome diagnosed; may repeat second dose 12 hr later	Administer each dose as 2 doses of 2.5 mL/kg each, giving each dose over 1-2 min; and turning newborn 45 degrees for 30 seconds to the right after the first dose and then similarly to the left after the second dose
Corticotropin	IM, IV, SC: 3-5 units/kg/day in 4 divided doses, usual maximum of 30 units/day	Hypertension, immunosuppression, electrolyte imbalance, cataracts, growth retardation, gastrointestinal ulcers, or dysfunction
Cosyntropin	40 mcg/kg/dose as stimulation test	Check serum cortisol 1-2 hr after dose
Cromolyn	Nebulization: 20 mg q6-8h; metered dose inhaler: 2 puffs q6-8h	Bronchoconstriction, nasal congestion; 8%-10% of dose is absorbed from the lung
Cyclopentolate 0.2% (may be combined with phenylephrine 1%)	1-2 drops each eye 10-30 min before examination	Hypertension with concentrations >0.5%; anticholinergic effects including fever, tachycardia, dry mouth, delayed gastric emptying, decreased gastrointestinal motility
Desoxycorticosterone acetate (DOCA)	*See* Fludrocortisone	
Dexamethasone	IM, IV: *for bronchopulmonary dysplasia*: 0.25 mg/kg/dose q8-12h for 3-7 days; *for severe chronic lung*: 0.05-0.25 mg/kg/dose q12h IV or PO for 3-7 days	Delayed head growth and developmental delay associated with treatment for as little as 3 days; weigh risk and benefit
Diazepam	PO, IV, IM: *sedative*: 0.02-0.3 mg/kg/dose q6-8h; *seizure:* 0.1-0.2 mg/kg/dose slow IV push	Diluted injection may precipitate; IM absorption is poor; respiratory depression, hypotension
Diazoxide	PO: 2-5 mg/kg/dose q8h for inhibition of insulin secretion	Eliminated renally; sodium and fluid retention
Dicloxacillin	PO: 4-8 mg/kg/dose q6h	Diarrhea, abdominal pain, nausea, vomiting; rare pancreatitis; may decrease absorption of ketoconazole and ciprofloxacin; may increase absorption of trimethoprim-sulfamethoxazole and ganciclovir
Digoxin	IV: Acute digitalization* *Premature* — *Loading dose* <1.5 kg — 10-20 mcg/kg 1.5-2.5 kg — 20 mcg/kg *Term newborns* — 30 mcg/kg *Infants (1-12 mo)* — 35 mcg/kg Maintenance dose: ⅛ loading dose q12h Begin 12 h after last digitalization dose	Risk of arrhythmias is increased during digitalization; IV formulation is twice as concentrated as oral; conduction defects, emesis, ventricular arrhythmias
Digoxin immune Fab	IV dose: mg digoxin immune Fab = total body digoxin load × 76 Total body digoxin load: mg digoxin elixir ingested × 0.8 or serum digoxin concentration (ng/mL) × 0.0056 × wt (kg)	Binds digoxin in circulation before renal excretion; serum digoxin levels within 6-10 hr of treatment will be falsely high
Diphenhydramine	PO: 5 mg/kg/day q6h	Somnolence
Diphenylhydantoin	*See* Phenytoin	
Diphtheria antitoxin	IM, IV: 20,000-50,000 units/day for 2-3 successive days	Hypersensitivity reaction
Dobutamine	IV: 2-20 mcg/kg/min by continuous infusion and titrate to desired effect	Tachycardia, hypotension
Dopamine	IV: 2-20 mcg/kg/min by continuous infusion and titrate to desired effect	Extravasation may lead to necrosis (phentolamine is an antidote); high dose may constrict renal arteries, but the dose for this effect is uncertain in neonates
Edrophonium	*Tensilon test for myasthenia gravis*: SC, IM: 0.2-0.5 mg/kg; IV: *preliminary test dose*: 0.04 mg slow push; *test dose:* 0.16 mg/kg (1 min later)	Cardiac arrhythmia, diarrhea, tracheal secretions may require atropine antagonism
Enalapril (PO), enalaprilat (IV)	IV enalaprilat: *for hypertension*: 5-10 mcg/kg/dose q8-24h PO enalapril *for CHF*: 0.1 mg/kg/day q day to maximum of 0.5 mg/kg/day	Reduce dose with renal failure; severe hypotension may occur, especially with volume depletion from diuretic treatment
Epinephrine	*Resuscitation*: IV, ET—1:10,000: 0.05-0.1 mL/kg q 3-5 min *Hypotension*: 0.01-0.1 mcg/kg/min by continuous infusion and titrate to desired effect	Tachycardia, arrhythmia
Ergocalciferol	*See* Vitamin D_2	

Appendix 33

Drugs—cont'd

Drug	Route and Dose	Contraindications and Cautions
Erythromycin	PO, IV: 10 mg/kg/dose; <7 days: q12h; >7 days: q8h *Eye prophylaxis at birth:* ophthalmic ointment 0.5% in each eye	IV administration is painful; may affect theophylline serum levels
Erythropoietin	200-300 units/kg/dose 3-5 times/wk SC: total weekly dose: 600-1400 units/kg/wk; treat 2-6 wk	Neutropenia; cotreat with iron
Famotidine	IV: 0.3-0.5 mg/kg/dose q8h PO: 1-2 mg/kg/day q8h	Monitor gastric pH for dosage adjustments
Fentanyl	IV, IM: 1-2 mcg/kg/dose, q4-6h prn, increase as needed	50-100 times the potency of morphine; muscle rigidity ("stiff man syndrome") may occur with rapid dose infusions; treat with muscle relaxants
Fibrinogen	IV: 50 mg/kg: repeated prn as determined by clotting time	
Fluconazole	IV or PO: loading dose: 12 mg/kg; maintenance: 6 mg/kg/dose <30 wk up to 2 wk age: q72h; >2 wk: q48h 30-36 wk up to 2 wk age: q48h; >2 wk: q24h 37-44 wk up to 1 wk age: q48h; >1 wk: q24h 45 wk: q24h	May reduce CYP3A4 metabolism of drugs, including caffeine, theophylline, midazolam; may interfere with metabolism of barbiturates, phenytoin
Flucytosine	PO: 20-40 mg/kg q6h	Monitor levels; effective antifungal concentration: 35-70 mcg/mL; bone marrow dysfunction: >100 mcg/mL; renal dysfunction decreases clearance
Fludrocortisone	PO: 0.025-0.2 mg/day	Mineralocorticoid replacement where 0.1 mg of fludrocortisone is equivalent to DOCA 1 mg
Folic acid	PO: 50 mcg/day for preterm newborns after feeding is established for maintenance; 500 mcg/day for therapy	Almost none in goat's milk; rash is very rare
Fosphenytoin	Fosphenytoin doses are expressed as phenytoin equivalents (PE), wherein fosphenytoin 1 mg PE = 1 mg phenytoin IV or IM: loading dose: 15-20 mg/kg given no faster than 0.5 mg/kg/min Maintenance: PO: 4-8 mg/kg/day divided q12h, although dosages as high as 15-20 mg/kg/day may be needed to reach therapeutic levels	Rapid IV infusions may cause bradycardia, hypotension, cardiovascular collapse, arrhythmias Therapeutic serum concentration range is 10-20 mcg/mL, although lower levels of 6-14 mcg/mL may be appropriate in premature newborns, due to reduced protein binding
Furosemide	IM, IV: 0.5-2 mg/kg/dose q12-24h PO: 1-2 mg/kg/dose q12-24h Bioavailability reduced by cor pulmonale; may require higher dosages	Hypokalemia, hyponatremia, hypochloremia; half-life prolonged in premature newborns
Gentamicin	IM, IV: postnatal age ≤7 days age: <1000 g and <28 wk, 2.5 mg/kg/dose q24h; <1500 g and <34 wk, 2.5 mg/kg/dose q18h; >1500 g and >34 wk, 2.5 mg/kg/dose q12h; >7-28 days age: <1200 g, 2.5 mg/kg/dose q18-24h; >28 days and <1200 g, 2.5 mg/kg/dose q8h; *initial loading dose*: 4 mg/kg for neonates ≤32 wk EGA shortens the time to reach therapeutic concentrations	Blood level monitoring indicated for efficacy; toxicity is rare in newborn (desirable levels: trough, <2 mcg/mL to avoid toxicity; peak, 5-10 mcg/mL)
Gentian violet	TOP (skin): as 1%-2% aqueous solution, bid TOP (oral): as 1% aqueous solution, bid	Stains skin
Glucagon	IM, IV: 30-300 mcg/kg; may be repeated after 20-30 min	Maximum dose 1 mg; higher doses possibly toxic
Granulocyte-stimulating factor	SC: bolus injection, IV infusion over 15-30 min, or continuous IV infusion: 5-10 mcg/kg once daily for 3 to 17 days Dilute in 5% dextrose with/without albumin; do not dilute with saline	Monitor blood neutrophil count; not considered useful for neutropenia from sepsis or NEC, unless it persists for more than 3 days with absolute neutrophil count <500/μL
Heparin	IV: initial dose: 50 units/kg; maintenance dose: 100 units/kg q4h or 20-25 units/kg/hr continuous infusion; titrate doses to 1½-2 times baseline whole blood clotting time or activated partial thromboplastin time	Intractable bleeding (reversible with protamine); heparin half-life: prematures < term < adults
Hepatitis B immune globulin	IM: 0.5 mL within 7 days of birth if mother is hepatitis B_S antigen positive or status is unknown; may be given with hepatitis B vaccine	Local pain and tenderness, thrombocytopenia
Hydralazine	PO, IM, IV: 0.1-0.5 mg/kg every 6 hr; increase as needed in 0.1-mg/kg increments up to 4 mg/kg/day	Tachycardia, lupus-like reactions
Hydrochlorothiazide	PO: 2.0-4.0 mg/kg/day q12h	Hypercalcemia, hypokalemia, hyperglycemia

Continued

Appendix 33

Drugs—cont'd

Drug	Route and Dose	Contraindications and Cautions
Hydrocortisone	Hypotension refractory to pressors: 1 mg/kg/dose IV; acute adrenal insufficiency: 0.25 mg/kg/dose q6h IV; physiologic replacement: 0.3 mg/kg/day IM	Treatment of more than 7-10 days requires gradual dosage reduction to avoid adrenal insufficiency; immunosuppression hyperglycemia, growth delay, leukocytosis, gastric irritation
Ibuprofen	PO: 4-10 mg/kg/dose q6-8h to a maximum of 40 mg/kg/day	Use cautiously in patients with active bleeding or renal or hepatic dysfunction Avoid in patients with ductal dependent cardiac malformations
Imipenem-Cilastatin	IV: <1.2 kg during first 4 wk: 20 mg/kg/dose q18-24h; 1.2-2 kg: 20 mg/kg/dose q12h; >2 kg first 7 days after birth: 20 mg/kg/dose q12h; >2 kg, older than 7 days: 20 mg/kg/dose q8h	Lengthen dosing interval for reduced renal function; early report of seizures has not been confirmed in later pediatric trials
Immunoglobulin intravenous, human	IV: 400-750 mg/kg/dose infused over 2-6 hr	Pyrogenic reactions, BP changes, tachycardia, necrotizing enterocolitis, volume overload
Indomethacin	PO, IV: 0.1-0.2 mg/kg/dose q12-24h for 2-7 days; 0.25 mg/kg/dose, >7 days	Transient renal dysfunction, decreased platelet aggregation; infuse over a minimum of 30-60 min to minimize reduction in CNS and mesenteric perfusion; avoid in patients with ductal dependent cardiac malformations
Insulin (Regular)	IV: hyperglycemia infusion dose, 0.01-0.1 unit/kg/hr; SC: intermittent dose, 0.1-0.2 unit/kg q6-12h	Hypoglycemia
Iron	PO: 2-6 mg/kg/day elemental iron	Avoid with hemochromatosis
Isoniazid	PO: 10-15 mg/kg/day, single dose or divided q12h	Newborns do not require pyridoxine supplement; monitor liver function test
Isoproterenol	IV: 0.05-0.5 mcg/kg/min by infusion	Arrhythmias, systemic vasodilation, tachycardia, hypotension, hypoglycemia
Kayexalate	*See* Sodium polystyrene sulfonate (Kayexalate)	
Levothyroxine	IV, PO: starting dose 10 mcg/kg/day (round off to nearest 12.5, 25.0, or 37.5 mcg to coincide with pill size); increase by 12.5-25 mcg/24 hr every 2 wk to desired effect; max 500 mcg/day, IV dose = 50%-75% of oral dose after initiation of therapy	Adjust dosage on 3-6 wk schedule by clinical response and T_4, optimal free T_4, TSH
Lidocaine	IV: 1 mg/kg infused over 5-10 min; may be repeated q 10 min 5 times, prn; infusion dose 10-50 mcg/kg/min or 1 mg/kg/hr	Monitoring of blood levels useful (therapeutic range 1-5 mcg/mL plasma); dilute for ET administration
Lorazepam	IV: 0.05-0.1 mg/kg infused over 2-5 min	Limited data in newborns, preparations may contain benzyl alcohol; dilute
Magnesium sulfate	IM, IV: 25-50 mg/kg q4-6h for 3-4 doses prn; use 50% solution IM, 1% solution IV	Hypotension, CNS depression; monitor serum concentration; calcium gluconate should be available as an antidote
Medium-chain triglyceride (MCT)	PO: 1-8 mL/24 hr divided in feedings (7.7 cal/mL)	Diarrhea; aspiration causes lipid pneumonia; may increase blood and CSF MCT levels causing coma with excess dose
Meropenem	IV: 20 mg/kg/dose q8-12h	Reduce dosage with reduced renal function; not well studied in premature neonates, but may be needed for resistant infections
Methadone	PO, IV: 0.05-0.2 mg/kg/dose q12-24h; reduce dose 10%-20% per week according to signs of withdrawal	Ileus, respiratory depression, delayed gastric emptying; difficult to taper due to long half-life
Methyldopa	IV, PO: 2-3 mg/kg q6-8h; increased as needed at 2-day intervals; maximum dosage 12-15 mg/kg/dose	Sedation, fever, false-positive Coombs test, hemolysis; sudden withdrawal of methyldopa may cause rebound hypertension
Methylene blue	IV: 1-1.5 mg/kg of 1% solution for methemoglobinemia, infused slowly	Do not use in patients with methemoglobinemia due to G6PD or cyanide poisoning Do not give subcutaneously due to risk of tissue necrosis
Methylprednisolone	IV, IM: 0.1-0.4 mg/kg/dose, q6h	Hydrocortisone preferred for physiologic replacement
Metoclopramide	PO, IV: 0.1-0.2 mg/kg/dose q6-8h or prior to each feeding	Dystonic reactions, irritability, diarrhea, decreases glomerular filtration rate in adults Efficacy for GERD shown at >6 mo
Metronidazole	IV or PO: loading dose: 15 mg/kg; maintenance: 7.5 mg/kg; infuse doses over 60 min <30 wk up to 4 wk age: q48h; >4 wk: q24h; 30-36 wk up to 2 wk: q24h; >2 wk: q12h; 37-44 wk up to 1 wk: q24h; >1 wk: q12h; 45 wk: q8h	Carcinogenic in rodents, not reported in humans. Prolonged treatment in adults rarely associated with seizures and sensory polyneuropathy

Appendix 33

Drugs—cont'd

Drug	Route and Dose	Contraindications and Cautions
Midazolam	IV, IM, intranasal: 0.07-0.20 mg/kg/dose q2-4h prn for sedation; infusion dosing: <33 wk: 30 mcg/kg hr; >33 wk: 60 mcg/kg/hr	Limited experience in newborns; respiratory depression, apnea Rapid infusion doses (<10 min) may cause tonic clonic movements
Morphine sulfate	IV, IM, SC: 0.05-0.1 mg/kg/dose q2-6h prn; 0.1-0.2 mg/kg/dose PO q3-6h	Respiratory depression reversible with naloxone; local urticaria from histamine release
Nafcillin	IV, IM: 25 mg/kg/dose, newborns 0-7 days: q12h, infants >7 days: q6-8h; double dosage for meningitis; maintenance: q12h for 4 wk for <1200 g	Agranulocytosis; granulocytopenia; hepatic dysfunction; may require dosage adjustment
Naloxone	IV, IM, SC: 0.1 mg/kg/dose; may be repeated as necessary; delivery room minimum, 0.5 mg for term newborn	Onset of action may be delayed 15+ min after IM or SC administration; narcotic effects may outlast naloxone antagonism; dilute for ET administration
Neomycin	PO: 10-25 mg/kg/dose q6h TOP: 0.5% ointment, 3-4 times daily	Renal toxicity and ototoxicity if absorbed
Neostigmine	IV: *Test for myasthenia gravis*: 0.02 mg/kg IM: *Test for myasthenia gravis*: 0.04 mg/kg PO: *Treatment for myasthenia gravis*: 0.33 mg/kg/day q3-6h	Cholinergic crisis; atropine pretreatment is recommended
Nitroprusside	IV: begin in dose of 0.25 mcg/kg/min and vary as needed up to 8 mcg/kg/min to control blood pressure	Profound hypotension possible; requires arterial line to monitor blood pressure; thiocyanate toxicity with long-term use or renal insufficiency
Nystatin	PO: 100,000-200,000 units q6h TOP: as 2% ointment (in petrolatum 95%, polyethylene 5%) 3-4 times daily	Poorly absorbed from GI tract; diarrhea
Omeprazole	PO: 0.5-1.5 mg/kg/dose q day	Hypergastrinemia; diarrhea; monitor gastric pH
Oxacillin	IV, IM: 25 mg/kg/dose Preterm <4 wk, <1200 g: q12h; <7 days, 1200-2000 g: q12h; ; 7 days, 1200-2000 g: q8h Term: 25-40 mg/kg/dose; <7 days: q12h; >7 days: q6h	Sterile abscess formation after IM doses; nephrotoxicity; monitor liver enzymes and complete blood count; colitis
Pancreatin	PO: 2000 units of lipase with each feeding PR and into colostomy: 0.3-0.5 g in sufficient liquid (for meconium ileus)	Bowel stricture associated with excessive dosages
Pancuronium	IV: 0.03-0.1 mg/kg/dose q1-4h prn; titrate to age and effect desired	Ensure adequate oxygenation and ventilation; tachycardia, bradycardia, hypotension, hypertension; potentiated by acidosis, hypothermia, neuromuscular disease, aminoglycoside antibiotics
Paraldehyde	PR: 0.3 mL/kg q4-6h	Reserve for refractory status epilepticus; local irritation, pulmonary edema, hemorrhage; hepatic dysfunction decreases clearance; avoid IM if possible; do not give by arterial catheter; avoid plastic containers
Penicillin G	IV, IM: *sepsis*: 25,000-50,000 units/kg/dose; *meningitis*: 75,000-100,000 units/kg/dose q8-12h: <7 days and q6-8h >7 days; *use higher doses for group B streptococcal infections;* maintain q12h for 4 wk for <1200 g	Use for susceptible organisms such as streptococci; syphilis
Pentobarbital	PO, IM, IV: 2-6 mg/kg prn	Blood level monitoring helpful (sedative level 0.5-3 mcg/mL); higher doses may depress respirations and cardiac contractility; monitor blood pressure
Phenobarbital	IV, IM, PO: *anticonvulsant loading dose:* 15-20 mg/kg, may repeat 10 mg/kg/dose twice for status epilepticus; maintenance dose: 3-5 mg/kg/day q12-24h, begin 12-24 h after loading dose *Sedation:* 2-3 mg/kg q8-12h prn	Blood level monitoring helpful (therapeutic range 15-40 mcg/mL); half-life 40-200 hr in infants, prolonged by asphyxia
Phentolamine	SC: dilute to 0.5 mg/mL, inject 0.2 mL at 5 sites around alpha-adrenergic drug infiltration maximum, 2.5 mg total dose	Marked hypotension, tachycardia, arrhythmia Do not treat hypotension with epinephrine, because hypotension may worsen due to alpha-adrenergic blockade
Phenytoin	IV: loading dose: 15-20 mg/kg, infused <0.5 mg/kg/min PO, IV: maintenance: 4-8 mg/kg/dose q24h; higher doses q8h >7 days; flush IV tubing with saline before/after dose	Therapeutic blood level monitoring indicated (desirable level 10-20 mcg/mL); infant clearance may be high
Phosphate, sodium, or potassium	PO: 1-3 mmol/kg/day in divided doses or supplement formula phosphorus intake to 75 mg/kg/day	Large amounts may cause catharsis; increase gradually to full supplementation; monitor electrolytes Several formulations available

Continued

Appendix 33

Drugs—cont'd

Drug	Route and Dose	Contraindications and Cautions
Piperacillin	IM, IV: 50-100 mg/kg/dose; ≤29 wk postmenstrual age at 0-4 wk age: q12h; ≤29 wk postmenstrual age >4 wk age: q8h; 30-36 wk postmenstrual age 0-2 wk age: q12h; 30-36 wk postmenstrual age >2 weeks age: q8h; 37-44 wk postmenstrual age 0-1 wk age: q12h; 37-44 wk postmenstrual age >1 wk age: q8h	Elimination is 60%-70% renal and reduced renal function may require longer dosing intervals
Pitressin	*See* Vasopressin	
Plasma	IV: 5-10 mL/kg; repeated prn	Volume overload, viral infection risk
Poractant alfa (Curosurf)	IT: 2.5 mL/kg/dose divided into 2 aliquots, followed by 1.25 mL/kg/dose q12h up to twice if needed	Do not filter or shake; suction prior to administration; administer in 2-4 aliquots with positioning of infant to improve distribution within the lungs; ventilate for at least 30 seconds after dose until infant is stable
Prednisone	PO: 0.5-2 mg/kg/day q6h	
Procainamide	IV: 1.5-2.5 mg/kg infused over 10-30 min; may be repeated in 30 min if needed; infusion: 20-60 mcg/kg/min PO: 40-60 mg/kg/day q4-6h	Asystole, myocardial depression, anorexia, vomiting, nausea Blood level monitoring helpful (therapeutic range: procainamide, 3-10 mcg/mL; *N*-acetyl procainamide, 10-20 mcg/mL)
Propranolol	IV: 0.01 mg/kg initial dose and 0.01-0.15 mg/kg infused over 10 min; may be repeated in 10 min and then q6-8h to maximum of 0.15 mg/kg/dose PO: 0.05-2 mg/kg q6h	Relatively contraindicated in low-output congestive heart failure and patients with bronchospasm
Propylthiouracil	PO: 2-4 mg/kg q8h; increase to maximum of 10 mg/kg/dose; onset of action may be delayed days to weeks	Dose is uncertain for newborns; monitor thyroid function
Prostaglandin E_1, alprostadil	IV: 0.03-0.1 mcg/kg/min; often, dose may be reduced by ½ after initial response; intra-arterial infusion offers no advantage	Apnea, seizures, fever, disseminated intravascular coagulation, diarrhea, cutaneous vasodilation, decreased platelet aggregation, cortical bone proliferation during prolonged infusion
Protamine sulfate	IV: 1 mg for each 100 units of heparin in previous 30 min; 0.5-0.75 for 30-60 min; and 0.25-0.375 for heparin given >2 hr before	Excessive doses induce coagulopathy; hypotension, bradycardia, anaphylaxis
Pyridoxine	*See* Vitamin B_6 (pyridoxine)	
Quinidine gluconate	PO, IM: 2-10 mg/kg/dose q2-6h until desired effect or toxicity occurs IV route not recommended in neonates (Dose is specific for the salt form)	Check electrocardiogram before each dose; discontinue if QRS interval increases 50% or more Maintain level of 2-6 mcg/mL; nausea, vomiting, diarrhea, fever, atrioventricular block
Ranitidine	PO, IV: 1-2 mg/kg q8-12h	Minimal inhibition of hepatic cytochrome P450 enzymes; monitor gastric pH
Ribavirin	6 g nebulized in hood with a solution of 20 mg/mL 12-18 hr/day for 3-7 days	May precipitate in endotracheal tube; avoid exposure of pregnant staff; possible teratogenic effects
Silver nitrate (1% solution)	Prophylaxis: 1 or 2 drops in each eye	Chemical conjunctivitis
Sodium bicarbonate (0.5 mEq/mL)	IV: 1-2 mEq/kg/dose infused slowly only if infant ventilated adequately	Intravascular hemolysis may be associated with rapid infusion
Sodium polystyrene sulfonate (Kayexalate)	PO, PR: 1 g/kg; approximately q6h	Usually administered as a solution with 20% sorbitol to prevent intestinal obstruction; 20% sorbitol solution may injure intestinal mucosa of very low-birthweight newborns; may decrease serum calcium or magnesium
Spironolactone	PO: 1-3 mg/kg/day q8-12h	Contraindicated with hyperkalemia; onset of action delayed; drowsiness; nausea; vomiting; diarrhea; androgenic effects in females; gynecomastia in males
Streptomycin	IM: 20-30 mg/kg/day q24h	Nephrotoxicity, ototoxicity; use in newborns as part of triple therapy for tuberculosis
Sulfisoxazole	PO, IV: 25 mg/kg q6h; aggressive therapy is used only in full-term neonates >2 weeks old	In prematures or in presence of jaundice, may lead to kernicterus
Survanta	*See* Beractant	
Tetanus immune globulin	IM: 250-500 units/dose	Optimal dosage not established for newborns

Appendix 33

Drugs—cont'd

Drug	Route and Dose	Contraindications and Cautions
Theophylline	PO, IV: loading dose: 5-6 mg/kg; maintenance dose: 1-2.5 mg/kg/dose q6-12h; aminophylline (IV) dose = theophylline (IV) dose × 1.25	Blood level monitoring indicated (therapeutic range: *apnea*: 7-12 mcg/mL, *bronchospasm*: 10-20 mcg/mL); tachycardia at 15-20 mcg/mL, seizures at >40 g/mL; avoid rectal dosing due to variable absorption, clearance decreased by asphyxia and prematurity; tachycardia
Thiamine	*See* Vitamin B_1 (thiamine)	
Ticarcillin	IM, IV: 75 mg/kg/dose; <7 days: q12h, >7 days: q8h; maintain q12h for 4 wk for <1200 g	Contains 5.2 mEq Na^+/g; may inhibit platelet function
Tobramycin	*See* Gentamicin dosing guidelines	
Ursodeoxycholic acid	PO: 10-15 mg/kg/day q8-24h	Nausea, vomiting, abdominal pain, constipation, flatulence
Vancomycin	PO: 10 mg/kg, q6h IV: postnatal age ≤7 days, <1200 g: 15 mg/kg/day q24h; 1200-2000 g: 15 mg/kg/day q12-18h; >2000 g: 30 mg/kg/day q12h; >7 days: <1200 g: 15 mg/kg/day q24h; 1200-2000: g 15 mg/kg/day q8-12h; >2000 g: 45 mg/kg/day q8h Cerebrospinal fluid: 5-10 mg/day (cerebrospinal fluid trough, <20 mcg/mL)	Ototoxicity (therapeutic levels: peak 25-40 mcg/mL; trough, 5-10 mcg/mL); rapid infusion may cause cutaneous vasodilation and shock Higher concentrations are recommended for resistant organisms and toxicity appears to be low
Vasopressin	IM, SC: 2.5-10 units 2-4 times daily	20 units/mL aqueous injection
Vecuronium	IV: 0.08-0.1 mg/kg/dose, repeat prn at 0.03-0.15 mg/kg/dose q1-2h; dose to effect	Neuromuscular blockade potentiated by calcium channel blockers such as verapamil and aminoglycoside antibiotics
Verapamil	IV: 0.1-0.2 mg/kg infused over 2 min; if response is inadequate, repeat in 30 min PO: 2-5 mg/kg/day in 3 divided doses	Monitor electrocardiogram during infusion; bradycardia, atrioventricular block, asystole; contraindicated in patients with 2nd- or 3rd-degree atrioventricular block during treatment with beta blockers
Vitamin A (oleovitamin A)	PO: *preventive,* 600-1500 units/day IM: *prevention of BPD*: 5000 IU 3 × per week for 4 wk	Pseudotumor cerebri; maintain plasma vitamin A concentration of 30 to 60 mcg/mL
Vitamin B_1 (thiamine)	PO: *preventive,* 0.5-1 mg q day; PO: *therapeutic,* 5-10 mg q6-8h	Unstable in alkaline solution
Vitamin B_6 (pyridoxine)	PO: *preventive*: 100 mcg/L of ingested formula; *therapeutic for deficiency*: 2-5 mg/day q6h; *test dose for pyridine dependency seizures*: 50-100 mg IV	May decrease serum levels of phenobarbital, phenytoin, or folic acid; hypersensitivity
Vitamin C (ascorbic acid)	IM, IV, PO: *preventive*: 25-50 mg/day (term infants); 100 mg/day (premature infants)	
Vitamin D_2 (ergocalciferol)	PO: *preventive*: 400-1000 IU/day (premature infants), 40-100 IU/day (term infants)	Hypercalcemia with excess dose
Vitamin E (*d*-alpha tocopherol)	PO: *prevention of hemolysis*: 25-50 IU/day (1 IU = 1 mg)	Some preparations are hyperosmolar
Vitamin K_1 (phytonadione)	SC, IM: *preventive*: 0.5-1.0 mg, single dose; *therapeutic*: 1-2 mg/kg/dose q6-12h according to prothrombin time	With thrombocytopenia, slow IV infusion at same dose; anaphylaxis observed with rapid injection IV, more common with vitamin K_3

From Taeusch HW, Ballard RA, Gleason CA: Avery's Diseases of the Newborn, 8th edition,. Philadelphia, Elsevier Saunders, 2005.
*PO dose increased 20%.
AV, Atrioventicular; *BP,* blood pressure; *BPD,* bronchopulmonary dysplasia; *CHF,* congestive heart failure; *CNS,* central nervous system; *CSF,* cerebrospinal fluid; *EGA,* estimated gestational age; *ET,* endotracheal; *GERD,* gastroesophageal reflux disease; *GI,* gastrointestinal; *NEC,* necrotizing enterocolitis; *PMA,* postmenstrual age; prn, *pro re nate* (as needed); T_4, thyroxine; *TSH,* thyroid-stimulating hormone.

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Appendix 34

Nucleated Red Blood Cells in Normal Infants and Infants of Diabetic Mothers

Variables	Control Infants (n = 102)	INFANTS OF DIABETIC MOTHERS: No Perinatal Asphyxia (n = 54)	INFANTS OF DIABETIC MOTHERS: Perinatal Asphyxia (n = 25)
Gestational age (weeks)	39.5 ± 1.5	38.0 ± 1.0*	37.9 ± 1.2*
Birthweight (kg)	3.3 ± 0.3	3.5 ± 0.6*	3.6 ± 0.6*
Leukocyte count†	27.3 ± 9.2	17.1 ± 5.1*	16.8 ± 6.1*
NRBCs (absolute count)	0.4 ± 1.3	1.4 ± 3.1*	1.8 ± 2.3*
NRBCs/100 leukocytes	1.7 ± 6.2	8.3 ± 17.8*	13.0 ± 18.9*

Adapted from Green DW, Mimouni F: J Pediatr 116:129, 1990.
*Significantly different from control infant values (P at least <.05).
†Data are expressed as $\times 10^9$/L.
NRBC, Nucleated red blood cell.

Taeusch et al., Avery's Diseases of the Newborn, 8th Edition, ISBN: 978-072-169-3477.

Appendix 35

Umbilical Artery Cord Blood Gas Values in Healthy Term Infants

		DISTRIBUTION VALUES (PERCENTILE)		
	Range	10th	50th	90th
pH	7.04-7.49	7.21	7.29	7.37
$PaCO_2$ (mm Hg)	27.2-75.4	38.9	49.5	62.0
PaO_2 (mm Hg)	4.6-48.4	10.1	18.0	32.0
HCO_3 (mmol/L)	13.6-29.4	20.3	23.4	25.9

Data from Dudenhausen JW, Luhr C, Dimer JS: Umbilical artery blood gases in healthy term newborn infants. Intl J Gynecol Obstet 57:251-258, 1997.

Taeusch et al., Avery's Diseases of the Newborn, 8th Edition, ISBN: 978-072-169-3477.

Appendix 36

Mean Umbilical Cord Blood Gas Values in Preterm Infants

	MEAN VALUE	
	Arterial	Venous
pH	7.26 ± 0.08	7.33 ± 0.07
PCO_2 (mm Hg)	53.0 ± 10.0	43.4 ± 8.3
PO_2 (mm Hg)	19.0 ± 7.9	29.2 ± 9.7
HCO_3 (mEq/L)	24.0 ± 2.3	22.8 ± 2.1
Base excess (mEq/L)	−3.2 ± 2.9	−2.6 ± 2.5

From Dickinson JE, Eriksen NL, Meyer BA, Parisi VM:. Obstet Gynecol 79:575-578, 1992.

Appendix 37

Smoothed Percentiles of Birthweight (g) for Gestational Age: U.S. 1991 Single Live Births to Resident Mothers

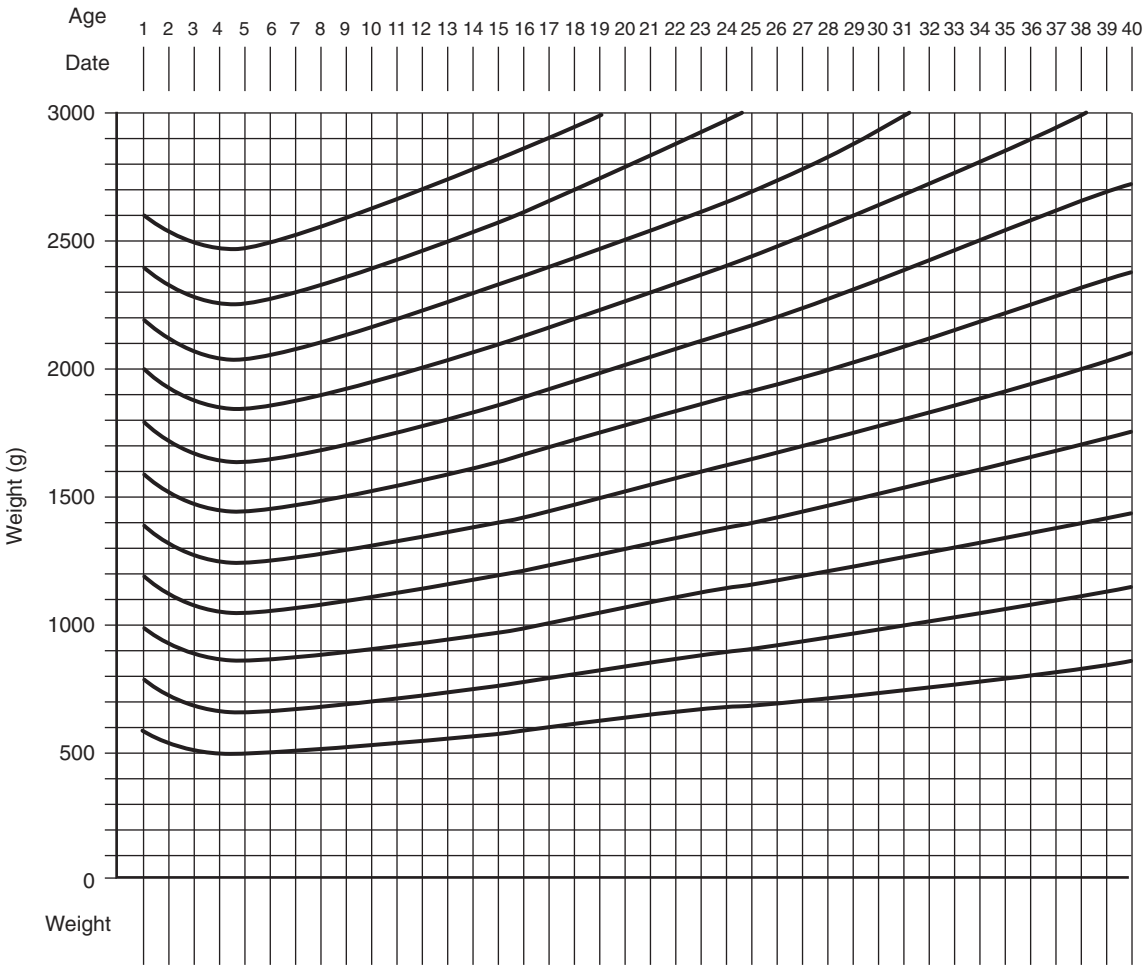
Gestational Age (wk)	PERCENTILE				
	5th	10th	50th	90th	95th
20	249	275	412	772	912
21	280	314	433	790	957
22	330	376	496	826	1023
23	385	440	582	882	1107
24	435	498	674	977	1223
25	480	558	779	1138	1397
26	529	625	899	1362	1640
27	591	702	1035	1635	1927
28	670	798	1196	1977	2237
29	772	925	1394	2361	2553
30	910	1085	1637	2710	2847
31	1088	1278	1918	2986	3108
32	1294	1495	2203	3200	3338
33	1513	1725	2458	3370	3536
34	1735	1950	2667	3502	3697
35	1950	2159	2831	3596	3812
36	2156	2354	2974	3668	3888
37	2357	2541	3117	3755	3956
38	2543	2714	3263	3867	4027
39	2685	2852	3400	3980	4107
40	2761	2929	3495	4060	4185
41	2777	2948	3527	4094	4217
42	2764	2935	3522	4098	4213
43	2741	2907	3505	4096	4178
44	2724	2885	3491	4096	4122

Data from Alexander GR, Himes JH, Kaufman RB, et al: Obstet Gynecol 87:163-168, 1996.

Taeusch et al., Avery's Diseases of the Newborn, 8th Edition, ISBN: 978-072-169-3477.

Appendix 38

Extrauterine Growth Chart



Extrauterine growth chart. (Data from Shaffer SG, Quimiro CL, Anderson JV, et al: Postnatal weight changes in low birth weight infants. Pediatrics 79[5]: 702, 1987.)

Index

D

E

I

J

Q

R

S

T

U