Invasive and Noninvasive Neonatal Mechanical Ventilation

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

become both patient- and disease-specific. The clinician has numerous choices among the noninvasive and invasive ventilatory treatments that are currently in use. This article reviews the pathophysiology of respiratory failure in the newborn and the available methods to treat it, including continuous positive airway pressure, conventional and high-frequency mechanical ventilation, extracorporeal membrane oxygenation, and styles of ventilation and monitoring. *Key words: pediatric, respiratory, pulmonary, neonatal, respiratory failure, mechanical ventilation, continuous positive airway pressure, CPAP, patient-triggered ventilation, high-frequency ventilation, permissive hypercapnia, extracorporeal membrane oxygenation, ECMO, monitoring.* [Respir Care 2003;48(4):426–439]. © 2003 Daedalus Enterprises]

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

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concepts of oxidant stress, inflammatory mediators, and infectious agents ("biotrauma") to the previous associations of "barotrauma," "volutrauma," and "atelectrauma" with chronic lung disease (CLD). Yet at the dawn of the new millennium there was still no consensus as to how to best manage neonatal respiratory failure.

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 retracting.[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.[1,6]

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 remains 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_T) 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 postconceptional 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 venti-

lation 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
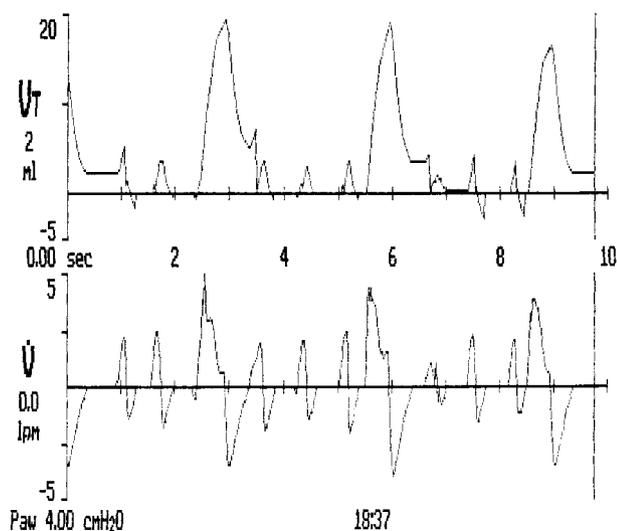
Fig. 1. Volume (top) and flow (bottom) waveforms. The patient was receiving intermittent mandatory ventilation. Note the regular time-cycling of the larger intermittent mandatory ventilation breaths and the relatively meager spontaneous breaths in between. V_T = tidal volume. $\dot{V}$ = flow. P_{aw} = airway pressure.
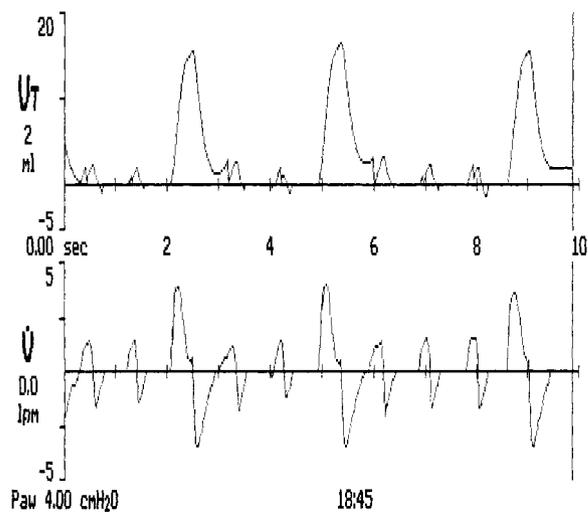

Fig. 2. Volume (top) and flow (bottom) waveforms. The patient was receiving synchronized intermittent mandatory ventilation. Note the larger ventilator breaths and smaller spontaneous breaths, and the inspiratory synchrony between patient and ventilator with the SIMV breaths. SIMV breaths occur at slightly irregular intervals because of the timing windows, during which the ventilator waits for detection of spontaneous effort. V_T = tidal volume. $\dot{V}$ = flow. P_{aw} = airway pressure.

of gas exchange but also has the potential to lead to gas trapping and air leaks.[26] Asynchrony is associated with irregularities in arterial blood pressure, cerebral blood flow velocity, and intraventricular hemorrhage in preterm infants.[27] 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.[28] 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 (T_I) 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).[28] 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 T_I exceeds the baby's spontaneous T_I. 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.[25,29]

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 T_I limit). Thus, its onset, duration, and frequency are controlled by the patient. The level of support (determined by the peak
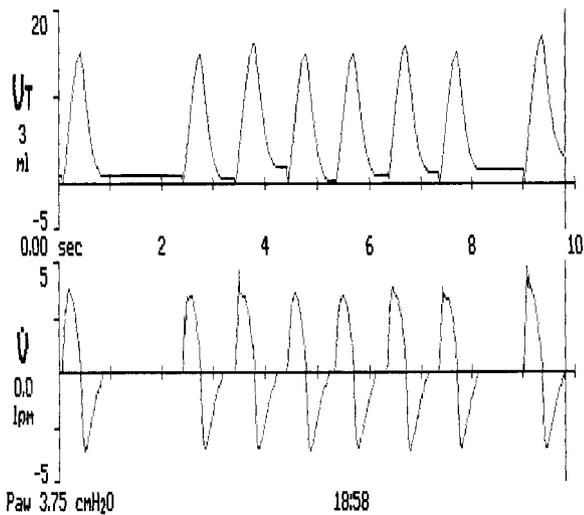
Fig. 3. Volume (top) and flow (bottom) waveforms. The patient was receiving flow-cycled assist/control ventilation. Note how the flow waveform cycles directly into expiration just prior to achieving a zero-flow state. V_T = tidal volume. $\dot{V}$ = flow. P_{aw} = airway pressure.

inspiratory pressure [PIP]) is chosen by the clinician. Spontaneous breaths can be fully supported (full V_T), 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]
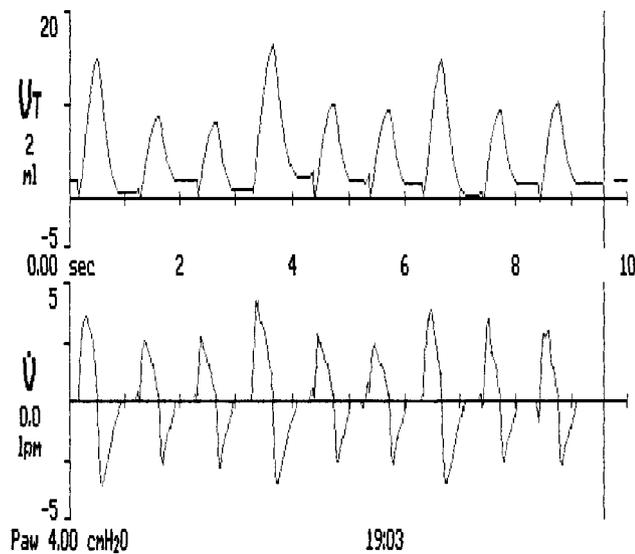

Fig. 4. Volume (top) and flow (bottom) waveforms. The patient was receiving synchronized intermittent mandatory ventilation (SIMV) and pressure-support ventilation (PSV). Larger SIMV breaths provide full volume support. PSV breaths are partially supported. V_T = tidal volume. $\dot{V}$ = flow. P_{aw} = airway pressure.

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 V_T 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 T_I, but not too high to cause turbulence. If flow cycling is used (see Figure 5B), the T_I will be set by the patient and can vary from breath to breath. Careful observation is needed to be sure that it
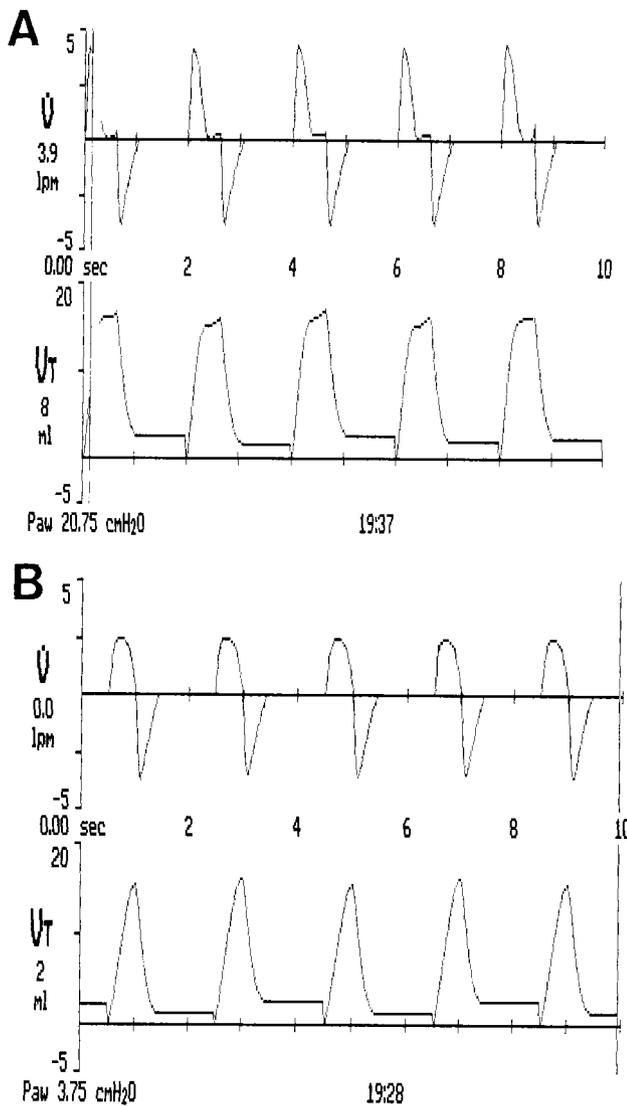
Fig. 5. Cycling mechanisms. A: Time cycling. Note how the flow waveform (top) returns fully to baseline and expiration does not begin until the inspiratory time limit has been reached. This results in a plateau on the volume waveform (bottom). B: Flow cycling. Note how the flow waveform (top) cycles directly from inspiration to expiration prior to reaching a zero-flow state. The resulting volume waveform is peaked. $\dot{V}$ = flow. V_T = tidal volume. P_{aw} = airway pressure.
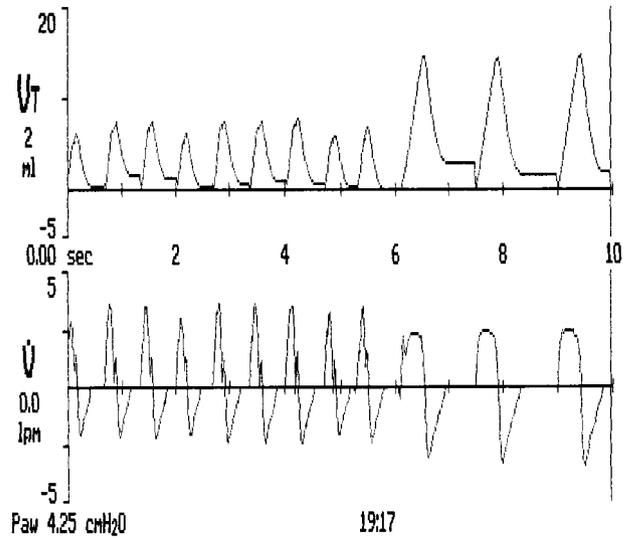

Fig. 6. Volume (top) and flow (bottom) waveforms. The patient was initially receiving pressure-limited assist/control ventilation. Note the sinusoidal flow waveform. The patient is switched to volume-targeted assist/control ventilation for the last 3 breaths. Note the square flow waveform, typical of volume-targeted modes. V_T = tidal volume. $\dot{V}$ = flow. P_{aw} = airway pressure.

provides adequate volume delivery, especially if the T_I is short.

Pressure-Controlled Ventilation

Pressure-controlled ventilation has recently been incorporated into neonatal ventilators. In this form of pressure-targeted ventilation, the T_I 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 pro-

vides a more rapid pressurization of the circuit and airway and has the intuitive advantage of overcoming situations in which there is high resistance.[14] 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.[39,40] 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 V_T 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, 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.[41] 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.[39,40,42,43] 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.[43] Babies with moderately severe RDS and who weighed $\geq$ 1,200 g were assigned to receive pressure-limited or volume-limited ventilation, controlled for identical V_T delivery. The group receiving volume-limited 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 Dräger Babylog 8000*plus* ventilator.[44] 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.[45]

Pressure-Regulated Volume Control

Pressure-regulated volume control is a feature of the Siemens Servo 300 ventilator.[46] 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.[47] 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.[14,28]

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 elastive and resistive un-

loading of respiratory musculature to achieve gas exchange at lower mean airway pressure than with other forms of conventional mechanical ventilation.[48] 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 (F_{IO_2}) and similar carbon dioxide removal rates.[49] 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_{aO_2} was maintained at 50–70 mm Hg and P_{aCO_2} at 40–60 mm Hg. Sedative and paralytic drugs were avoided. All 15 infants survived, and only 1 developed CLD.[50] 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.[51]

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_{CO_2} 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.[52] A second retrospective study, by Garland et al in 1995, showed a relationship between hypocapnia and CLD prior to surfactant treatment.[53]

These reports formed an attractive hypothesis that purposefully allowing P_{CO_2} 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.[54] In the study 49 preterm infants were randomized to normocapnic management (P_{aCO_2} 35–45 mm Hg) or hypercapnic management (P_{aCO_2} 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.[55] These babies were randomized to either normocapnia ($P_{aCO_2} < 48$ mm Hg) or hypercapnia ($P_{aCO_2} > 52$ 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.[56–58] More research will be necessary to determine whether permissive hypercapnia is indeed a lung-protective strategy.[59]

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.[60] 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.[61] 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.[62]

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.[63]

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.[64] 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.[65] 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 a 1:2 inspiratory/expiratory ratio can be used and the frequency can generally be held constant, making management relatively straightforward.[66]

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,[67] 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),[68] Gerstmann et al in 1996 (HFOV improved survival without CLD and decreased surfactant need),[69] Plavka et al in 1999 (HFOV reduced CLD at 30 d but not at 36 wk),[70] Moriette et al in 2001 (HFOV reduced the need for surfactant but did not lessen CLD),[71] and Courtney et al in 2001 (HFOV was associated with shorter duration of ventilation and better survival without CLD, vs SIMV).[72] 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.[73–75]

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. Venoarterial

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.[78] 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.

REFERENCES

1. Nelson M, Becker MA, Donn SM. Basic neonatal respiratory disorders. In: Donn SM, editor. Neonatal and pediatric pulmonary graphics: principles and clinical applications. Armonk, NY: Futura Publishing Co; 1998:253–278.
2. Wiswell TE. Meconium aspiration syndrome. In: Sinha SK, Donn SM, editors. Manual of neonatal respiratory care. Armonk, NY: Futura Publishing Co; 2000:266–272.
3. Wiswell TE, Fuloria M. Management of meconium-stained amniotic fluid. Clin Perinatol 1999;26:6(3)59–668.
4. Halliday HL. Endotracheal intubation at birth for preventing morbidity and mortality in vigorous, meconium-stained infants born at term (Cochrane Review). In: The Cochrane Library, Issue 1 2003. Oxford: Update Software. Available at http://www.update-software.com/abstracts/titlelist.htm (accessed Feb 13, 2003)
5. Wiswell TE. Expanded uses of surfactant therapy. Clin Perinatol 2001;28(3):695–711.
6. Faix RG. Neonatal pneumonia. In: Sinha SK, Donn SM, editors. Manual of neonatal respiratory care. Armonk, NY: Futura Publishing Co; 2000:273–280.
7. Walsh MC, Stork EK. Persistent pulmonary hypertension of the newborn: rational therapy based on pathophysiology. Clin Perinatol 2001;28(3):609–627.

8. Northway WH Jr, Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline membrane disease: bronchopulmonary dysplasia. N Engl J Med 1967;276(7):357–68.

9. Attar MA, Donn SM. Mechanisms of ventilator-induced lung injury in premature infants. Semin Neonatol 2002;7(5):353–360.

10. Jobe AJ. The new BPD: an arrest of lung development. Pediatr Res 1999;46(6):641–643.

11. Davis JM. Bronchopulmonary dysplasia. In: Sinha SK, Donn SM, editors. Manual of neonatal respiratory care. Armonk, NY: Futura Publishing Co; 2000:310–315.

12. Jobe AH, Ikegami M. Mechanisms initiating lung injury in the preterm. Early Hum Devel 1998;53(1):81–94.

13. Nicks JJ, Becker MA, Donn SM. Ventilatory management casebook. Bronchopulmonary dysplasia: response to pressure support ventilation. J Perinatol 1994;14(6):495–497.

14. Donn SM, Sinha SK. Newer techniques of mechanical ventilation: an overview. Semin Neonatol 2002;7(5):401–408.

15. Sinha SK, Donn SM. Weaning from assisted ventilation: art or science? Arch Dis Child Fetal Neonatal Ed 2000;83(1):F64–F70.

16. Gregory GA, Kitterman JA, Phibbs RH, Tooley WH, Hamilton WK. Treatment of the idiopathic respiratory distress syndrome with continuous positive airway pressure. N Engl J Med 1971;284(24):1333–1340.

17. Polin RA, Sahni R. Newer experience with CPAP. Semin Neonatol 2002;7(5):379–389.

18. Wung JT, Koons AH, Driscoll JM Jr, James LS. Changing incidence of bronchopulmonary dysplasia. J Pediatr 1979;95(5 Pt 2):845–847.

19. Poets CF, Sens B. Changes in intubation rates and outcome of very low birth weight infants: a population-based study. Pediatrics 1996;98(1):24–27.

20. Gitterman MK, Fusch C, Gitterman AR, Regazzoni BM, Moessinger AC. Early nasal continuous positive airway pressure treatment reduces the need for intubation in very low birth weight infants. Eur J Pediatr 1997;156(5):384–388.

21. Lindner W, Vossbeck S, Hummler H, Pohlandt F. Delivery room management of extremely low birth weight infants: spontaneous breathing or intubation? Pediatrics 1999;103(5 Pt 1):961–967.

22. Thomson MA. Non-invasive ventilation. Biol Neonate 2000;78:262–268.

23. Hagus CK, Donn SM. Pulmonary graphics: basics of clinical applications. In: Donn SM, editor. Neonatal and pediatric pulmonary graphics: principles and clinical applications. Armonk, NY: Futura Publishing Co; 1998:81–127.

24. Sinha SK, Donn SM. Advances in neonatal conventional ventilation. Arch Dis Child Fetal Neonatal Ed 1996;75(2):F135–F140.

25. Donn SM, Nicks JJ, Becker MA. Flow-synchronized ventilation of preterm infants with respiratory distress syndrome. J Perinatol 1994;14(2):90–94.

26. Lipscomb AP, Thorburn RJ, Reynolds EO, Stewart AL, Blackwell RJ, Cusick G, Whitehead MD. Pneumothorax and cerebral hemorrhage in preterm infants. Lancet 1981;1(8217):414–416.

27. Perlman JM, Goodman S, Kreusser KL, Volpe JJ. Reduction in intraventricular hemorrhage by elimination of fluctuating cerebral blood flow velocity in preterm infants with respiratory distress syndrome. N Engl J Med 1985;312(21):1353–1357.

28. Donn SM, Sinha SK. Newer modes of mechanical ventilation for the neonate. Curr Opin Pediatr 2001;13(2):99–103.

29. Donn SM, Sinha SK. Controversies in patient-triggered ventilation. Clin Perinatol 1998;25(1):49–61.

30. Sinha SK, Donn SM. Pressure support ventilation. In: Sinha SK, Donn SM, editors. Manual of neonatal respiratory care. Armonk, NY: Futura Publishing Co; 2000:157–160.

31. Greenough A. Update on patient-triggered ventilation. Clin Perinatol 2001;28(3):533–546.

32. Bernstein G, Mannino F, Heldt GP, Callahan JD, Bull DH, Sola A, et al. Randomized multicenter trial comparing synchronized and conventional intermittent mandatory ventilation in neonates. J Pediatr 1996;128(4):453–463.

33. Visveshwara N, Freeman B, Peck M, Caliwag W, Shooks S, Rajani KB. Patient-triggered synchronized assisted ventilation of newborns: report of a preliminary study and three years' experience. J Perinatol 1991;11(4):347–354.

34. Chan V, Greenough A. Neonatal patient-triggered ventilators: performance in acute and chronic lung disease. Br J Intens Care 1993;3:216–219.

35. Chen JY, Ling UP, Chen JH. Comparison of synchronized and conventional intermittent mandatory ventilation in neonates. Acta Paediatr Jpn 1997;39(5):578–583.

36. Beresford MW, Shaw NJ, Manning D. Randomised controlled trial of patient triggered and conventional fast rate ventilation in neonatal respiratory distress syndrome. Arch Dis Child 2000;82(1):F14–F18.

37. Baumer JH. International randomized controlled trial of patient triggered ventilation in neonatal respiratory distress syndrome. Arch Dis Child 2000;82(1):F5–F10.

38. Donn SM, Greenough A, Sinha SK. Patient triggered ventilation. Arch Dis Child Fetal Neonatal Ed 2000;83(3):F225–F226.

39. Sinha SK, Donn SM. Volume-controlled ventilation: variations on a theme. Clin Perinatol 2001;28(3):547–560.

40. Bandy KP, Nicks JJ, Donn SM. Volume-controlled ventilation for severe neonatal respiratory failure. Neonatal Intensive Care 1992;5(3):70–73.

41. Cannon ML, Cornell J, Tripp-Hamel DS, Gentile MA, Hubble CL, Meliones JN, Cheifetz IM. Tidal volumes for ventilated infants should be determined with a pneumotachometer placed at the endotracheal tube. Am J Respir Care Crit Care Med 2000;162(6):2109–2112.

42. Franckx J, Vandenplas Y, Sacre-Smits L. Volume limited ventilation for treatment of severe respiratory distress in neonates. Acta Anaesth Belg 1984;35(Suppl):379–386.

43. Sinha SK, Donn SM, Gavey J, McCarty M. Randomised trial of volume controlled versus time cycled, pressure limited ventilation in preterm infants with respiratory distress syndrome. Arch Dis Child 1997;77(3):F202–F205.

44. Mrozek JD, Bendel-Stenzel EM, Meyers PA, Bing DR, Conett JE, Mammel MC. Randomized controlled trial of volume-targeted synchronized ventilation and conventional intermittent mandatory ventilation following initial exogenous surfactant therapy. Pediatr Pulmonol 2000;29(1):11–18.

45. Cheema IU, Ahluwailia JS. Feasibility of tidal volume-guided ventilation in newborn infants: a randomized, crossover trial using the volume guarantee modality. Pediatrics 2001;107(6):1323–1328.

46. Piotrowski A, Sobala W, Kawczynski P. Patient-initiated, pressure-regulated, volume-controlled ventilation compared with intermittent mandatory ventilation in neonates: a prospective, randomized study. Intensive Care Med 1997;23(9):975–981.

47. Keenan HT, Martin LD. Volume support ventilation in infants and children: analysis of a case series. Respir Care 1997;42(3):281–287.

48. Schulze A, Bancalari E. Proportional assist ventilation in infants. Clin Perinatol 2001;28(3):561–578.

49. Schulze A, Gerhardt T, Musante G, Schaller P, Claure N, Everett R, et al. Proportional assist ventilation in low birth weight infants with acute respiratory disease: a comparison to assist/control and conventional mechanical ventilation. J Pediatr 1999;135(3):339–344.

50. Wung JT, James LS, Kilchevsky E, James E. Management of infants with severe respiratory and persistence of fetal circulation, without hyperventilation. Pediatrics 1985;76(4):488–492.

51. Dworetz AR, Moya FR, Sabo B, Gladstone I, Gross I. Survival of infants with persistent pulmonary hypertension without extracorporeal membrane oxygenation. Pediatrics 1989;84(1):1–5.

52. Kraybill EN, Runyan DK, Bose CL, Khan JH. Risk factors for chronic lung disease in infants with birth weights of 751 to 1000 grams. J Pediatr 1989;115(1):115–120.

53. Garland JS, Buck RK, Allred EN, Leviton A. Hypocarbia before surfactant therapy appears to increase bronchopulmonary dysplasia risk in infants with respiratory distress syndrome. Arch Pediatr Adolesc Med 1995;149(6):617–622.

54. Mariani G, Cifuentes J, Carlo WA. Randomized trial of permissive hypercapnea in preterm infants. Pediatrics 1999;104(5 Pt 1):1082–1088.

55. Carlo WA, Stark AR, Wright LL, Tyson JE, Papile LA, Shankaran S, et al. Minimal ventilation to prevent bronchopulmonary dysplasia in extremely-low-birth-weight infants. J Pediatr 2002;141(3):370–374.

56. Szymonowicz W, Yu VY, Wilson FE. Antecedents of periventricular haemorrhage in infants weighing 1250 g or less at birth. Arch Dis Child 1984;59(1):13–17.

57. Miall-Allen VM, de Vries LS, Dubowitz LM, Whitelaw AG. Blood pressure fluctuation and intraventricular hemorrhage in the preterm infant of less than 31 weeks' gestation. Pediatrics 1989;83(5):657–661.

58. Wallin LA, Rosenfeld CR, Laptook AR, Maravilla AM, Strand C, Campbell N, et al. Neonatal intracranial hemorrhage: II. Risk factor analysis in an inborn population. Early Hum Dev 1990;23(2):129–137.

59. Thome U, Carlo WA. Permissive hypercapnia. Semin Neonatol 2002;7(5):409–419.

60. Friedlich P, Lecart C, Posen R, Ramicone E, Chan L, Ramanocthan R. A randomized trial of nasopharyngeal synchronized intermittent mandatory ventilation versus nasopharyngeal continuous positive airway pressure in very low birth weight infants after extubation. J Perinatol 1999;19(6 Pt 1):413–418.

61. Keszler M, Durand DJ. Neonatal high-frequency ventilation. Past, present, and future. Clin Perinatol 2001;28(3):579–607.

62. Bunnell JB. General concepts of high-frequency ventilation. In: Sinha SK, Donn SM, editors. Manual of neonatal respiratory care. Armonk, NY: Futura Publishing Co; 2000:226–234.

63. Keszler M. High-frequency jet ventilation and the Bunnell Life Pulse ® high-frequency jet ventilator. In: Sinha SK, Donn SM, editors. Manual of neonatal respiratory care. Armonk, NY: Futura Publishing Co; 2000: 235–241.

64. Keszler M, Donn SM, Bucciarelli RL, Alverson DC, Hart M, Lunyong V, et al. Multicenter controlled trial comparing high-frequency jet ventilation and conventional mechanical ventilation in newborn infants with pulmonary interstitial emphysema. J Pediatr 1991;119(1 Pt 1):85–93.

65. Keszler M, Modanlou HD, Brudno DS, Clark FI, Cohen RS, Ryan RM, et al. Multicenter controlled clinical trial of high-frequency jet ventilation in preterm infants with uncomplicated respiratory distress syndrome. Pediatrics 1997;100(4):593–599.

66. Clark RH, Gerstmann DR. High-frequency oscillatory ventilation. In: Sinha SK, Donn SM, editors. Manual of neonatal respiratory care. Armonk, NY: Futura Publishing Co; 2000:242–252.

67. High-frequency oscillatory ventilation compared with conventional mechanical ventilation in the treatment of respiratory failure in preterm infants. The HIFI Study Group. N Engl J Med 1989;320(2):88–93.

68. Clark RH, Gerstmann DR, Null DM Jr, deLemos RA. Prospective randomized comparison of high-frequency oscillatory and conventional ventilation in respiratory distress syndrome. Pediatrics 1992; 89(1):5–12.

69. Gerstmann DR, Minton SD, Stoddard RA, Meredith KS, Monaco F, Bertrand JM, et al. The Provo multicenter early high-frequency oscillatory ventilation trial: improved pulmonary and clinical outcome in respiratory distress syndrome. Pediatrics 1996;98(6 Pt 1):1044–1057.

70. Plavka R, Kopecky P, Sebron V, Svihovec P, Zlatohlavkova B, Janus V. A prospective randomized comparison of conventional mechanical ventilation and very early high frequency oscillatory ventilation in extremely premature newborns with respiratory distress syndrome. Intensive Care Med 1999;25(1):68–75.

71. Moriette G, Paris-Llado J, Walti H, Escande B, Magny JF, Cambonie G, et al. Prospective randomized multicenter comparison of high-frequency oscillatory ventilation and conventional ventilation in preterm infants less than 30 weeks with respiratory distress syndrome. Pediatrics 2001;107(2):363–372.

72. Courtney SE, Durand DJ, Asselin JM, Hudak ML, Aschner JL, Shoemaker CT. Early high frequency oscillatory ventilation vs. synchronized intermittent mandatory ventilation in very low birth weight infants. N Engl J Med 2003;347(9):643–652.

73. Rettwitz-Volk W, Veldman A, Roth B, Vierzig A, Kachel W, Varnholt V, et al. A prospective, randomized, multicenter trial of high-frequency oscillatory ventilation compared with conventional ventilation in preterm infants with respiratory distress syndrome receiving surfactant. J Pediatr 1998;132(2):249–254.

74. Thome U, Kossel H, Lipowsky G, Porz F, Furste HO, Genzel-Boroviczeny O, et al. Randomized comparison of high-frequency ventilation with high-rate intermittent positive pressure ventilation in preterm infants with respiratory failure. J Pediatr 1999;135(1):39–46.

75. Moriette G, Brunhes A, Jarreau PH. High-frequency oscillatory ventilation in the management of respiratory distress syndrome. Biol Neonate 2000;77(Suppl 1):14–16.

76. Donn SM. ECMO indications and complications. Hosp Prac (Off Ed) 1990;25(6):143–157.

77. Schumacher RE, Baumgart S. Extracorporeal membrane oxygenation 2001: the odyssey continues. Clin Perinatol 2001;28(3):629–653.

78. Donn SM, editor. Neonatal and pediatric pulmonary graphics: principles and clinical applications. Armonk, NY: Futura Publishing Co; 1998.

79. Sinha SK, Nicks JJ, Donn SM. Graphic analysis of pulmonary mechanics in neonates receiving assisted ventilation. Arch Dis Child Fetal Neonatal Ed 1996;75(3):F213–F218.

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 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

will, hopefully, be definitive? What do you think that improvement will be?

Donn: Those are great questions, and I think they should be asked by and of every neonatologist who manages babies on ventilators. And I share your frustrations. I guess the silver lining that I see in the cloud, looking at the glass as half full rather than half empty, is that we *have* changed things. We've changed the demographics of the diseases. That's why I showed the Northway data.[1] Those were babies who today would, for the most part, not need mechanical ventilation. Though we're not seeing a change in the *incidence*, and maybe not the *severity*, the gestational age of the patients is getting lower. I see that as progress.

However, I also agree with you that we really need to examine this. I think the choices can be overwhelming, and the way I have tried to approach this is like we were taught in pharmacology; there are dozens of cephalosporins and you can't learn every one, so you study the prototype drug, learn what it can and can't do, master it, and then go on to the next one. I think what happens is that too much of a "shotgun approach" often leads to even more frustration, because you don't stick with something long enough to learn its limitations or its applications. I think as a discipline we need to do this.

My fear of the large, randomized, controlled trial is that we're going to get results like Harry Baumer did.[2] He conducted an open trial of patient-triggered ventilation, and it was a poorly performed study, and took 5 years to complete. He used various devices and the numbers of babies enrolled per center ranged from 2 to several hundred. A large percentage of the babies didn't get the assigned ventilatory mode, and the mortality rate was unacceptably high. So the study really told us nothing, but is going to hinder meta-analysis for years to come because there were so many babies

enrolled in it. I don't know what the ultimate answer is, other than to keep trying.

REFERENCES

1. Northway WH Jr, Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline-membrane disease: bronchopulmonary dysplasia. N Engl J Med 1967;276(7):357–368.
2. Baumer JH. International randomised controlled trial of patient triggered ventilation in neonatal respiratory distress syndrome. Arch Dis Child Fetal Neonatal Ed 2000; 82(1):F5-F10.

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 [biphasic 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

dealing with a prototypical disease of lung compliance such as neonatal RDS. 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 describe 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 drawbacks.

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 F_{IO_2} with those babies more than with the other 2 modalities. So it's become my least preferred mode of CPAP delivery.

REFERENCE

1. Courtney SE, Pyon KH, Saslow JG, Arnold GK, Pandit PB, Habib RH. Lung recruitment and breathing pattern during variable versus continuous flow nasal continuous positive airway pressure in premature infants: an evaluation of 3 devices. Pediatrics 2001;107(2):304–308.

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 V_T data with neonates.[1] Do you use the Servo 300?

REFERENCE

1. Cannon ML, Cornell J, Tripp-Hamel DS, Gentile MA, Hubble CL, Meliones JN, Cheifetz IM. Tidal volumes for ventilated infants should be determined with a pneumotachometer placed a the endotracheal tube. Am J Respir Crit Care Med 2000; 162(6):2109–2112.

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 V_T of 5 mL and you have a 1 mL inaccuracy in measurement, a V_T of 6 mL represents a 20% excess V_T delivery. If you were managing an adult and trying to provide a 500 mL V_T 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.