Invasive and Noninvasive Neonatal Mechanical Ventilation

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Neonatal respiratory failure consists of several different disease entities, with different pathophys- iologies. During the past 30 years technological advances have drastically altered both the diagnostic and therapeutic approaches to newborns requiring mechanical assistance. Treatments have
Introduction

The spectrum of mechanical support for neonatal respiratory failure has widened substantially over the past 4 decades. Continuous positive airway pressure (CPAP) and time-cycled, pressure-limited intermittent mandatory ventilation (IMV) became the primary treatment modalities for a quarter of a century, until the technologic breakthroughs of the 1980s and 1990s introduced high-frequency ventilation (HFV) and advanced ventilatory techniques into neonatal intensive care. In conjunction with the enhanced monitoring capabilities, the strategies for treating neonatal respiratory failure have become both patient- and disease-specific. Unfortunately, the advancement of the technology has occurred over a very relatively short period of time, limiting the ability to establish an evidence-based approach for comparisons and decision-making. However, this should not preclude clinicians from using the principles of pulmonary mechanics and respiratory physiology in applying these techniques to critically ill newborns.

Philosophies of respiratory management differ widely, even in highly developed countries. Some institutions favor a very conservative approach to treatment, whereas others are more aggressive in their strategies. Treatments range from the relatively noninvasive CPAP to the most invasive, extracorporeal membrane oxygenation (ECMO). This review discusses the most widely used modalities and the rationale for each. Particular emphasis will be placed on nomenclature, which has been a source of confusion and has sometimes made interpretation of the literature difficult.

Background

The earliest attempts to treat neonatal respiratory failure involved the use of CPAP and time-cycled, pressure-limited IMV. The various causes of neonatal pulmonary disease were not well understood, and equipment was rudimentary, with monitoring limited to clinical assessment and intermittent radiography and blood gas assessment. Little thought was given to disease-specific strategies, and in reality most newborns were treated similarly irrespective of the underlying disease.

In the late 1970s development of continuous monitoring devices, such as transcutaneous oxygen sensors, led to a better appreciation of the dynamic nature of neonatal lung disease. Echocardiography demonstrated the unique interdependence of the newborn’s heart and lungs and the role of the ductus arteriosus in several disease states. Additional styles of ventilation emerged, as did newer equipment specifically designed for neonatal use.

The 1980s were marked by a proliferation of new techniques, widespread clinical trials, and the emergence of specific strategies aimed at the differences in pulmonary pathophysiology that characterize the array of neonatal lung disorders. By the end of the decade pulse oximetry had become a standard of care, and testing of surfactant replacement therapy was well underway. HFV had become established as an alternative technique, and ECMO had become accepted as the ultimate rescue therapy for term and near-term infants.

The 20th century closed with a flurry of new technology. Surfactant replacement therapy and antenatal corticosteroid treatment became accepted practices. Real-time pulmonary graphic monitoring achieved widespread clinical applicability. Many new ventilatory techniques were introduced, including patient-triggered ventilation, volume-targeted ventilation, and pressure-support ventilation (PSV). The efficacy of inhaled nitric oxide as a selective pulmonary vasodilator was demonstrated. Extensive basic investigation into the mechanisms of lung injury added the
Neonatal Respiratory Disorders

Neonatal respiratory failure is not a single disease entity. Rather it is a condition of impaired gas exchange that can result from a number of lung parenchymal or vascular abnormalities. These diverse disease states respond differently to therapeutic interventions and require specific strategies to achieve resolution. A brief review of the 5 most common disorders will serve to emphasize the need for this disease-specific approach to treatment.

Respiratory Distress Syndrome

Respiratory distress syndrome (RDS) is the leading pulmonary disorder among premature infants. Its incidence increases with decreasing gestational age. It is characterized by both structural and biochemical immaturity of the lung. Very premature infants will have deficient alveolarization and therefore have diminished surface area for gas exchange and an increased distance from the alveolus to its adjacent capillary, which makes diffusion more difficult. Surfactant deficiency results in high alveolar surface tension and progressive atelectasis. Increased capillary permeability causes deposition of exudative debris in the air spaces and further inactivation of surfactant, which gave rise to the original description of RDS as hyaline membrane disease.

The diagnosis of RDS is made radiographically. Typical findings include the reticulogranular, “ground glass” appearance, with air bronchograms and diminished lung volumes. Affected infants display the usual cardinal signs of respiratory distress: tachypnea, grunting, nasal flaring, and retraction.1

Although surfactant replacement therapy has significantly altered the treatment of RDS, mortality has not been eradicated, and complications such as air leaks and CLD continue to occur with unacceptable frequency. Management styles differ widely, and there is a very limited evidence base from which to draw conclusions.

Meconium Aspiration Syndrome

Meconium aspiration syndrome results from the effects of meconium in the airways and lung parenchyma. Meconium can be aspirated in utero or intrapartum. It may result in obstructed airways and diminished gas exchange, or it may work its way into the lung parenchyma where it can cause chemical pneumonitis and alveolar-capillary block. Meconium aspiration can also lead to gas trapping and all forms of thoracic air leaks. Severe meconium aspiration syndrome can result in secondary persistent pulmonary hypertension of the newborn (PPHN), with attendant intrapulmonic shunting, profound hypoxemia, and diminished pulmonary blood flow.

The diagnosis of meconium aspiration syndrome is made from the finding of meconium in the airway and clinical respiratory distress, combined with the radiographic findings of patchy infiltrates and early hyperinflation. Blood gas analysis may initially show a respiratory alkalosis from hyperventilation, followed by a mixed acidosis.1-3

Affected infants are almost always term or post-term, as the incidence of meconium passage in utero rises dramatically at term and beyond. Treatment is controversial, but it depends to a large extent on whether PPHN is present (see below). Recently the longstanding practice of routinely suctioning the infant’s trachea immediately after birth has been questioned.4 Since meconium has been shown to inactivate surfactant, the potential role of surfactant replacement is being actively explored.5

Pneumonia

Congenital pneumonia can be caused by numerous microorganisms, but the most commonly cultured infectious agents are Group B β-hemolytic streptococci and Escherichia coli among infants with early-onset disease (first 3–5 d of life). The role of other agents, such as Chlamydia trachomatis and Ureaplasma urealyticum, in the development of CLD is currently under extensive investigation.

Infectious pneumonia leads to widespread inflammatory changes in the lung, including consolidation, edema, and both proteinaceous and hemorrhagic exudates, which can exacerbate difficulties with gas exchange. Pneumonia can be complicated by systemic manifestations of sepsis, including hypotension and acidosis, causing diminished pulmonary blood flow and secondary PPHN, and disseminated intravascular coagulopathy resulting in pulmonary hemorrhage.3,6

Treatment of the underlying infection and its systemic complications augments the respiratory management. Unfortunately, some of these complications can alter the ventilatory approach. For example, the impaired cardiac output that accompanies the sepsis syndrome may be a relative contraindication to high-frequency oscillatory ventilation (HFOV), which itself may decrease cardiac output.

Persistent Pulmonary Hypertension of the Newborn

PPHN is a disorder characterized by elevated pulmonary vascular resistance, resulting in the shunting of blood away from the pulmonary vascular bed, through the fetal
channels, the ductus arteriosus, and the foramen ovale. The resultant venous admixture causes profound hypoxemia, decreased tissue oxygen delivery, metabolic acidosis, and further pulmonary vasoconstriction.

Traditionally, PPHN has been thought of as either “primary” or “secondary.”1 Recently, it has been suggested that 3 pathophysiologic mechanisms exist, reflective of the following conditions: (1) a decrease in the number of pulmonary arteries (such as primary lung malformations), (2) a normal number of arteries but increased vascular musculature (such as maladaptation after chronic fetal injury), and (3) a normal number of vessels and normal vascular musculature (such as immaturity, or maladaptation after acute fetal injury).7

The diagnosis of PPHN is generally made by echocardiography, though it may be suspected from evidence of ductal shunting, extreme lability, or a response to hyperoxia-hyperventilation. The differential diagnosis includes severe parenchymal lung disease and cyanotic congenital heart disease with fixed right-to-left shunting.

Treatment of PPHN presents highly controversial and spans a wide gamut, from conservative ventilation (discussed below) to aggressive hyperventilation and induced alkalosis. In the latter, hypocapnia, hyperoxygenation, and extreme alkalosis are used to decrease pulmonary vasoconstriction and increase pulmonary blood flow. Although this approach constituted the major treatment for a long period of time, it is based on anecdotal experience. Unfortunately, no prospective, randomized, clinical trial has been conducted to compare these 2 diametrically opposed approaches to respiratory management.

Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia (BPD), first described by Northway et al in 1967,8 is now more commonly referred to as CLD. It is the aftermath of underlying lung disease and its treatment, which can lead to pulmonary fibrosis and reactive airways disease.1 Interestingly, the population of babies first described by Northway et al ranged from 1,474–3,204 g in birthweight and 30–39 weeks’ gestational age. That group of infants has, for the most part, been replaced by very-low-birthweight, extremely premature infants previously treated with surfactant and mechanical ventilation for RDS.

The etiology and pathogenesis of CLD are clearly multifactorial and include the effects of positive-pressure ventilation (barotrauma), overdistention of the lungs by large tidal volume (V\text{VT}) ventilation (volutrauma), the effects of repetitive opening and closing of lung units (atelectrauma), and the effects of oxidant stress and inflammation (biotrauma). The term “ventilator-induced lung injury” has been used to describe these phenomena.1,9–12

Several definitions of CLD are presently in use. These include oxygen dependence at 28 days or 36 weeks post-conceptional age. Unfortunately, many infants with reasonably normal pulmonary function require oxygen for the treatment of episodic apnea and/or desaturation, making interpretation of the literature difficult.

Treatments for CLD include the use of mechanical ventilation, augmented by bronchodilators, diuretics, and corticosteroids. Very few well-designed, prospective, randomized, controlled trials have been done to evaluate these. However, the advent of pulmonary mechanics testing may enable objectification of results in individual patients.13

Goals of Mechanical Ventilation

Irrespective of the technique or mode of ventilation chosen, the goals of mechanical ventilation remain the same: (1) to achieve and maintain adequate pulmonary gas exchange, (2) to minimize the risk of lung injury, (3) to reduce patient work of breathing (WOB), and (4) to optimize patient comfort. The challenge is to identify the most appropriate device, technique, and strategy.14 Weaning infants from mechanical ventilation is another controversial subject but is beyond the scope of this review.15

Noninvasive Neonatal Ventilation

Continuous Positive Airway Pressure

The use of CPAP to treat RDS was first described by Gregory et al in 1971.16 CPAP applies continuous distending pressure to the alveoli throughout the respiratory cycle, maintaining a degree of alveolar inflation during expiration and preventing complete collapse, and thus taking advantage of the Laplace law, since a partially inflated alveolus is easier to expand than a fully collapsed one. Although the first application of CPAP was through the endotracheal tube, it soon became apparent that it could also be applied nasally, since most newborns are obligate nasal breathers. At the same time, the mouth acts as a pressure relief valve if the applied pressure is too high. Use of nasal CPAP also obviated face masks, face chambers, and head boxes, all of which had potential deleterious nonrespiratory effects.17

In addition to recruiting alveoli and increasing lung volume, CPAP may also offer nonspecific positive benefits for neonatal ventilatory management. For example, it produces a more regular pattern of breathing in preterm infants. This may be attributed to reducing thoracic distortion and stabilizing the chest wall, splinting the airway and the diaphragm, decreasing obstructive apnea, and enhancing surfactant release.17

CPAP delivery systems contain 3 major components. The first is a circuit to provide a continuous flow of in-
spired gas, which must be warmed and humidified. The second is an interface to connect the circuit to the airway. Binasal tubes or prongs are the most commonly used. Newer devices use fluidics to reduce expiratory resistance and decrease the WOB. The third component is a device to generate positive pressure. This is most frequently accomplished by varying the resistance to exhalation. Bubble CPAP devices use a water column rather than a variable resister. There is some evidence to suggest that the small vibrations it produces in the infant’s chest (at a frequency of 15–30 Hz) may facilitate gas exchange and decrease both the respiratory rate and minute ventilation, without increasing \( P_{CO_2} \). Variable-flow nasal CPAP devices produce positive pressure by converting kinetic energy from a jet of gas in the vicinity of the nasal airway in response to patient effort during inhalation. When the baby exhales, the increase in nasal pressure deflects the flow of gas toward the expiratory outlet, and thus the alterations in flow and pressure follow the baby’s own pattern of breathing.17

Although CPAP is well tolerated by most infants, there are a number of acute complications. CPAP can cause abdominal distention and feeding disturbances because of the gas flow to the stomach. The nasal prongs or tubes can cause nasal irritation and excoriation. At high pressures, thoracic air leaks can occur and venous return and cardiac output can be impaired.17

CPAP as a primary strategy for treating RDS was popular in the 1970s but gradually began to lose favor as experience with mechanical ventilation became more widespread. The advent of surfactant replacement therapy all but relegated CPAP to postextubation treatment, except in a handful of centers, most notably Babies’ Hospital at Columbia University. The anecdotal experience of Wung et al promoted a “gentle” or conservative approach to treating neonatal RDS, using nasal CPAP as the primary strategy and accepting “marginal” blood gases and pH.18 This approach has generated the lowest incidence of CLD in the United States. However, Wung’s work is not widely accepted because it is nonrandomized and uncontrolled, and because no data have been published regarding long-term neurologic outcomes. At issue is whether this approach merely substitutes improved pulmonary outcomes for poorer neurologic outcomes.

Recent European reports have suggested that the early use of nasal CPAP in preterm infants with RDS could decrease the need for subsequent intubation and mechanical ventilation.19–21 A study by Thomson with infants 27–29 weeks’ gestational age assessed the potential benefits of early nasal CPAP and prophylactic administration of surfactant.22 Four subgroups were investigated: (1) early nasal CPAP with prophylactic surfactant, (2) early nasal CPAP with rescue surfactant if necessary, (3) early ventilation with prophylactic surfactant, and (4) early ventilation with rescue surfactant, if necessary. Early nasal CPAP, with or without surfactant, reduced the need for mechanical ventilation in the first 5 days of life. In addition, early nasal CPAP and prophylactic surfactant reduced the need for subsequent surfactant administration. Unfortunately, there were no differences in the incidence of CLD between the 4 groups.22

Much work still needs to be done to properly define the relationship between CPAP, surfactant replacement therapy, and mechanical ventilation. Until more data are available, the present level of information does not support the use of nasal CPAP as a primary modality to treat preterm infants suffering RDS. However, several ongoing clinical trials may yield information that addresses this issue more fully.

**Invasive Neonatal Ventilation**

**Conventional Mechanical Ventilation**

The term “conventional” is a misnomer when applied to mechanical ventilation, in light of the myriad of recent advances. Rather, the term “conventional” is used to distinguish this genre of tidal ventilation from HFV. “Traditional” modes of ventilation describe how mechanical breaths are delivered to the patient and also the relationship between mechanical and spontaneous breaths. These modes include IMV, synchronized IMV (SIMV), and assist/control ventilation.23 Newer ventilation modes, including hybrids, have recently been added to neonatal ventilators and will be addressed below.

In addition to the ventilatory mode, a target variable is described. This is usually pressure or volume, although again, hybrid breath types have emerged. There are also limit variables, such as pressure, time, or volume, which may not be exceeded during the delivery of a mechanical breath. Finally, the cycling mechanism is described. Cycling refers to the condition(s) that causes inspiration to end and expiration to begin, and expiration to end and inspiration to begin. Cycling mechanisms include time and changes in airway flow or volume (although true volume-cycling does not occur in newborns [see below]).24

**Intermittent Mandatory Ventilation**

For more than 2 decades IMV was virtually the only mode used with newborns. With IMV the clinician sets a rate at which the ventilator will deliver mechanical breaths, which cycle at regular intervals (Figure 1). The patient may breathe spontaneously between mechanical breaths, but, unfortunately, babies often breathe asynchronously with the ventilator.25 Gas exchange may vary widely, depending on whether the baby is breathing with or against the ventilator. Asynchrony results not only in inefficiency
of gas exchange but also has the potential to lead to gas trapping and air leaks. Asynchrony is associated with irregularities in arterial blood pressure, cerebral blood flow velocity, and intraventricular hemorrhage in preterm infants. Methods to resolve asynchrony have been limited. An attempt can be made to “overdrive” the baby by choosing a high ventilator rate. Alternatively, sedatives or paralytics can be used to decrease or abolish spontaneous respiratory drive. However, none of these methods offers a satisfactory long-term solution.

**Synchronized Intermittent Mandatory Ventilation**

SIMV represents an improvement over IMV. In this mode the onset of inspiration of a mechanical breath is timed to the onset of a spontaneous breath if it occurs within a “timing window.” For example, if the SIMV rate is set at 30 breaths/min, the ventilator will cycle every 2 seconds. Each time it is supposed to cycle it will look for a spontaneous breath and will start or delay the mechanical breath if spontaneous effort is detected within the timing window (Figure 2). Although the onset of inspiration is synchronized, expiratory asynchrony may occur if the baby’s own inspiratory time (T1) is shorter than that chosen by the clinician, as the baby will begin to exhale while positive pressure is still being applied by the ventilator. The baby may also breathe spontaneously between mechanical breaths, but the only additional support is provided by positive end-expiratory pressure (PEEP).

**Assist/Control Ventilation**

In assist/control ventilation (A/C) all spontaneous breaths that exceed a trigger threshold result in the delivery of mechanical breaths at the onset of inspiration (assist). In the event of apnea or insufficient effort, mechanical breaths are provided at a rate set by the clinician (control). The control rate thus serves as a true back-up rate and is not used as long as the patient’s spontaneous rate exceeds it.

If A/C breaths are cycled strictly by time, expiratory asynchrony can still occur if the machine T1 exceeds the baby’s spontaneous T1. That asynchrony can be avoided by using flow cycling, in which the breath is terminated when airway flow declines to a set percentage of peak inspiratory flow, indicating that the baby is about to end the spontaneous breath (Figure 3). Thus, full synchrony can be achieved.

**Pressure-Support Ventilation**

PSV is a way of providing an inspiratory pressure assist to spontaneous breaths during mechanical ventilation. It is intended to overcome the imposed WOB created by the narrow lumen of the endotracheal tube, ventilator circuit, and demand valve. A spontaneous breath that meets the trigger threshold causes delivery of a mechanical breath that is pressure-limited and flow-cycled (with a T1 limit). Thus, its onset, duration, and frequency are controlled by the patient. The level of support (determined by the peak
inspiratory pressure (PIP) is chosen by the clinician. Spontaneous breaths can be fully supported (full VT), partially supported (Figure 4), or minimally supported. Flow delivery during PSV is variable and proportional to patient effort. It is primarily a weaning mode, used in conjunction with SIMV, or it may be used alone in a patient who has reliable respiratory drive.28,30

**Patient-Triggered Ventilation**

“Patient-triggered ventilation” is a generic term that refers to modes of ventilation in which a mechanical breath is provided in response to measured or presumed respiratory effort by the patient. SIMV, A/C, and PSV are all forms of patient-triggered ventilation.29,31

The trigger signal needs to be a measure or surrogate of spontaneous respiratory effort, but it should minimize artifacts that come from other sources. Various trigger signals have been used with newborns, including changes in airway flow or pressure, abdominal motion, and thoracic impedance.25,32,33

A key to the success of patient-triggered ventilation is the response time, also referred to as the trigger delay. It is the time that elapses between reaching the trigger threshold and a measurable rise in pressure at the proximal airway. Long trigger delays increase failures because the infant may be substantially into the inspiratory phase before support is provided by the ventilator.29

Weaning during A/C is different than during IMV. As long as the baby is breathing above the control rate, reductions in the ventilator rate (the standard practice during IMV) will make no effective change in the ventilator’s cycling. Instead, the preferred method is to reduce PIP.24 This should reduce complications associated with higher pressures, such as air leaks and CLD, but whether this putative advantage actually accrues remains to be seen.

Almost all clinical trials comparing any form of patient-triggered ventilation to IMV have demonstrated superiority of patient-triggered ventilation.25,31–36 Only the open trial by Baumer had contrary results,37 and that study has been rightly criticized for its methodology and design flaws.38

**Ventilatory Techniques**

**Pressure-Limited Ventilation**

For more than 30 years time-cycled, pressure-limited ventilation has been the technique most frequently applied to neonatal respiratory failure (Figure 5A). It is easy to use and results in breaths that have a consistent PIP. However, the VT delivered to the patient is dependent on pulmonary compliance. If compliance is poor, less volume will be delivered at the same PIP.14 Moreover, rapid improvement in compliance, as is seen following surfactant administration, can result in excessive volume delivery if inadequate attention is paid to the patient-ventilator interaction. The bias flow needs to be sufficient to allow the ventilator to reach PIP in the allotted Ti, but not too high to cause turbulence. If flow cycling is used (see Figure 5B), the Ti will be set by the patient and can vary from breath to breath. Careful observation is needed to be sure that it
provides adequate volume delivery, especially if the TI is short.

Pressure-Controlled Ventilation

Pressure-controlled ventilation has recently been incorporated into neonatal ventilators. In this form of pressure-targeted ventilation, the TI is constant and the flow is variable so that the PIP can be reached early in the inspiratory phase and held at a plateau pressure. This provides a more rapid pressurization of the circuit and airway and has the intuitive advantage of overcoming situations in which there is high resistance. Some ventilators also offer an adjustable rise time, which enables the clinician to alter the slope of the pressure waveform as the patient’s status changes. As with pressure-limited ventilation, the PIP is set and volume delivery is a function of pulmonary compliance.

Volume Ventilation

Volume ventilation differs from the pressure-limited modes in that it provides for a clinician-chosen volume. Inspiration ends when a pre-set volume of gas has been delivered to the patient, at whatever pressure is necessary to do so. This is referred to as volume-cycling with adults and older children, but true volume-cycling does not occur with newborns, because cuffed endotracheal tubes are not used and there is almost always some volume loss around the endotracheal tube. The terms “volume-targeted,” “volume-limited,” and “volume-controlled” are thus preferred. For safety reasons the inspiratory pressure can be limited, but care must be taken to avoid defeating the main advantage of volume ventilation, which is providing a stable, consistent VT and minute ventilation, independent of the respiratory compliance. This provides an “auto-weaning” feature, meaning that as lung compliance improves, the ventilator automatically adjusts by lowering inspiratory pressure. Volume ventilation produces a square flow waveform (Figure 6) and a “shark’s fin” pressure waveform.
waveform, where peak volume delivery occurs at end inspiration. Newer ventilators also offer a decelerating flow waveform. $T_I$ is a function of the flow. Because there may be considerable compressible volume loss in the ventilator circuit when pulmonary compliance is poor, it is crucial to measure delivered volume as close to the proximal airway as possible. The main disadvantages of volume ventilation relate to the slow rise to peak pressure, which may result in unequal distribution of ventilation within the lung.

Volume ventilation has only relatively recently been reintroduced in the neonatal intensive care unit, after a less than stellar experience in the early 1980s. This has been made possible by technologic advances enabling the measurement of very small $V_T$ and the provision of very low flows. One of the first evaluations of volume ventilation was the single-center, 50 patient, randomized clinical trial by Sinha et al. Babies with moderately severe RDS and who weighed $\approx 1,200$ g were assigned to receive pressure-limited or volume-limited ventilation, controlled for identical $V_T$ delivery. The group receiving volumelimited ventilation had a much shorter duration of mechanical ventilation, no higher incidence of air leaks, and showed far fewer abnormalities on neuroimaging. These findings are intriguing and warrant further study in even smaller babies.

**Hybrid Techniques**

In recent years attempts have been made to combine the best features of pressure-limited and volume-limited ventilation in either a combination of breath types or a single breath type, to respond to the changing needs of the patient. Early clinical experience has been promising, but extensive study will be required to determine the best applications of each.

**Volume Guarantee**

The volume guarantee mode is available with the Draeger Babylog 8000plus ventilator. Volume guarantee delivers a pressure-limited breath at a fixed flow. The clinician chooses a targeted $V_T$, and, based on the volume delivered during the previous breath, the ventilator will adjust the pressure to achieve the “guaranteed” volume. However, because the increase in pressure cannot exceed the pressure limit, the volume guarantee sometimes cannot be reached unless a pressure plateau is generated by extending inspiration at a higher flow. The volume guarantee is also based on the expired $V_T$ of the preceding 8 breaths. Early investigation revealed promise in achieving gas exchange comparable to SIMV at lower peak airway pressures.

**Pressure-Regulated Volume Control**

Pressure-regulated volume control is a feature of the Siemens Servo 300 ventilator. Used only with A/C, pressure-regulated volume control produces a variably decelerating flow waveform, and breaths are time-cycled. During pressure-regulated volume control there is a “learning period” in which lung compliance is assessed, and then pressure and volume are regulated. The learning period consists of 4 breaths of incremental pressure. The pressure-volume relationship is determined and compliance is calculated. This is compared to a target $V_T$ and inspiratory pressure is adjusted to approach the target volume. This technique is intended for management during the acute phase of illness and is not suitable for weaning, which requires a change to volume support. Additionally, this ventilator measures volume at the machine and not at the patient’s airway.

**Volume-Assured Pressure Support**

Volume-assured pressure support (VAPS) is available on VIASYS Healthcare’s VIP Bird Gold infant/pediatric ventilator. It is a true hybrid technique combining the best features of volume and pressure ventilation in a single breath type. The clinician chooses a volume target. VAPS breaths begin as pressure-limited, flow-cycled breaths, either spontaneously (ie, pressure support) or mechanically. When inspiratory flow has decelerated to the minimum set level, delivered volume is measured. If the target volume has been met or exceeded, the breath ends. If the delivered volume has not met the volume assurance target the breath is transitioned to a volume-targeted breath by prolonging inspiration at the minimum flow and increasing inspiratory pressure until the desired volume has been delivered. Safety features include the ability to limit high pressure and $T_I$. VAPS breaths, depending on circumstances, could be flow-, time-, or volume-cycled. VAPS can be thought of as variable flow-volume ventilation.

Potential benefits of VAPS include decreased WOB, lower peak airway pressure, better gas distribution, enhanced patient comfort, and less need for sedation. VAPS can be used during the acute phases of illness to assure adequate tidal delivery in a situation of changing lung compliance or during convalescence when respiratory drive may be variable. Its major advantage is its immediate response, rather than using a breath-averaging methodology. VAPS experience with newborns has been limited to date.

**Proportional Assist Ventilation**

With proportional assist ventilation (PAV) the level of ventilatory support is proportional to patient effort. PAV is based on the use of combined elastic and resistive un-
loading of respiratory musculature to achieve gas exchange at lower mean airway pressure than with other forms of conventional mechanical ventilation. Thus far there is one published clinical trial of PAV with newborns. The study evaluated PAV, A/C, and IMV in a crossover design study with 36 infants, weighing 600–1,200 g, with mild to moderate acute respiratory illness. PAV resulted in lower mean airway and transpulmonary pressures at an equivalent fraction of inspired oxygen (FIO₂) and similar carbon dioxide removal rates. Further investigation of this promising technique is needed.

### Ventilatory Styles

Ventilatory modes and techniques have been variously utilized in specific circumstances to accomplish therapeutic success. These approaches have not yet been established by adequate clinical evidence, but they are extremely controversial, and as such are included in this review.

### Conservative or “Gentle” Ventilation

Conservative or “gentle” ventilation is an extension of the research by Wung et al with CPAP, at Babies’ Hospital at Columbia University, in which minimally acceptable gas exchange was achieved with the least possible ventilatory support. In an approach that was contrary to many, they reported on a series of 15 PPHN infants treated with very modest ventilator settings to achieve “marginal” target arterial blood gas values. P_aO₂ was maintained at 50–70 mm Hg and P_aCO₂ at 40–60 mm Hg. Sedative and paralytic drugs were avoided. All 15 infants survived, and only 1 developed CLD. Several years later Dworetz et al published another small series with similar findings, using a comparable approach with PPHN patients who were thought to be ECMO candidates.

Although the studies by Wung and Dworetz are an intriguing departure from the dogma of hyperventilation and alkalosis for the treatment of PPHN, the gentle ventilation theory remains anecdotal, though it appears to have had some impact in tempering the unbridled enthusiasm for hyperventilation/alkalosis. Again, neither of these approaches has been compared to the other in a clinical trial, nor even to a course of “normal” ventilation.

### Permissive Hypercapnia

In 1989, before the advent of surfactant, Kraybill et al reported a retrospective analysis of 235 infants, among whom a higher incidence of CLD was seen in those with low P_CO₂ in the second and fourth days of life. Interestingly, there were no significant differences in ventilator settings among the infants who did or did not develop CLD, suggesting that injury might have resulted from a larger V_T that was received because of better pulmonary compliance. A second retrospective study, by Garland et al in 1995, showed a relationship between hypocapnia and CLD prior to surfactant treatment.

These reports formed an attractive hypothesis that purposefully allowing P_CO₂ to remain above normal might reduce the incidence of CLD while also reducing other complications and the duration of mechanical ventilation. The results of a prospective, randomized trial were published by Mariani et al in 1999. In the study 49 preterm infants were randomized to normocapnic management (P_aCO₂ 35–45 mm Hg) or hypercapnic management (P_aCO₂ 45–55 mm Hg) for 96 hours. Those in the hypercapnic group were more likely to be extubated within the 96-hour study period, but there were no other statistically significant differences in any of the variables examined, including CLD.

A second prospective trial, conducted by the National Institute of Child Health and Human Development Neonatal Network, included 220 mechanically ventilated infants with birthweights of 501–1,000 g. These babies were randomized to either normocapnia (P_aCO₂ < 48 mm Hg) or hypercapnia (P_aCO₂ > 52 mm Hg) for 10 days. Although there were differences in the need for mechanical ventilatory support at 36 weeks post-menstrual age (16% in the normocapnic group vs 1% in the hypercapnic group), hypercapnia did not alter the incidence of death, CLD, or severe intraventricular hemorrhage. The latter finding is important, however, because there are numerous reports that link hypercapnia with intraventricular hemorrhage, presumably through an increase in cerebral blood flow. More research will be necessary to determine whether permissive hypercapnia is indeed a lung-protective strategy.

### Nasopharyngeal Synchronized Intermittent Mandatory Ventilation

The concept of ventilating an infant through a nasopharyngeal tube has been investigated. Friedlich et al randomized 41 infants (mean gestational age 28 wk) to receive either postextubation nasal CPAP or nasopharyngeal SIMV in which mechanical breaths were delivered to the nasopharynx, analogously to endotracheal SIMV. In this study, failure was defined as deterioration in blood gas values, increased ventilatory requirements, or apnea. Failures occurred in 7 of the 19 babies in the CPAP group, but in only 1 of the 22 babies in the nasopharyngeal SIMV group, up to 48 hours after extubation. Though this study examined only postextubation management, it suggests that the technique might be useful to treat mild-to-moderately ill babies prior to intubation.
High-Frequency Ventilation

HFV is a radical departure from standard, conventional mechanical ventilation. There are several types of HFV devices, including high-frequency flow interrupters, high-frequency jet ventilation (HFJV), HFOV, and hybrids. Common to all of these devices is “nontidal” ventilation, in which the delivered gas volume is less than the anatomic dead space and is delivered at very rapid rates. The rationale for HFV is that the provision of tiny gas volumes at rapid rates results in much lower alveolar pressure, decreasing the injury attributable to excessive pressure and volume. HFV produces vibratory energy, which may facilitate gas exchange and help to mobilize pulmonary secretions. One drawback is the inability to monitor pulmonary mechanics and gas volume delivery, as can be done with conventional ventilation (see below). Direct comparison of the published clinical trials is difficult because the studies used different strategies, devices, and objectives.

High-Frequency Jet Ventilation

HFJV involves the use of a jet injector, either at the proximal or distal trachea, through which a small volume of rapidly moving gas is introduced into the airway. The only United States Food and Drug Administration-approved device is the Bunnell Life Pulse High Frequency “Jet” Ventilator. It is used in tandem with a conventional ventilator that provides PEEP and background conventional breaths. HFJV uses passive exhalation, relying on the elastic recoil of the lung to help drive exhaled gases from the lung. The frequency range is 240–660 breaths/min.

Because the flow of gas is so rapid during HFJV, it has been used to treat thoracic air leaks. The first prospective randomized trial of the device examined its effect on preterm infants with pulmonary interstitial emphysema. This multicenter study, which used a crossover design and involved 144 infants, demonstrated the superiority of HFJV to conventional IMV in resolving pulmonary interstitial emphysema. HFJV did not produce a higher incidence of CLD in surviving infants.

A second multicenter controlled trial investigated the effect of HFJV versus conventional IMV with preterm RDS infants. This 130-patient study demonstrated that infants assigned to HFJV had a lower incidence of CLD (at 36 wk post-conceptional age) and less need for home oxygen. Interestingly, HFJV did not reduce the incidence of air leaks.

Management of infants on HFJV is complicated and requires experience. Although the basic principles are the same as for conventional ventilation, in which oxygenation is a function of mean airway pressure and ventilation is determined by amplitude and frequency, there are other issues that need to be addressed, such as the management of the conventional ventilator.

High-Frequency Oscillatory Ventilation

HFOV differs from HFJV in a number of ways. Most HFOV devices use a piston or diaphragm to move gas into and out of the lung, creating active exhalation. With HFOV the gas volume is small and the respiratory rate is fast, usually in the 8–12 Hz range. In the United States the major approved device is the SensorMedics 3100A. This device is used alone. Adjustments for oxygenation (mean airway pressure) and ventilation (amplitude) are made independently and thus may be done simultaneously. Because the power of this device is high at 1:2 inspiratory/expiratory ratio can be used and the frequency can generally be held constant, making management relatively straightforward.

The question of whether HFOV can reduce the incidence of CLD is unanswered at this time. It is unfortunate that the largest trial to date, the 1989 report by the HIFI Study Group, was performed at a time when there was little experience with HFOV, used a suboptimal device, and chose an inappropriate strategy, thus adversely affecting all meta-analyses in which it has been included. Positive HFOV benefits were found by Clark et al in 1992 (lower incidence of CLD among babies treated exclusively with HFOV), Gerstmann et al in 1996 (HFOV reduced survival without CLD and decreased surfactant need), Plavka et al in 1999 (HFOV reduced CLD at 30 d but not at 36 wk), Moriette et al in 2001 (HFOV reduced the need for surfactant but did not lessen CLD), and Courtney et al in 2001 (HFOV was associated with shorter duration of ventilation and better survival without CLD, vs SIMV).

Although HFOV appears to be a useful rescue technique, there does not appear to be sufficient evidence to justify it as a primary treatment modality for RDS infants. Other studies have failed to demonstrate a lower incidence of CLD with HFOV.

Extracorporeal Membrane Oxygenation

ECMO is a form of extracorporeal life support in which the circulation is diverted from the body and into a membrane oxygenator that acts as an artificial lung. Blood is oxygenated, carbon dioxide and water are removed, and the blood is warmed and returned to the body. ECMO was originally done through catheters placed in the right common carotid artery and right internal jugular vein (venoarterial ECMO), but this necessitates permanent ligation of these vessels, and there are concerns about jeopardizing cerebral blood flow. Venoarterial ECMO has largely been replaced by venovenous ECMO, using a double-lumen catheter in the right internal jugular vein.
ECMO allows total bypass, so that both the heart and lungs are at rest. Venovenous ECMO does not allow total bypass and depends on the native lung for gas exchange. Both forms require systemic anticoagulation to prevent clotting within the ECMO circuit.76 ECMO is generally reserved for infants with intractable but potentially reversible respiratory failure that has not responded to less invasive treatments. It is usually applied when there is a > 80% chance of death with an infant > 2 kg and ≥ 34 weeks’ gestational age. Criteria for instituting ECMO are institution-specific and are usually objective measures of respiratory failure, such as the oxygenation index or alveolar-arterial oxygen difference.

There was a wide acceptance of ECMO in the United States in the 1980s despite a paucity of clinical trials, and thousands of newborns were treated with this modality. As ventilatory techniques such as HFV, surfactant replacement, and inhaled nitric oxide evolved, the use of neonatal ECMO dropped dramatically. However, the overall survival of ECMO-treated newborns has exceeded 80%, and the rate of serious handicap is no higher than that reported for PPHN treated “conventionally.” ECMO is expensive and labor-intensive, and the long-term outcomes have yet to be reported. It seems intuitive that as the use of ECMO has declined, the technique should be confined to a limited number of regional centers that have sufficient volume to maintain skills and economy of scale.77

Monitoring

The technologic advances in microprocessor-based ventilators and small but highly sophisticated transducers have enabled real-time assessment of pulmonary waveforms and mechanics on a breath-to-breath basis, as well as measurements of $V_T$ and minute ventilation.79 An understanding of pulmonary graphics is essential to managing infants with the newer ventilatory techniques.79 Moreover, pulmonary graphic monitoring enables assessment of patient-ventilator interaction (synchrony), effects of therapeutic interventions such as bronchodilators and diuretics, and the customization of ventilator settings in a patient- and disease-specific way. Monitoring provides early evidence of potentially dangerous conditions such as gas trapping and hyperinflation. It can be used to determine optimal PEEP and to estimate WOB. It gives the clinician immediate feedback on the effects of changes in ventilator parameters. Real-time monitoring should decrease the need for and frequency of many ancillary tests, such as chest radiography and blood gas analysis, thus decreasing the cost of health care. Forthcoming advances will include displays that distinguish inspiratory and expiratory flow and mechanical and spontaneous breathing.

Summary

The past 30 years have brought a technologic revolution to the neonatal intensive care unit. Gone are the days when all neonatal lung diseases, devices, and treatment strategies were perceived as the same. Advances in neonatal respiratory care have included the unraveling of the puzzle of pathophysiology, the development of accurate and user-friendly diagnostic tools, and the implementation of microprocessor-based, sophisticated neonatal ventilators and monitoring devices.

The treatment choices are extensive and appear to become more extensive every day. Noninvasive techniques are regaining popularity, and nasal CPAP is again being explored as a primary strategy. Time-cycled, pressure-limited ventilators are being replaced by multi-modal, patient-triggered devices. Various techniques, such as volume-controlled ventilation, proportional assist ventilation, and hybrid forms are being used. HFV and ECMO remain valuable rescue therapies for infants who fail conventional therapy.

Clinicians have an obligation to harness all of this new “power” wisely. The evidence base is as yet unestablished for most of the treatments described in this review. The time is right to organize well-designed randomized clinical trials to answer the myriad questions that the new technologies have raised.

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such as CPAP, HFV, or patient-triggered ventilation. My frustration is that people are right now with several other therapies such as ECMO and surfactants to where we have not made any difference in mortality, CLD, or other morbid sequelae in neurological injury. Essentially what we have is a lot of therapies that we hoped were going to help. I’m frustrated and I want your perspective on whether you think we’re going to find a method of ventilatory support that will be a true improvement, and can we have the kind of evidence a large, well-performed, randomized, controlled trial would provide and that have good, consistent evidence that these therapies are better than standard IMV. None of the levels of evidence supporting these therapies is of the highest evidence classifications. Thus, we’re not making any difference, at least with ventilation. We have made a difference in mortality with surfactant therapy. However, the aforementioned methods of ventilation have not made any difference in mortality, CLD, or other morbid sequelae in neurological injury. Essentially what we have is a lot of therapies that we hoped were going to help. I’m frustrated and I want your perspective on whether you think we’re going to find a method of ventilatory support that will be a true improvement, and can we have the kind of evidence a large, well-performed, randomized, controlled trial would provide and that

Discussion

Wiswell: During 3 decades of neonatology, we started out with CPAP and IMV and went on to the era of ECMO and surfactants to where we are right now with several other therapies. My frustration is that people jump on the bandwagon for therapies such as CPAP, HFV, or patient-triggered ventilation, but we really don’t
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**Wagener:** I actually like the fact we have so many choices and I don't think we need just one solution. In today's world the pulmonologist rarely sees premature infants with typical CLD on long-term ventilation. Instead we frequently see congenital heart disease kids on long-term ventilation. I think the advantage of having multiple therapies is that we are not talking about one disease; we are talking about different diseases that will need different approaches. With regard to multiple options, do you think BIPAP [bi-phasic positive airway pressure] will ever be used in neonates?

**Donn:** My reflex reaction is to say “no way,” but I've seen so many things happen in the last 25 years that I never would have expected. It might be possible. I think the issue is going to be how to effectively apply it to a struggling baby. The whole issue of sedatives is another bailiwick that we’re trying to get away from.

**Wiswell:** I think Doug Hansell and/or Ric Rodriguez have some experience with the Infant Flow Driver made by EME Inc, in Brighton, United Kingdom. That device, as well as the new SensorMedics CPAP version, which also is a variable-flow nasal CPAP generator, has a miniature soft mask that goes over just the patient’s nose, like what we use to treat adult sleep apnea. It’s not what we used historically in the 1970s, maybe the early 1980s, with face mask CPAP, which infants just could not tolerate. I’ve used the Infant Flow Driver and really like it. My problem is that EME Inc doesn’t produce a lot of them. In addition, they are manufacturing a new bi-level CPAP technique that they want to disseminate. To date the company has some supportive anecdotal data available that a couple of United Kingdom investigators have provided. However, there are no clinical trials currently planned. I’ve been nudging them to do trials in that area, because that would be a very nice noninvasive kind of ventilation, giving a couple levels of pressure support, which makes it very intriguing. I think that may be a good way to go with noninvasive neonatal ventilation.

**Donn:** I think probably the biggest challenge we have, no matter what type of device we use, is keeping the CPAP applied. Frequently when I’m on rounds I find that the nasal prongs are out a little bit, or that one’s in and one’s out.

**Davis:** Your presentation addressed the respiratory aspects of ventilator weaning, but when do you consider adding diuretics or steroids during the wean?

**Donn:** I think right now the pendulum has clearly swung against the use of steroids, particularly early in the course of RDS, given the information that’s come from the National Institute of Child Health and Human Development Neonatal Network and the long-term issues related to cerebral growth. We have tended as well to back away from using them. We tend to use diuretics if we get a situation of stalled weaning, chest radiograph evidence of pulmonary edema, or if we’re dealing with a situation where we can’t get enough calories into the baby by fluid restriction; thus, it’s an adjunct.

**Rotta:** Our neonatology colleagues recognized very early on the impact of mechanical ventilation strategies in the progression of lung disease while...
I was glad you discussed ventilator-induced lung injury, including volutrauma, barotrauma, atelectrauma, and biotrauma. The neonatal literature seems to focus mostly on barotrauma and volutrauma, while very little attention is given to atelectrauma, which animal studies have shown is just as important as—if not more important than—volutrauma alone. Do you have any insights on why that is and whether there is still reluctance on the part of neonatologists to apply adequate PEEP to the neonatal patient?

Donn: It’s hard to answer for the entire community of neonatology. I think the first part of your question relates primarily to what we are able to monitor now. Ten years ago we didn’t have a clue about tidal volumes. We made inferences based on chest excursions and what we saw on a once-a-day radiograph. I think there is a fair amount that has been studied and published in the last few years that’s relatively new, and it’s just a matter of time before “atelectrauma” is as easy to say as “barotrauma” and “volutrauma.” I also think that we are seeing, through the use of pulmonary mechanics monitoring, a better appreciation of what PEEP can do, and this concept of needing higher PEEP to achieve better alveolar opening pressure is one thing we’ve stressed in our management. We do things now that we weren’t able to do before—optimal PEEP studies that measure changes in compliance at various PEEP levels. So I think it’s something that’s an outgrowth of the improved technology.

Black: I’ve also had some experience with the mask Dr Wiswell mentioned. I like it very much. The problem is getting a good seal on the face, obviously, which is the problem with all bi-pressure noninvasive ventilation. But it really is almost a bi-pres-sure because it has that Coanda effect in which the expiratory pressure is actually lower than the inspiratory pressure. Could you comment on that? Do you know of any data that show that’s superior to regular nasal CPAP?

Donn: No, I haven’t seen anything. It’s interesting. This is one of those “what goes around comes around” things. One of the reasons that CPAP was abandoned in the late 1970s as a primary strategy was this concept of needing to get a really good seal no matter how you applied it. There was a very disturbing report about a high incidence of cerebellar hemorrhage because of the need to secure the mask with binding that went around the back of the head. I think that’s going to remain a problematic issue. That’s the one thing we probably have to solve more than anything else: how do you maintain a seal without causing adverse effects? But I haven’t seen anything that has addressed it.

Black: Could you comment on the use of high-flow nasal cannulae to achieve CPAP? I’ll be right up front about it: I have a very strong bias against them.

Donn: I guess the best way to de-scribe it is as the poor man’s CPAP. We use a lot of it postextubation, and there are now nomograms that allow you to figure out approximately how much CPAP you’re generating at various flows. It seems to work in some babies, but again the issue is careful monitoring and setting up objectives about what you’re trying to accomplish with it. If you have too high a flow it becomes uncomfortable and may interfere with feeding by producing gas distension of the stomach, so, just like everything else, it has its draw-backs.

Rodriguez: A recent report compared the nasal cannula and the infant flow device and CPAP delivered with a ventilator, and the cannula performed the worst.¹ The WOB was much higher with the cannula, and they also had to increase the FIO₂ with those babies more than with the other 2 modalities. So it’s become my least preferred mode of CPAP delivery.

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Salyer: It’s been kind of disturbing to me that I’m hearing of a lot of places (and this is true in Seattle also) using the Siemens Servo 300 for neonatal ventilation. We have a growing awareness of the need for volume-targeted ventilation in neonates, and there is now published data that the Servo 300 does not give accurate VT data with neonates.¹ Do you use the Servo 300?

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Donn: No, we don’t. It’s used in our pediatric intensive care unit, but I share your concern. I think that if you’re going to do volume-targeted or volume-controlled ventilation, the place to measure that delivered tidal volume is at the proximal airway. Just to give you an example, with a very small baby if you attempt to deliver a VT of 5 mL and you have a 1 mL inaccuracy in measurement, a VT of 6 mL represents a 20% excess VT delivery. If you were managing an adult and trying to provide a 500 mL VT, but the ventilator was delivering 600 mL, it would be totally unacceptable. So I’m very concerned about that. Small babies, small tidal volumes; there’s not much leeway for error.