

Neonatal Noninvasive Ventilation Techniques: Do We Really Need to Intubate?

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Summary

The current trend for supporting neonates with respiratory distress syndrome is nasal continuous positive airway pressure (CPAP). Nearly half of all neonates who are supported with CPAP will still develop respiratory failure that requires potentially injurious endotracheal intubation and invasive ventilation. Thus, the role of any neonatal clinician is to minimize invasive ventilation whenever possible, to avoid the multitude of complications that can arise when using this form of therapy. Noninvasive ventilation (NIV) is a form of respiratory assistance that provides greater respiratory support than does CPAP and may prevent intubation in a larger fraction of neonates who would otherwise fail CPAP. With the inception of nasal airway interfaces, clinicians have ushered in many different forms of NIV in neonates, often with very little experimental data to guide management. This review will explore in detail all of the different forms of neonatal NIV that are currently focused within an area of intense clinical investigation. Key words: nasal ventilation; infant mechanical ventilation; neonatal intensive care; noninvasive intermittent positive pressure ventilation; nasal continuous positive airway pressure. [Respir Care 2011;56(9):1273–1294. © 2011 Daedalus Enterprises]

Introduction

The lungs of premature neonates lack structural development, ability to produce surfactant, and surface area for

gas exchange to occur. The problem is further complicated by apnea and the infant's inability to maintain the high work of breathing (WOB) necessary to overcome the op-

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GE Healthcare. Seattle Children's Research Institute has submitted a patent application to the World Intellectual Property Organization (PCT/US2009/039957) concerning one of the devices mentioned in this paper, and Mr DiBlasi is listed as an inventor on the application and could benefit from the invention.

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posing forces that resist lung inflation during spontaneous breathing. As such, severe respiratory failure is prevalent in premature neonates with the respiratory distress syndrome (RDS). Endotracheal intubation and mechanical ventilation, or invasive ventilation has been the prevailing intervention for supporting neonates with RDS over the last 40 years. This practice has probably accounted for some of the notable reductions in infant mortality prior to the development of artificial surfactant and the widespread use of antenatal corticosteroids.¹ However, even short-term invasive ventilation in animal models of respiratory distress has been associated with lung inflammation and injury,² reduced efficacy of endogenous surfactant,³ and arrest of alveolar growth and development.⁴⁻⁶ Ventilator-induced lung injury (VILI) is characterized by excessive tidal volume (V_T) delivery (volutrauma),⁷ shear injury related to repetitive cycling of distal airways at suboptimal lung volumes (atelectrauma),⁸ and the consequent release of biochemical substances that instigate pulmonary inflammation (biotrauma).⁹ VILI has been implicated as a major factor predisposing neonates to chronic lung disease or bronchopulmonary dysplasia (BPD).^{10,11} Interpreted in a literal sense, the term “VILI” underscores the potentially deleterious effects of other confounding factors within the ventilator system: specifically, the endotracheal tube (ETT).

“Endotrauma is the name given to injury to the airways and lungs from the disruption of homeostasis that occurs during, and sometimes after, artificial ventilation through an ETT.”¹² Although it is difficult to decouple and evaluate the injurious effects related to the ETT from those of the ventilator, the ETT is probably a major factor adding to causal respiratory failure and injury during invasive ventilation. Endotracheal intubation is a traumatic and painful procedure that requires sedation and can be associated with hemodynamic instabilities, airway emergencies, acute airway injury, colonization of the trachea, reduced ciliary movement, secretions, high resistance to air flow, and increased WOB.¹³ The ETT bypasses the glottis and hinders the neonate’s adaptive mechanism (grunting¹⁴) for preserving the end-expiratory lung volume. The ETT also provides a direct route into the lower, sterile airway, which increases the risk of ventilator-associated pneumonia and sepsis.¹⁵

Nasal continuous positive airway pressure (CPAP) is an alternative to invasive ventilation that does not require an ETT and permits spontaneous breathing during continuous pressure applied with prongs in the nares. CPAP improves gas exchange, increases functional residual capacity, stabilizes the chest wall, enhances surfactant production, reduces WOB, and reduces the need for intubation and surfactant replacement therapy.¹⁶ A recent large multicenter randomized controlled trial (RCT)¹⁷ found that premature neonates supported initially with CPAP in the delivery room and given surfactant only for respiratory failure had

less need for invasive ventilation and greater survival without high-frequency oscillatory ventilation (HFOV) or conventional ventilation at 7 days than did neonates assigned to intubation and early surfactant treatment.

CPAP has redefined the care of premature neonates but does not sufficiently off-load the burden of high WOB, nor is CPAP capable of providing effective alveolar ventilation for neonates whose condition worsens. As such, approximately 50–67% of very-low-birth-weight premature neonates supported initially with CPAP develop severe respiratory failure requiring intubation and invasive ventilation.^{17,18} Approximately 25–38% of infants fail CPAP following surfactant administration, resulting in re-intubation and invasive ventilation.^{19,20}

Noninvasive ventilation (NIV) is a form of respiratory assistance that provides a greater level of respiratory support than does CPAP and may prevent intubation in a larger fraction of neonates who would otherwise fail CPAP. In addition to the CPAP effect of the ventilator, the patient’s spontaneous breaths are assisted by patient-triggered (synchronized) or machine-triggered, time-cycled inflations during NIV. NIV has been used successfully in adult and pediatric patients, with oronasal mask and with nasal mask. With advances in ventilator technology and nasal interfaces, clinicians have begun implementing off-label NIV in neonates, often with very little experimental clinical data to guide therapy. The most commonly used NIV modes are intermittent mandatory ventilation (IMV), neurally adjusted ventilatory assist, sigh positive airway pressure, and high-frequency ventilation. This paper reviews these NIV modes, management strategies, and the available evidence related to these interventions.

Proposed Benefits of Noninvasive Ventilation

Short-term application of NIV in neonates is not a new concept in the neonatal respiratory care community. In fact, manual resuscitators affixed with oronasal masks and PEEP valves are commonly used to assist neonates with insufficient respiratory efforts and respiratory failure. The long-term use of automated NIV in neonates was first reported in 1952 by Donald and Lord²¹ in a paper entitled, “Augmented Respiration: Studies in Atelectasis Neonatorum,” nearly 2 decades prior to the initial description of neonatal CPAP by Gregory et al.²² Donald and Lord “amplified spontaneous breathing efforts” in neonates with a setup that included a rubber face mask and a spirometer with a spring-loaded one-way valve that collected and measured exhaled gas. Based on changes in the measured exhaled minute volume (\dot{V}_E), different positive and negative pressures could be applied to the chest wall of the neonate, enclosed in a sealed plethysmograph. Further, the patient could synchronize all of his or her spontaneous respiratory efforts with the applied pressure by deflecting a light beam

from an electrical cell to an adjacent light mirror during inhalation, which triggered the machine. Over the next few decades many negative-pressure ventilators incorporated into isolettes were tried, with less than promising outcomes.²³

Following many failed attempts at providing invasive ventilation with adult-specific ventilators in neonates, Llewelyn et al²⁴ described the often unforeseen complications arising from prolonged endotracheal intubation in 1970:

It has become evident that the advantages of such a technique must be weighed against its complications. Tube displacement and blockage are a constant hazard. Laryngeal edema and loss of ciliated tracheal mucosa with ulceration are common necropsy findings after prolonged intubation, and these predispose to permanent laryngeal and tracheal damage. Infection is readily established in these infants, doubtless due in part to the repeated introduction of suction catheters.

In an effort to avoid intubation but to retain the clinical benefits of positive-pressure ventilation, Llewelyn et al²⁴ and Helmrich et al²⁵ reported separately in 1970 their initial experiences with ventilation applied with a firmly attached oronasal mask, using pressure-cycled intermittent positive-pressure devices and pediatric volume-cycled ventilators. NIV via face mask resulted in better gas exchange, ability to wean oxygen, less lung infection, and less need for invasive ventilation than did standard treatment with oxygen therapy.²⁴ In 1976, Pape et al²⁶ described severe head molding from the straps used to secure the face mask during NIV, especially in preterm neonates < 1,500 g. Although the use of mask NIV reduced the neonatal mortality rate from 75% to 45% in their intensive care unit, this practice was associated with an alarmingly higher rate of cerebellar hemorrhage at autopsy than in neonates supported with invasive ventilation via nasal ETT. Attempts were made during this time to develop new techniques for securing the face mask that would decrease the risk of head molding and consequent neurologic complications during NIV.²⁷

Following the initial description of nasal prongs by Katiwinkler et al²⁸ and Caliumi-Pellegrini et al²⁹ to deliver CPAP, Moretti et al³⁰ described the first successful application of NIV with bi-nasal prongs in preterm neonates with respiratory failure and apnea. The widespread use of NIV was temporarily hampered following the publication of a paper by Garland et al,³¹ who found that neonates ventilated with either oronasal mask or nasal prongs were 30 times more likely to develop gastrointestinal perforations than were neonates ventilated with ETT. Following the advent of neonatal-specific, patient-triggered ventilators, Friedlich et al³² introduced patient-triggered (or syn-



Fig. 1. A premature neonate with bi-nasal short prongs and an improvised chin strap secured with cloth and tape to prevent oral air leakage. (Courtesy of Rose DeKlerk, Vermont Oxford Network.)

chronized) nasal IMV in neonates, and clinicians became interested in using NIV again.

As mentioned previously, the goals of NIV are to assist weak or ineffective spontaneous breathing, avoid endotrauma, and noninvasively support a larger fraction of premature neonates who would otherwise fail CPAP or remain intubated and mechanically ventilated. In theory, minimizing invasive ventilation may reduce BPD and other neonatal complications. In addition to supporting premature neonates with RDS, NIV has been used successfully in neonates with other forms of respiratory failure, including congenital pneumonia, meconium aspiration syndrome, transient tachypnea of the newborn, and neuromuscular disorders. Based on the successes of NIV in neonates, interest in using NIV in larger infants and toddlers with respiratory distress has increased, but these approaches have been hampered by the lack of available nasal airway interfaces designed for this population.

Neonatal nasal airway interfaces and fixation techniques during NIV are similar to those used for CPAP.¹⁶ Bi-nasal short-prongs (Fig. 1) are the most commonly used nasal interface because they impose lower resistance and, hence, less WOB than do ETTs.³³ Obviating the ETT during mechanical ventilation may avoid many of the complications associated with endotrauma, but may not avoid all of the complications associated with VILI. The approach and settings used to manage neonates during NIV are similar to invasive ventilation, so VILI is still a concern during NIV. However, during NIV, a natural lung-protective pressure-relief valve exists via leaky nasal airway interfaces and the oropharynx, which may prevent excessive pressure transmission to the distal airways.¹³ As such, some clini-

cians still prefer nasopharyngeal ETTs, placed 2–3 cm into a single nare during NIV, because the contralateral nare acts as an additional pressure-relief valve that can further vent excessive pressure to the atmosphere more readily than a tracheal tube or bi-nasal prongs. A potential limitation of excessive airway leak during NIV is that sufficient pressure may not be delivered to maintain lung inflation.

Perhaps the greatest known benefit of NIV is that it maintains a higher mean airway pressure than CPAP. This provides a greater ability to recruit collapsed alveoli, maintain end-expiratory lung volume, and improve oxygenation. Providing inflations above CPAP pressure augments V_T and can provide sigh breaths, which may also improve gas exchange and recruit areas of microatelectasis or airway collapse. Additionally, NIV preserves the neonate's natural ability to augment lung volume, because the glottis is unimpeded by an ETT. Neonates who are apneic may not always receive sufficient support from NIV, but NIV should reduce the magnitude and severity of apneas.

In a recent survey, Owen et al³⁴ found that 45% of all neonatal intensive care units (NICUs) in England used some form of NIV to support neonates. How many hospitals in the United States are currently using nasal IMV is unclear, but the results of some compelling new clinical research suggest that this number is likely to be large and growing. The proposed physiologic benefits of NIV as well as management strategies and clinical data, as they relate to the different forms of NIV being used to support neonates with lung disease, are discussed below.

Noninvasive Ventilation Modes in Neonates

Nasal Intermittent Mandatory Ventilation

The most widely used and studied form of NIV in neonates is nasal IMV. Nasal IMV is a useful intermediate strategy for neonates weaning from mechanical ventilation or who cannot be supported by CPAP alone. Nasal IMV embraces spontaneous breathing, with a conventional neonatal ventilator equipped with bi-nasal prongs or a single nasopharyngeal ETT. In some settings, clinicians have also adapted small nasal masks to be used during nasal IMV. The most commonly used mode for nasal IMV is time-cycled, pressure control ventilation, with or without a pre-set constant flow. Similar to CPAP, unassisted spontaneous breathing occurs at a pre-set PEEP level, but mandatory pressure control breaths are either patient-triggered (synchronized) or machine-triggered (non-synchronized).

Although pressure support ventilation (PSV) is commonly used during adult NIV, it is not used to support spontaneous breaths during nasal IMV or as a singular mode during NIV, because it cannot flow-cycle breaths in the presence of a large airway leak. I will only briefly

review the 2 studies that have evaluated the noninvasive application of PSV in infants. In one study,³⁵ a prototype nasal mask was used to apply PSV to larger infants (approximately 4 kg) with respiratory failure. The infants supported with PSV had lower respiratory rates ($P < .001$) and indices of WOB ($P < .01$) than did spontaneously breathing infants given no support.³⁵

The only randomized crossover study in neonates that has evaluated nasal PSV used the IV-200 SAVI ventilator (Sechrist Industries, Anaheim, California) and short bi-nasal prongs.³⁶ Nasal PSV was delivered with the SAVI mode, which is different from conventional PSV. Rather than using a flow signal to trigger and cycle the breath, SAVI triggers and cycles the inspiration based on signals from respiratory inductance plethysmography bands placed on the chest. Nasal PSV did not measurably augment alveolar ventilation, but did provide lower indices of WOB and respiratory effort. The SAVI ventilator is no longer available, and it is unclear whether this form of NIV will appear in future ventilators. Clinical data supportive of the efficacy of nasal PSV are lacking, and conventional flow-triggered, flow-cycled PSV is unlikely to be effective in this population, especially if large leaks are present. Thus, it appears safer and easier to implement IMV, instead of PSV, to assure proper breath-termination during NIV.

Triggering Options. The noninvasive application of machine-triggered IMV involves time-triggered mandatory breaths that may or may not be in phase with the neonate's spontaneous inspiratory or expiratory efforts. Clinicians have often speculated that positive pressure delivered during the expiratory phase may increase the airway pressure beyond the set inspiratory pressure; elicit active expiratory efforts; and increase WOB, the risk of air leak, and gastric insufflation. Owen et al³⁷ evaluated the range and variability of delivered pressure in preterm neonates receiving machine-triggered IMV via bi-nasal short prongs, fitted with chin-strap attachment, and found that airway pressure can vary considerably from the set pressure: approximately 5 cm H₂O less than the pre-set inspiratory pressure 37% and 83% of the time when inspiratory pressure was set at 20 cm H₂O and 25 cm H₂O, respectively. With nasal IMV, only actively moving patients exceeded the set inspiratory pressure 13% and 6% of the time, when inspiratory pressure was set at 20 cm H₂O and 25 cm H₂O, respectively. And 63% of mechanical inflations were delivered during spontaneous exhalation, but airway pressure did not vary according to whether ventilator inflation timing was during spontaneous inspiration or expiration. Many of the current ventilators being used for nasal IMV will automatically limit inspiratory pressure to 2 cm H₂O greater than the set inspiratory pressure. Nonetheless, adjusting the high-pressure limit is important, to assure lung protection and reduce the risk of gastric insufflation during nasal IMV.

Despite not being able to trigger the ventilator, several of the clinical benefits of patient-triggered nasal IMV can still be appreciated with machine-triggered nasal IMV. Patients supported by machine-triggered nasal IMV can usually easily adapt to the ventilator within a short period, especially if the ventilator rate is set to at least 50% of their total respiratory rate.³⁸ The ability to adapt to the inflations is most likely related to stimulation of the Hering-Breuer reflex or mediated by a reflex activated by a jet of gas flow into the nasal passages.³⁹ Older-generation ventilators may have been better suited for this purpose than are current-generation ventilators, which incorporate flow-triggering options and numerous disconnect alarms. Clinicians have circumvented auto-triggering by disabling the set flow and pressure trigger levels; however, many ventilators have disconnect alarms that cannot be silenced in the face of large leaks. There have been anecdotal reports of clinicians bleeding gas into the ventilator's exhalation limb from an auxiliary flow meter to quiet the disconnect alarms, but that practice is not recommended, as it may pose safety risks. Ventilator manufacturers are now releasing FDA-approved modes of neonatal noninvasive IMV, but many of the devices offer only machine-triggered nasal IMV.

Although patient-triggered IMV has been implemented with proximal hot-wire flow sensors³⁸ and pressure sensors placed at the nares, appropriate triggering may be difficult, if not impossible, because of the large positional leaks that can develop between the patient's airway and the nasal interface.⁴⁰ This often results in auto-triggering and/or failed triggering. Additionally, the risks posed by the added weight and dead space from a proximal flow sensor may outweigh the clinical benefits of patient-triggered breaths during nasal IMV. Newer-generation neonatal ventilators incorporate flow-triggering and leak-compensation algorithms that can automatically adjust the trigger level based on large airway leaks. Anecdotal reports suggest that these triggering options work well in premature neonates during nasal IMV, but no data have been published on the trigger performance of these modes during neonatal nasal IMV.

Traditionally, the most commonly used device for patient-triggered nasal IMV has been the Infrasonics Infant Star ventilator (Mallinckrodt, St Louis, Missouri) with the StarSynch module, which incorporates an abdominal pneumatic (Graseby) capsule, attached below the xiphoid process, that detects diaphragm descent, so triggering is independent of oral or nasal leak. The Infant Star ventilator is no longer being supported by the manufacturer, and machine-triggered nasal IMV breath types are being used with apparent success. With the demise of the Infant Star ventilator, clinicians have tried to modify other ventilators to provide patient-triggered nasal IMV with Graseby capsules and respiratory impedance bands.

In theory, patient-triggered nasal IMV is preferred because the inflations are timed with the respiratory effort, and when the glottis is open, the inflations are more likely to be transmitted effectively to the lungs. Patient-triggered nasal IMV may offer several other clinical advantages over machine-triggered IMV for neonates; however, the results of a recent Cochrane meta-analysis concluded that invasive patient-triggered IMV (synchronized IMV) in neonates resulted in shorter duration of ventilation and weaning than did invasive machine-triggered ventilation.⁴¹ It is interesting to note that there were no differences in air leak, BPD, or any other chronic morbidities between neonates supported by these 2 forms of triggered ventilation. However, there have been no studies designed to assess differences in long-term outcomes related to the available noninvasive IMV triggering options.

Chang et al⁴² compared short-term (one-hour) physiologic effects of machine-triggered nasal IMV (20 and 40 breaths/min) and patient-triggered nasal IMV (20 and 40 breaths/min) with CPAP in 16 clinically stable preterm infants. Overall, there were no differences in V_T , \dot{V}_E , gas exchange, chest-wall distortion, apnea, hypoxemia spells, or abdominal girth between the different forms of noninvasive support. Patient-triggered nasal IMV provided lower breathing effort and better infant/ventilator interaction than did machine-triggered IMV or CPAP. These findings were more striking at 40 breaths/min than at 20 breaths/min during nasal IMV. Nonetheless, these differences in ventilator interaction did not appear to affect patient comfort or any other measured variable. Further, the low inspiratory pressure setting (10 cm H₂O) was much lower than is typically used in the clinical setting, and may not have resulted in sufficient pressure transmission the lungs, especially if a leak was present. These findings in part are different from those reported by investigators who supported sicker neonates and with higher inspiratory pressures than those reported in the Chang et al study. The results from the latter studies will be discussed in the next section.

Based on the findings from nearly 2 decades of research evaluating outcomes in patient-triggered ventilation during invasive ventilation, a large clinical trial to compare long-term outcomes in premature neonates supported by machine-triggered or patient-triggered nasal IMV is unlikely to be conducted. Such studies would require a large number of patients and a tremendous amount of time and funding. Anecdotal reports and the limited clinical data available suggest that new modes or ventilator platforms that offer patient-triggered nasal IMV may be preferable, but may not be absolutely necessary at this time.

Physiologic Effects. The physiologic mechanisms by which nasal IMV works in preterm neonates are not fully understood, and whether nasal IMV is more effective than

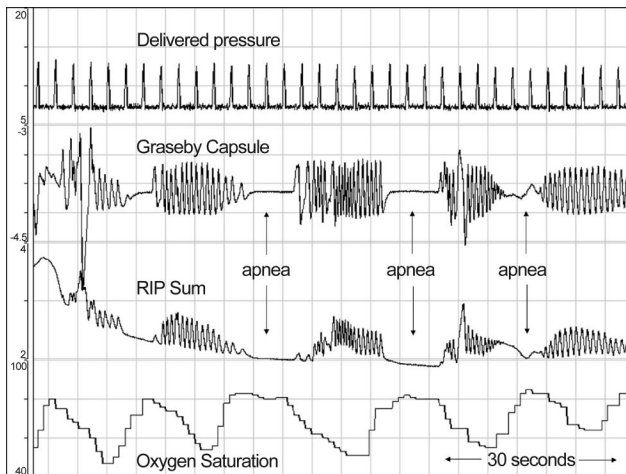


Fig. 2. A 2-min recording showing periodic breathing, stable delivered pressure, and fluctuating oxygen saturation in a premature neonate supported by nasal intermittent mandatory ventilation (IMV) with a set peak inspiratory pressure of 20 cm H₂O and a respiratory rate of 20 inflations per minute. The loss of end-expiratory lung volume, denoted by the decrease in the respiratory impedance pneumography (RIP) sum trace at the onset of apnea suggests central apnea with an open glottis. Based on the absence of chest-wall excursions during apnea, nasal IMV did not sufficiently augment tidal volume, despite the use of a chin strap. (Adapted from Reference 37, with permission.)

CPAP or invasive ventilation is a topic of intense clinical research. In premature neonates, compared to CPAP, patient-triggered nasal IMV has been associated with greater V_T and \dot{V}_E , and reduced thoracoabdominal asynchrony (chest-wall stabilization),⁴³ respiratory rate, gas exchange,⁴⁴ and WOB,^{38,45} but nasal IMV may cause more discomfort due to the high flow rate, local nasal irritation, and asynchrony. In premature neonates, Kugelman et al⁴⁶ found that nasal IMV was associated with higher blood pressure and discomfort score than was unassisted spontaneous breathing. However, Kulkarni et al⁴⁷ found no difference in nutrition intake or weight gain between neonates supported by CPAP versus IMV.

Nasal IMV is more effective than is CPAP in reducing the incidence of apnea in preterm neonates.^{48,49} However, nasal IMV is more likely to prevent apnea than to support a patient who is apneic. Neonates with existing apnea may not always be adequately supported by nasal IMV, because the pressure is not always transmitted to the lungs (Fig. 2), due to large airway leaks, reduced compliance, and/or airway obstruction.^{48,50} The physiologic mechanisms responsible for the notable reductions in central and obstructive apnea are not fully understood. Since nasal IMV provides more support than CPAP, the higher inflation and mean airway pressure improve gas exchange, which can reduce the frequency and severity of central apnea episodes. Nasal IMV also creates higher pharyngeal pressure than does nasal CPAP, and by intermittent infla-

tion of the pharynx, nasal IMV can stent open the airway, activate the dilator muscles of the pharynx, and increase the respiratory drive to abort obstructive apneas.⁴⁸ Additionally, higher inspiratory flow may produce a fast rise in the airway pressure so that the soft palate can be pushed against the tongue and seal the oral cavity, resulting in better breath delivery during an obstructive apnea.³⁰ IMV augments a neonate's spontaneous respiratory effort or increases "sighing," which may be useful for recruiting and maintaining distal air spaces and preventing apnea.

In a report by Lin et al⁴⁸ the chest wall excursions of neonates were monitored during machine-triggered nasal IMV and CPAP, using respiratory impedance bands. A biphasic inspiratory response was observed in infants treated with nasal IMV, indicating that the onset of a positive-pressure breath may induce sighing. A similar reflex was described by Head et al in spontaneously breathing rabbits receiving positive-pressure ventilation, and has since been called "the Head paradoxical maneuver" and is thought to arise from sensors in the lung.⁵¹

Greenough et al^{52,53} reported a similar phenomenon in spontaneously breathing neonates instrumented with an esophageal balloon and supported with invasive ventilation, wherein (Fig. 3) augmented spontaneous inspiratory efforts were provoked at the onset of rapid positive-pressure inflation and were prevalent in preterm neonates with reduced compliance, higher inspiratory pressure, and ventilator rate < 15 breaths/min. They also found that neonates receiving theophylline and those following recovery from chemical paralysis had a higher incidence of this beneficial reflex.^{52,53}

As mentioned previously, the beneficial lung-protective effects of nasal IMV have been attributed to the use of a "leaky" nasal airway interface. Only one animal study has tested the hypothesis that noninvasive IMV results in less lung injury than invasive IMV. Lampland et al⁵⁴ compared differences in pathophysiologic and pathologic conditions in surfactant-deficient, lung-lavaged piglets supported by patient-triggered invasive IMV or noninvasive IMV. Animals from both groups were managed using a standardized ventilator protocol. Animals supported by noninvasive IMV had higher arterial blood gas pH ($P < .001$), lower P_{aCO_2} ($P < .05$), and lower respiratory rate ($P < .001$) than did piglets treated with synchronized IMV. The piglets in the invasive IMV group had a higher ratio of P_{aO_2} to alveolar P_{O_2} ($P < .04$) and more pulmonary interstitial inflammation than did noninvasive IMV treated piglets. The results from this short-term study (6 hours) demonstrate that noninvasive IMV may be less injurious to the lung and provide better ventilation with less need for support than does invasive IMV.

Complications. Many of the same complications that arise during CPAP and invasive ventilation can present

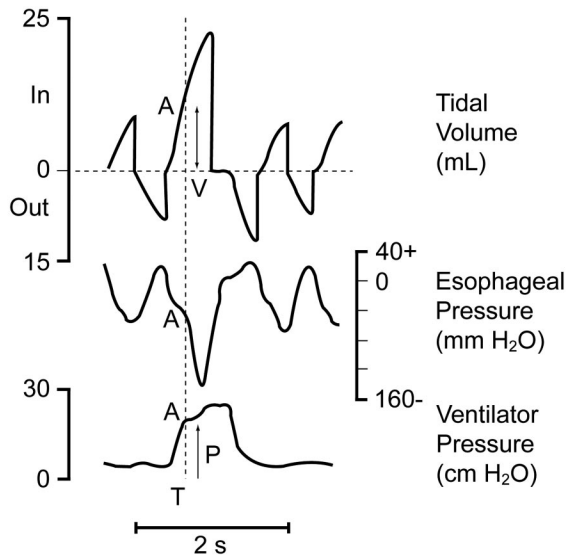


Fig. 3. Provoked augmented inspiratory response in a neonate receiving invasive ventilation. In the tidal volume trace the integrator resets to zero at zero air flow, so an upward deflection represents inspiration and a downward deflection represents expiration. In the esophageal pressure trace, downward deflections (ie, increasing negative pressure) are caused by spontaneous respiratory activity. The provoked augmented inspiration commences at point A, shown by the large deflection in the esophageal trace, during ventilator inflation, which is at least twice the size of that caused by spontaneous (unassisted) inspiration. At point A the volume (V) and the inflating pressure (P) provoke the reflex. T is the time from the start of the inflation to the beginning of the augmented inspiration. A similar response has been observed in neonates receiving nasal IMV. (Adapted from Reference 53, with permission.)

during nasal IMV, and can present with all forms of neonatal NIV. The most frequently reported complication is local irritation and trauma to the nasal septum, which may occur due to misalignment or improper fixation of nasal prongs. This can also result in nasal snubbing and circumferential distortion (widening) of the nares,¹⁶ especially if nasal IMV is being used for more than just a few days. Clinicians have improved the level of nasal care and are more wary of avoiding nasal airway trauma. Cannulaide (Beevers Manufacturing, McMinnville, Oregon) is a tailored hydrocolloid material with an adhesive backing that is fitted over the nose and moustache area to protect skin and prevent nasal breakdown (Fig. 4). The holes on the Cannulaide are a smaller diameter than the nares, so when prongs are placed, the Cannulaide may reduce nasal leak. Owen et al⁵⁵ evaluated the clinical effects prior to and following Cannulaide placement during neonatal nasal IMV and found that the Cannulaide increased airway pressure and resulted in a nonsignificant trend toward fewer desaturations and apneas.

Ramanathan and colleagues have reported successful use of high-flow nasal cannula as a means of avoiding



Fig. 4. Cannulaide (Beevers Manufacturing, McMinnville, Oregon) barrier device being applied to a doll (left) and in use with a premature neonate. (Courtesy of Louise Owen MD.)

complicated fixation techniques and consequent nasal injury during nasal IMV. In an observational cohort, 70 premature neonates were treated with nasal cannula IMV.⁵⁶ All the neonates tolerated nasal cannula IMV, and there were no cases of nasal injury, air leaks, or gastric or eardrum perforation. The nasal cannula IMV failure rate (ie, required re-intubation) was 8%. Nasal cannula IMV has also been evaluated in a realistic neonatal nasal airway/lung model⁵⁷ with infant and intermediate size high-flow nasal cannula (Fisher Paykel, Auckland, New Zealand) and a new prototype nasal cannula (RAM, NeoTech, Valencia, California) which has larger-bore tubing than a standard oxygen or high-flow nasal cannula. The intended purpose of the larger-bore tubing is to reduce resistance so that more pressure can be transmitted to the nares without adding imposed WOB during spontaneous breathing. Despite a nasal airway leak, IMV provided through these hybrid prongs resulted in acceptable pressure and volume delivered to the lung model. Compared with bi-nasal short prongs and nasal masks that are used during NIV, nasal cannula IMV represents a less cumbersome interface that may reduce complications and still provide sufficient ventilatory assistance during IMV.

Like CPAP, gastric insufflation of gases is a frequently reported risk during nasal IMV. In a recent study, anesthetized neonates had gastric insufflation at inspiratory pressures of > 15 cm H₂O during NIV with a manual resuscitator.⁵⁸ However, these neonates were not breathing spontaneously, did not have orogastric or nasogastric tubes in place, and were ventilated with oronasal mask. Inspiratory pressures > 15 cm H₂O probably can be used safely and effectively with bi-nasal prongs during IMV. An orogastric tube is placed to vent insufflated gas from the stomach and decompress the gastrointestinal tract. Abdominal girth should be monitored frequently during nasal IMV to assure that the orogastric tube is working properly.

The major risk from gastric insufflation is gastrointestinal perforation and necrotizing enterocolitis, which have been frequently observed during face-mask NIV in neonates. Despite the use of an orogastric tube, Garland et al³¹ reported gastric perforation in a small series of neonates during IMV via bi-nasal prongs and inspiratory pressure of

approximately 19 cm H₂O (range 10–30 cm H₂O). Based on these findings, it was suggested that “nasal prongs should not be routinely used to ventilate critically ill neonates with respiratory failure.” However, neonates in that study also had chin straps in place to avoid excessive air leak, which may have increased the risk of gastric insufflation and perforation. The next section will review all of the observed complications during clinical studies. In all of these clinical studies, nasal IMV does not place the neonate at any greater reported risk for developing any of the above-mentioned complications than does CPAP.

Clinical Data. Historically, nasal IMV has been used as a means for weaning preterm neonates with apnea from invasive ventilation to CPAP. Today nasal IMV is being implemented in premature neonates with the following strategies:

After Extubation, Following Long-Term Invasive Ventilation. Extubation following prolonged mechanical ventilation is frequently associated with post-extubation respiratory failure due to apneas, atelectasis, hypoxemia, respiratory acidosis, and apnea.³² Compared to extubation to no respiratory support, extubation to CPAP has been associated with lower incidence of respiratory failure, need for mechanical ventilation, and risk of developing BPD in preterm neonates.⁵⁹ However, nearly half of these neonates fail CPAP and require re-intubation.

Nasal IMV is being used immediately following extubation or when a patient is failing CPAP. Clinicians may assess patients for IMV following administration and confirmation of adequate serum aminophylline level, and once the patient has weaned to a mandatory breath rate of 12 breaths/min, inspiratory pressure \leq 23 cm H₂O, PEEP \leq 6 cm H₂O, and F_{IO₂} \leq 0.40.³² Table 1 shows the study designs, devices, initial settings, and outcomes in studies where nasal IMV was used in neonates following extubation from prolonged invasive ventilation.

A Cochrane Collaboration comprehensive systematic review and meta-analysis of randomized trials of nasal IMV in preterm neonates⁶⁰ included 3 studies.^{32,49,61} The objective of the meta-analysis was to determine whether NIV was associated with a lower extubation-failure rate, without adverse effects, in preterm infants extubated following prolonged invasive ventilation than was nasal CPAP. All 3 trials used patient-triggered nasal IMV. The meta-analysis⁶⁰ found statistically significant and clinically important reductions in the risk of meeting extubation failure criteria: typical risk ratio 0.21 (95% CI 0.10–0.45), typical risk difference -0.32 , (95% CI -0.45 to -0.20), number-needed-to-treat 3 (95% CI 2–5). No gastrointestinal perforations were reported in any of the trials. The differences in the rates of chronic lung disease approached but did not reach statistical significance, favoring nasal IMV: typical

risk ratio 0.73 (95% CI 0.49–1.07), typical risk difference -0.15 (95% CI -0.33 to 0.03).

A small retrospective study⁴⁷ that was not included in the Cochrane review⁶⁰ compared outcomes in premature neonates supported by CPAP and patient-triggered nasal IMV following prolonged invasive ventilation. The nasal IMV group had less supplemental oxygen requirement ($P < .02$) and BPD ($P < .01$) than did infants supported by CPAP, and there were no differences in complications related to either form of respiratory support. Another study, by Ryan et al,⁵⁰ reported no differences in apnea, bradycardia, or transcutaneous CO₂ between neonates on nasal IMV versus CPAP. However, that was a short-term study with a small number of patients and used a ventilator that provided only machine-triggered IMV.

After Extubation, Following Surfactant Replacement and Short-Term Invasive Ventilation. One of the primary reasons preterm neonates (< 34 weeks) develop severe respiratory failure with any form of noninvasive respiratory support is that the lungs are incapable of producing and secreting sufficient quantities of mature endogenous surfactant. In recent years the practice of intubation, administering surfactant replacement (10–15 min), and short-term ventilation (usually < 1 h), with extubation to prophylactic CPAP has become a widely applied approach for preterm neonates. A meta-analysis⁶² evaluated outcomes from 6 RCTs to compare early (prophylactic) surfactant administration with brief ventilation versus selective surfactant and continued mechanical ventilation in premature infants with or at risk for RDS. Intubation and early surfactant administration followed by extubation to CPAP was associated with a lower incidence of mechanical ventilation (typical risk ratio 0.67, 95% CI 0.57–0.79), air leak syndromes (typical risk ratio 0.52, 95% CI 0.28–0.96), and infant chronic lung disease (typical risk ratio 0.51, 95% CI 0.26–0.99). Despite this novel approach, neonates still develop respiratory failure while receiving CPAP, which further highlights the need for intermediary forms of respiratory support as an alternative to intubation and invasive ventilation.

Table 2 shows the study designs, devices, initial settings, and outcomes in studies in which nasal IMV was used in neonates following surfactant replacement and short-term ventilation. All but one of these trials used patient-triggered nasal IMV.

Santin et al⁶³ conducted a prospective pilot study that compared outcomes of neonates supported with early nasal IMV (immediately following surfactant and extubation) and later nasal IMV (following surfactant, continued ventilator support, and extubation). The early-nasal IMV infants had shorter duration of ventilation ($P = .001$), less supplemental oxygen requirement ($P = .04$), shorter stay ($P = .04$), and less parenteral nutrition ($P = .002$) than did

Table 1. Clinical Studies That Evaluated Outcomes in Premature Neonates Supported With Nasal IMV Following Prolonged Invasive Ventilation

First Author	Year	Study Design	Ventilator	Nasal Airway Interfaces	Nasal IMV Triggering Mechanism	Initial Settings	Failure Criteria	Outcomes Summary
Friedlich ³²	1999	Prospective RCT CPAP (n = 19) vs nasal IMV (n = 22)	Infant Star	Bi-nasopharyngeal long prongs	Patient-triggered (Graseby abdominal capsule/StarSynch module)	CPAP per clinician Nasal IMV: inspiratory pressure pre-extubation value, PEEP 4–6 cm H ₂ O, respiratory rate 10 breaths/min, F _{IO₂} set to keep S _{pO₂} > 92–95%	pH < 7.25, P _{aCO₂} change of > 25% of pre-extubation value, respiratory rate ≥ 20 breaths/min, inspiratory pressure ≥ 26 cm H ₂ O, PEEP ≥ 8 cm H ₂ O, severe apnea	Less respiratory failure after extubation in the nasal IMV group (5%) than the CPAP group (37%, P = .02). No intestinal perforation or necrotizing enterocolitis in either group
Ryan ⁵⁰	1989	Prospective RCT CPAP vs nasal IMV (n = 20)	Baby Bird	Bi-nasopharyngeal long prongs or nasopharyngeal endotracheal tube	Machine-triggered	CPAP 4 cm H ₂ O Nasal IMV: inspiratory pressure 20 cm H ₂ O, PEEP 4 cm H ₂ O, respiratory rate 20 breaths/min, F _{IO₂} set to keep S _{pO₂} > 92–95%	Not mentioned	No differences between the groups in apnea, bradycardia, or transcutaneous CO ₂
Barrington ⁴⁹	2001	Prospective RCT CPAP (n = 27) vs nasal IMV (n = 27)	Infant Star	Bi-nasal short prongs, orogastric tube	Patient-triggered (Graseby abdominal capsule/StarSynch module)	CPAP 6 cm H ₂ O Nasal IMV: inspiratory pressure 16 cm H ₂ O, PEEP 6 cm H ₂ O, respiratory rate 12 breaths/min, F _{IO₂} set to keep S _{pO₂} > 92%	P _{aCO₂} > 70 mm Hg, F _{IO₂} > 0.70 to maintain S _{pO₂} > 92%, or severe recurrent apnea	Nasal IMV group had a lower incidence of failed extubation and apnea than CPAP group (P < .05). No intestinal perforation or necrotizing enterocolitis in either group
Khalaf ⁶⁰	2001	Prospective RCT CPAP (n = 30) vs nasal IMV (n = 34)	Bear Cub for CPAP Infant Star for nasal IMV	Bi-nasal short prongs	Patient-triggered (Graseby abdominal capsule/StarSynch module)	CPAP 4–6 cm H ₂ O Nasal IMV: inspiratory pressure 2–4 cm H ₂ O > invasive ventilation, PEEP ≤ 5 cm H ₂ O, respiratory rate same as invasive ventilation, flow 8–10 L/min, F _{IO₂} set to keep S _{pO₂} 90–96%	pH < 7.25, P _{aCO₂} > 60 mm Hg, severe apnea with bradycardia, F _{IO₂} to 1.0, or P _{aO₂} < 50 mm Hg despite F _{IO₂} of 1.0	Nasal IMV group had a significantly higher extubation success rate than CPAP group (94% vs 60%, P = .01) at 72 h after extubation
Kulkarni ⁴⁷	2006	Retrospective CPAP (n = 30) vs nasal IMV (n = 30)	Bear Cub for CPAP Infant Star for nasal IMV	Bi-nasal short prongs	Patient-triggered (Graseby abdominal capsule/StarSynch module)	CPAP 4–6 cm H ₂ O Nasal IMV: inspiratory pressure 2–4 cm H ₂ O > ventilation, PEEP ≤ 5 cm H ₂ O, respiratory rate same as invasive ventilation, flow 8–10 L/min, F _{IO₂} set to keep S _{pO₂} 90–96%	pH < 7.25, P _{aCO₂} > 60 mm Hg, severe apnea with bradycardia, F _{IO₂} to 1.0, or P _{aO₂} < 50 mm Hg despite F _{IO₂} of 1.0	Nasal IMV group had less supplemental oxygen requirement (P = .02) and bronchopulmonary dysplasia (P = .01) than CPAP group. No complications

IMV = intermittent mandatory ventilation
RCT = randomized controlled trial
CPAP = continuous positive airway pressure

Table 2. Clinical Studies That Evaluated Outcomes in Premature Neonates Supported With Nasal IMV Following Surfactant Replacement and Short-Term Ventilation

First Author	Year	Study Design	Ventilators	Nasal Airway Interfaces	Nasal IMV Triggering Mechanism	Initial Settings	Failure Criteria	Outcomes Summary
Santin ⁶³	2004	Prospective pilot Nasal IMV immediately after surfactant, (<i>n</i> = 24) vs later nasal IMV following surfactant and prolonged ventilation (<i>n</i> = 35)	Bear Cub for CPAP Infant Star for nasal IMV	Bi-nasopharyngeal (long) prongs	Patient-triggered (Graseby abdominal capsule/StarSynch module)	Nasal IMV: inspiratory pressure 2–4 cm H ₂ O > invasive ventilation, PEEP ≤ 5 cm H ₂ O, respiratory rate same as invasive ventilation, flow 8–10 L/min, F _{IO₂} set to keep S _{pO₂} 90–96%	pH < 7.25, P _a CO ₂ > 60 mm Hg, severe apnea with bradycardia, F _{IO₂} to 1.0, or P _a O ₂ < 50 mm Hg despite F _{IO₂} of 1.0	Early nasal IMV group had shorter duration of ventilation (<i>P</i> = .001), less supplemental oxygen requirement (<i>P</i> = .04), shorter stay (<i>P</i> = .04), and less parenteral nutrition (<i>P</i> = .002) than the later nasal IMV group. No differences in rate of necrotizing enterocolitis or intestinal rupture.
Bhandari ⁶⁴	2007	Prospective RCT Nasal IMV immediately after surfactant (<i>n</i> = 20) vs later nasal IMV following surfactant and prolonged ventilation (<i>n</i> = 21)	Bear Cub or Infant Star for invasive ventilation Infant Star for nasal IMV	Nasopharyngeal (long) prongs, chin straps, pacifiers, large-bore orogastric tube	Patient-triggered, hot-wire for invasive ventilation. Graseby abdominal capsule StarSynch module for nasal IMV	Invasive: inspiratory pressure 16–20 cm H ₂ O, PEEP 4–6 cm H ₂ O, inspiratory time 0.35–0.45 s, respiratory rate 40–60 breaths/min, F _{IO₂} set to keep S _{pO₂} 90–96% Nasal IMV: inspiratory pressure 2–4 cm H ₂ O > invasive ventilation, PEEP ≤ 5 cm H ₂ O, respiratory rate same as invasive ventilation, flow 8–10 L/min, F _{IO₂} set to keep S _{pO₂} 90–96%	pH < 7.25, P _a CO ₂ > 60 mm Hg, severe apnea with bradycardia, F _{IO₂} to 1.0, or P _a O ₂ < 50 mm Hg despite F _{IO₂} of 1.0.	Early nasal IMV group had less BPD/death (52% vs 20%, <i>P</i> = .03) and less BPD (33% vs 10%, <i>P</i> = .04) than later nasal IMV. No complications

(continued)

Table 2. Clinical Studies That Evaluated Outcomes in Premature Neonates Supported With Nasal IMV Following Surfactant Replacement and Short-Term Ventilation (continued)

First Author	Year	Study Design	Ventilators	Nasal Airway Interfaces	Nasal IMV Triggering Mechanism	Initial Settings	Failure Criteria	Outcomes Summary
Bhandari ⁴⁴	2009	Retrospective CPAP (<i>n</i> = 227) vs nasal IMV (<i>n</i> = 242) both as initial form of support and following surfactant/short-term ventilation	Infant Star	Bi-nasal short-prongs, chin strap, pacifier, large-bore orogastric tube	Patient-triggered (Graseby abdominal capsule/StarSynch module)	CPAP 4–6 cm H ₂ O Nasal IMV: inspiratory pressure 2–4 cm H ₂ O > invasive ventilation, PEEP 4 cm H ₂ O, respiratory rate same as invasive ventilation, F _I O ₂ set to keep S _p O ₂ 85–95%, flow 8–10 L/min	Resuscitation and/or respiratory failure necessitating surfactant (F _I O ₂ > 0.4 to keep S _p O ₂ > 90%	Nasal IMV group had lower mean birth weight and gestational age, and a higher incidence of BPD or death (<i>P</i> < .01) than CPAP group. Subgroup analysis (infants 500–700 g): nasal IMV group had less BPD (<i>P</i> = .01), BPD/death (<i>P</i> < .01), neurodevelopmental impairment (<i>P</i> = .04), and neurodevelopmental impairment/death (<i>P</i> = .006) than CPAP group
Sai Sunil Kishore ⁶⁵	2009	Prospective RCT CPAP (<i>n</i> = 39) vs nasal IMV (<i>n</i> = 37), both as initial form of support and following surfactant	VIP Bird or Babylog	Nasopharyngeal endotracheal tube, customized chin strap, orogastric tube	Machine-triggered	CPAP 5 cm H ₂ O, flow 6–7 L/min Nasal IMV: inspiratory pressure 15–16 cm H ₂ O, PEEP 5 cm H ₂ O, inspiratory time 0.3–0.35 s, respiratory rate ~50 breaths/min, flow 6–7 L/min. F _I O ₂ set to keep S _p O ₂ 88–93%	P _a CO ₂ ≥ 60 mm Hg with pH < 7.20, severe apnea, bradycardia, or frequent desaturation (S _p O ₂ ≤ 85%)	Failure rate lower with nasal IMV than CPAP (14% vs 36%, <i>P</i> = .02). Need for intubation and mechanical ventilation by 7 d was less with nasal IMV (19% vs 41%, <i>P</i> = .036). Failure rate with nasal IMV was less in the subgroups of neonates born at 28–30 weeks (<i>P</i> = .02) and who did not receive surfactant (<i>P</i> = .02).

IMV = intermittent mandatory ventilation
CPAP = continuous positive airway pressure
BPD = bronchopulmonary dysplasia

the later-nasal IMV infants. In a similar follow-up prospective randomized study by Bhandari et al,⁶⁴ premature neonates supported by early nasal IMV had less BPD or death (52% vs 20%, $P = .03$) and less BPD (33% vs 10%, $P = .04$) than did the later-nasal IMV neonates.

Bhandari et al⁴⁴ conducted a retrospective study of outcomes in premature neonates supported with CPAP or IMV as an initial form of support immediately following surfactant, short-term ventilation, and extubation. A small number of patients who never received any previous intubation were also enrolled. The nasal IMV group had lower mean birth weight and gestational age, and a higher incidence of BPD or death ($P < .01$) than did the CPAP infants. However, subgroup analysis of the smallest neonates (500–700 g) revealed that the nasal IMV group had less BPD ($P = .01$), combined outcome of BPD/death ($P < .01$), neurodevelopmental impairment ($P = .04$), and combined outcome of neurodevelopmental impairment/death ($P = .006$) than did the infants supported by CPAP. Additionally, P_{aCO_2} was lower on days 7, 21, and 28 in the nasal IMV infants ($P < .01$).

More recently, Kishore et al⁶⁵ conducted a small prospective RCT with a study design similar to that of Bhandari et al.⁴⁴ The extubation failure rate was lower in the nasal IMV group (14% vs 36%, $P = .02$), and the need for intubation and mechanical ventilation by 7 days was less (19% vs 41%, $P = .036$). The failure rate with nasal IMV was lower in the subgroup of neonates born at 28–30 weeks ($P = .02$) who did not receive surfactant ($P = .02$). These studies suggest clinical benefit from early IMV, compared to later nasal IMV or CPAP for the initial form of noninvasive respiratory support following surfactant administration. These data also indicate the need for a large RCT enrolling premature neonates and neonates with other lung diseases.

A common concern is that chin straps may permit delivery of excessive pressure and increase the risk of gastric insufflation and pulmonary air leaks. All but one of the studies,⁶³ discussed above used chin straps or pacifiers to maximize pressure delivery during nasal IMV, in combination with an orogastric tube, and there were no gastrointestinal complications during IMV.

As the Initial Form of Support. A number of studies have been conducted to assess whether differences between CPAP and nasal IMV would be observed in outcomes of premature neonates when initiated prior to intubation, surfactant administration, and mechanical ventilation. The goal of this approach is to eliminate the need for any invasive ventilation. Table 3 shows the study designs, devices, initial settings, and outcomes of studies in which IMV was used as an initial form of support for neonates with clinical signs of respiratory distress and apnea.

Moretti et al³⁰ conducted an observational study wherein 10 premature neonates with moderate apnea and one neonate with progressive respiratory failure were placed on nasal IMV for 5 days. Endotracheal intubation was never performed in any of the patients during the study period, and no evidence of BPD was observed. Lin et al⁴⁸ conducted an RCT in a series of neonates with apnea, who were supported with CPAP or nasal IMV over a 4-hour period. The infants treated with nasal IMV had fewer apneas per hour than the CPAP infants ($P < .02$).

Manzar et al⁶⁶ conducted a prospective pilot study wherein premature neonates with moderate to severe respiratory failure (defined as a respiratory rate of > 60 breaths/min, grunting, nasal flaring, subcostal or intercostal retractions, and a positive chest radiograph) were supported with nasal IMV. Eighty-one percent of the neonates were adequately supported, without needing invasive ventilation. Bisceglia et al⁶⁷ conducted an RCT with neonates with mild to moderate RDS, defined as $F_{IO_2} < 0.4$ for S_{pO_2} of 90–96%, and radiograph suggestive of early hyaline membrane disease (ie, ground glass appearance and air bronchograms). Neonates were randomized to CPAP or IMV. Neonates supported by nasal IMV had lower P_{aCO_2} , less apnea, and a shorter duration of ventilation than the CPAP group ($P < .05$). Kugelman et al⁴⁰ compared CPAP and IMV in a prospective RCT in premature neonates with respiratory distress (tachypnea, grunting, flaring of nostrils, retractions, and radiographic evidence of RDS). In the total cohort, the nasal IMV group had less noninvasive failure ($P = .04$) and a lower BPD rate ($P < .03$).

Obviating invasive ventilation, with or without surfactant replacement, is an attractive option for reducing many of the complications experienced by premature neonates. Although the numbers of neonates enrolled in the studies have been small, nasal IMV appears to be a better alternative than CPAP in neonates with apnea and/or mild to moderate respiratory distress. Additional studies may be useful to evaluate the clinical effects of nasal IMV in neonates with moderate to severe respiratory distress as a rescue strategy, as a primary mode of noninvasive respiratory support, or following CPAP.

Management and Monitoring. A standardized approach to optimize nasal IMV delivery is unknown. Institutions considering nasal IMV for their patient population should consider reviewing the approaches used in clinical studies (see Tables 1–3) or collaborating with individuals from organizations with established management protocols. The ongoing clinical management during nasal IMV depends on careful patient monitoring and clinicians' ability to recognize differences in the pathophysiologic condition with changes in disease severity. Because of the inherently leaky nature of the nasal airway interface, lung mechanics and

Table 3. Clinical Studies That Evaluated Outcomes in Neonates Supported With Nasal IMV as an Initial (Pre-intubation) Form of Support for Premature Neonates With Signs of Respiratory Distress

First Author	Year	Study Design	Ventilators	Nasal Airway Interfaces	Nasal IMV Triggering Mechanism	Initial Settings	Failure Criteria	Outcomes Summary
Moretti ³⁰	1981	Observational Nasal IMV initiated for apnea or severe respiratory distress (<i>n</i> = 10)	Cavitron PV-10	Bi-nasopharyngeal (long) prongs, orogastric tube	Machine-triggered. Some patients given nasal IMV only when apneic on CPAP. Nasal IMV triggered following bradycardia alarm on cardiac monitor	Inspiratory pressure 12–20 cm H ₂ O, PEEP 4–6 cm H ₂ O, respiratory rate 20 breaths/min, F _{IO₂} set to keep S _{PO₂} > 85–95%	None	Endotracheal intubation was never performed in any of the patients during the study period. No evidence of BPD in these neonates
Lin ⁴⁸	1998	Prospective RCT CPAP (<i>n</i> = 16) vs nasal IMV (<i>n</i> = 18)	Bear Cub 750	Bi-nasal short prongs, orogastric tube	Machine-triggered	CPAP 4–6 cm H ₂ O Nasal IMV: inspiratory pressure 12–20 cm H ₂ O, PEEP 4–6 cm H ₂ O, respiratory rate 20 breaths/min, F _{IO₂} set to keep S _{PO₂} > 85–95%	Not mentioned	Nasal IMV group had a greater reduction in apneas per hour than nasal CPAP group (<i>P</i> < .02)
Manzar ⁶⁶	2004	Prospective pilot Early nasal IMV (<i>n</i> = 16)	Dräger Babylog 8000	Bi-nasal short prongs	Machine-triggered	Nasal IMV: inspiratory pressure 18 cm H ₂ O, PEEP 4 cm H ₂ O, respiratory rate 25 breaths/min, F _{IO₂} 0.5, flow 8–10 L/min	F _{IO₂} > 0.60 to keep S _{PO₂} > 90%, P _{aCO₂} > 60 mm Hg, persistent severe apnea	81% of neonates were supported adequately with nasal IMV. No complications related to nasal IMV
Bisceglia ⁶⁷	2007	Prospective RCT CPAP (<i>n</i> = 46) vs nasal IMV (<i>n</i> = 42)	Bear Cub 750	Bi-nasal short prongs	Machine-triggered	CPAP 4–6 cm H ₂ O Nasal IMV: inspiratory pressure 14–20 cm H ₂ O, PEEP 4–6 cm H ₂ O, respiratory rate 40 breaths/min, flow 10 L/min, F _{IO₂} set to keep S _{PO₂} 90–96%	pH < 7.20, P _{aCO₂} > 60 mm Hg, P _{aO₂} < 50 mm Hg	Nasal IMV group had lower P _{aCO₂} , less apnea, and shorter duration of ventilation than CPAP group (<i>P</i> < .05)
Kugelman ⁴⁰	2007	Prospective RCT CPAP (<i>n</i> = 41) vs nasal IMV (<i>n</i> = 43)	SLE 2000	Bi-nasal short prongs	Patient-triggered, airway pressure sensor	CPAP 4–7 cm H ₂ O Nasal IMV: inspiratory pressure 14–20 cm H ₂ O, PEEP 4–7 cm H ₂ O, respiratory rate 12–30 breaths/min, inspiratory time 0.3 s, F _{IO₂} set to keep S _{PO₂} 88–92%	pH > 7.20 and P _{aCO₂} > 60 mm Hg, or P _{aO₂} < 50 mm Hg, or S _{PO₂} > 88% on F _{IO₂} > 0.50, or recurrent substantial apnea	Nasal IMV group had less noninvasive failure (<i>P</i> = .04) and lower BPD rate (<i>P</i> < .03) than CPAP group

(continued)

Table 3. Clinical Studies That Evaluated Outcomes in Neonates Supported With Nasal IMV as an Initial (Pre-intubation) Form of Support for Premature Neonates With Signs of Respiratory Distress (continued)

First Author	Year	Study Design	Ventilators	Nasal Airway Interfaces	Nasal IMV Triggering Mechanism	Initial Settings	Failure Criteria	Outcomes Summary
Bhandari ⁴⁴	2009	Retrospective CPAP (<i>n</i> = 227) vs nasal IMV (<i>n</i> = 242); both as initial form of support and following surfactant/short-term ventilation	Infant Star	Bi-nasal short-prongs, chin strap, pacifier, large-bore orogastric tube	Patient-triggered (Graseby abdominal capsule/StarSynch module)	CPAP 4–6 cm H ₂ O Nasal IMV: inspiratory pressure 2–4 cm H ₂ O > invasive ventilation, PEEP 4 cm H ₂ O, respiratory rate same as invasive ventilation, F _{IO₂} set to keep S _{PO₂} 85–95%, flow 8–10 L/min	Resuscitation and/or respiratory failure necessitating surfactant, F _{IO₂} > 0.4 to keep S _{PO₂} > 90%	Nasal IMV group had lower mean birth weight and gestational age, and a higher incidence of BPD or death (<i>P</i> < .01) than CPAP group. Subgroup analysis of infants 500–700 g: nasal IMV group had less BPD (<i>P</i> = .01), BPD/death (<i>P</i> < .01), neurodevelopmental impairment (<i>P</i> = .04), and neurodevelopmental impairment/death (<i>P</i> = .006) than CPAP group
Sai Sunil Kishore ⁶⁵	2009	Prospective RCT CPAP (<i>n</i> = 39) vs nasal IMV (<i>n</i> = 37), both as initial form of support and following surfactant	VIP Bird or Babylog	Nasopharyngeal endotracheal tube, customized chin strap, orogastric tube	Machine-triggered	CPAP 5 cm H ₂ O, flow 6–7 L/min Nasal IMV: inspiratory pressure 15–16, PEEP 5, inspiratory time 0.3–0.35 s, respiratory rate ~50 breaths/min, flow 6–7 L/min. F _{IO₂} set to keep S _{PO₂} 88–93%.	P _{aCO₂} ≥ 60 mm Hg with pH < 7.20, severe apnea, bradycardia, or frequent desaturation (S _{PO₂} ≤ 85%)	Failure rate was lower with nasal IMV than CPAP (14% vs 36%, <i>P</i> = .02). Need for intubation and mechanical ventilation by 7 d was less with nasal IMV (19% vs 41%, <i>P</i> = .036). Failure rate with nasal IMV was less in the subgroups born at 28–30 weeks (<i>P</i> = .02) who did not receive surfactant (<i>P</i> = .02).

IMV = intermittent mandatory ventilation
CPAP = nasal continuous positive airway pressure
RCT = randomized controlled trial
BPD = bronchopulmonary dysplasia

end-expiratory lung volume are not easily measured at the bedside during nasal IMV, so lung recruitment is assessed more on changes in respiratory distress, chest-wall expansion, WOB, and gas exchange. Some institutions use a respiratory scoring system such as the Silverman-Anderson score to evaluate respiratory distress and manage respiratory support and patient comfort.⁶⁵ Chest radiograph may be useful to diagnose changes in patient condition, but is a poor surrogate for determining lung inflation. Transcutaneous CO₂ monitoring and pulse oximetry may offer reliable correlates for determining gas exchange in patients supported by nasal IMV and are preferable to repeated analysis of blood samples, as long as correlation with blood gas values has been confirmed.

Few reports suggest a standardized weaning approach to nasal IMV, but some evidence suggests weaning, once neonates are at ventilator settings of PIP/PEEP 14/4 cm H₂O, respiratory rate of ≤ 20 breaths/min, and F_{IO₂} ≤ 0.3 , with acceptable blood gas values.⁶³ The patient can then be transitioned to CPAP or high-flow nasal cannula.⁶⁵

Not all neonates can be supported by nasal IMV alone, and intubation is indicated for severe ventilatory impairment (pH < 7.25 , P_{aCO₂} > 60 mm Hg), refractory hypoxemia (P_{aO₂} < 50 mm Hg on F_{IO₂} of > 0.6), and frequent apnea that does not respond to stimulation or intravenous caffeine therapy during IMV.⁶⁴ No consensus exists on determining the maximal settings during nasal IMV. Owen et al⁵⁵ showed that increasing the inspiratory pressure during nasal IMV may not always result in a linear increase in delivered pressure at the nasal airway interface. When inspiratory pressure was increased from 20 to 25 cm H₂O, the pressure increase at the nasal prongs was only 1.3 cm H₂O. In fact, one of the most likely reasons neonates fail nasal IMV is related to poor pressure transmission applied to the lungs, because of an inadequate seal between the tongue and soft palate,⁵⁰ nasal airway interface, or as a consequence of the asynchrony that often occurs. As lung compliance decreases, a larger leak can develop. In some cases, upsizing the nasal prongs using a chin-strap, Cannulaide, or pacifier, may prevent excessive leak and improve pressure delivery in patients who are deteriorating on nasal IMV.⁴⁴

Nasal Neurally Adjusted Ventilatory Assist

Nasal neurally adjusted ventilatory assist (NAVA) is a novel form of noninvasive respiratory support that uses the electrical activity of the diaphragm (EAdi) to determine the timing and magnitude of inspiratory pressure delivery during spontaneous breathing. The EAdi signal is obtained with an indwelling 5.5 French feeding tube equipped with 10 electrodes. The tube is placed in the esophagus so that the electrodes are at the level of the diaphragm.^{68,69} When

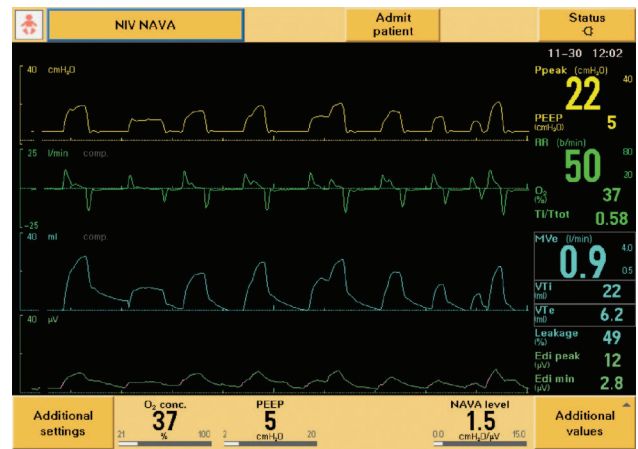


Fig. 5. Example ventilator screen during nasal neurally adjusted ventilatory assist in a premature neonate (23 weeks gestational age, 560 g) with respiratory distress syndrome. The yellow, green, blue, and gray lines represent airway pressure, flow, volume, and electrical activity of the diaphragm (Edi) signal, respectively. The inspiratory pressure, trigger, and cycle is proportional to the Edi, and is captured with every spontaneous effort made by the patient. (Courtesy of Robert Tero RRT-NPS.)

positioned properly, the electrodes and consequent EAdi signal can accurately and reliably trigger and cycle a positive-pressure breath, independent of airway leak. Additionally, the magnitude of the inspiratory pressure assist is a product of the EAdi signal and the pre-set NAVA level.^{68,69} This feature has been available as an invasive mode with the Servo-i ventilator (Maquet, Solna, Sweden) for about 2 years, but was FDA approved for noninvasive application only recently. Nasal NAVA appears to work well, even in the smallest of patients. Figure 5 shows Servo-i ventilator graphics from a very-low birth-weight premature neonate during nasal NAVA.

NAVA has many proposed advantages over nasal IMV; however, only 2 reports have been published, from short-term studies that evaluated patient-ventilator interaction during nasal NAVA. There have been no studies evaluating long-term outcomes in premature neonates on IMV, but many studies are underway.

Beck et al⁶⁸ conducted a prospective controlled experiment in 10 lung-lavaged, spontaneously breathing juvenile rabbits. Following lung lavages the animals sequentially underwent (1) NAVA level 1 during invasive ventilation, with and without PEEP, (2) extubation with no support, and (3) NAVA with a single nasal prong, with progressively increasing NAVA levels and no PEEP. Blood gases, hemodynamics, and esophageal pressures were measured at each condition. Despite extremely leaky nasal airway interfaces (approximately 75% leak), no differences were observed in the animals' abilities to initiate and cycle breaths between invasive and noninvasive NAVA. In addition, no differences were observed in gas exchange or

gastric insufflation of gases during the study period. A nearly 4-fold increase in the NAVA level allowed the animals' spontaneous breathing efforts to be restored to the pre-extubation values. This required inspiratory pressure of approximately 15 cm H₂O. In these hypoxemic animals, NAVA appears to be a reasonable NIV approach for unloading the respiratory system, promoting gas exchange, and improving synchrony, independent of leak.

A similar study by Beck et al⁶⁹ was performed in 7 human premature neonates (25–29 weeks gestational age) with resolving lung disease and who were ready to be extubated. In the first phase of the study, a NAVA catheter was placed, and airway pressure and EAdi were measured during a 60-min period on a conventional ventilator. The neonates were then placed on invasive NAVA at a level that provided airway pressure similar to that of conventional ventilation. Following a short period of NAVA, the neonates were extubated and supported with NAVA via a single nasal prong and at similar NAVA as when they were extubated. No PEEP was used because of excessive leak during NAVA. NAVA resulted in lower mean airway pressure ($P = .002$) and higher oxygen requirement ($P = .003$) than did the other testing conditions, due to poor pressure transmission from the leak. Interestingly, NAVA (without PEEP) resulted in a lower neural respiratory rate ($P = .004$), less breath-cycling delay, and better correlation between EAdi and airway pressure ($P < .001$) than did invasive ventilation. This short-term study identifies nasal NAVA as a reasonable way to support spontaneously breathing premature neonates following and potentially prior to intubation.

Similar to other forms of NIV, NAVA requires that the patient is breathing spontaneously. Premature neonates who are apneic may not be able to be supported by nasal NAVA, even with use of a back-up ventilator mode. These published studies were performed with a prototype Servo 300 ventilator (Maquet, Solna, Sweden), and NAVA is currently commercially available only on the Servo-i ventilator. Nasal NAVA is an invasive mode, requires frequent bedside attendance, and is relatively expensive. Future studies with larger numbers of neonates will help to assess outcomes to evaluate NAVA as a standard NIV approach for supporting neonates with lung disease.

Sigh Continuous Positive Airway Pressure

The Infant Flow nasal “sigh” positive airway pressure (SiPAP) device (Carefusion, Yorba Linda, California) is a second-generation noninvasive respiratory support device, similar to the Infant Flow Advance that is being used in Europe. This device is being implemented more frequently in NICUs to assist spontaneously breathing neonates with lung disease and apnea. Infant Flow SiPAP uses the same nasal prongs, mask, fixation, and fluidic-flip mechanism

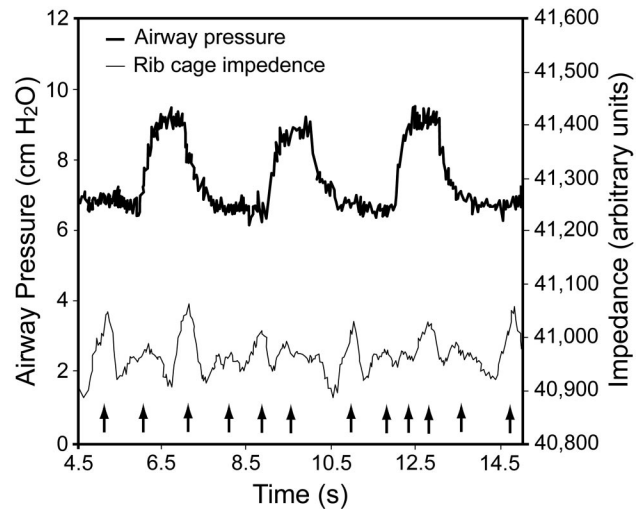


Fig. 6. Example airway pressure and rib-cage impedance in a premature infant supported with the biphasic mode of SiPAP (“sigh” positive airway pressure) from the Infant Flow nasal continuous positive airway pressure system. The arrows indicate patient-initiated breaths. (From Reference 70, with permission.)

used in Infant Flow nasal CPAP. SiPAP differs from other forms of NIV in that it allows the neonate to breathe continuously at 2 separate CPAP levels. The primary CPAP level is set at 4–6 cm H₂O by adjusting flow through a flow meter, and airway pressure is displayed by an internal manometer. The secondary CPAP level or “sigh” is set with a second flow meter, to obtain a pressure 2–4 cm H₂O higher than the baseline CPAP setting. The breath-hold is adjusted to between 0.5 second and 2 seconds, and the respiratory rate controls the frequency of intermittent “sigh” breaths (Fig. 6).

In combination with spontaneous breathing, these “sighs” are intended to recruit unstable air spaces, maintain end-expiratory lung volume, avoid apnea, and reduce the need for invasive ventilation. Alveolar ventilation depends on both the neonate’s spontaneous \dot{V}_E and the \dot{V}_E created by SiPAP transitioning between the 2 CPAP levels. Outside the United States, SiPAP allows patient-triggered SiPAP breaths triggered with a Graseby capsule placed on the abdomen. In the United States, the Graseby capsule is used only to monitor respiratory rate. The rise in pressure from the primary CPAP level to the secondary CPAP level is gradual and differs from pressure support provided by conventional ventilators. Whether patient-triggering will be made available is unclear. Nonetheless, investigators are evaluating the effectiveness and physiologic benefits related to patient-triggering with this form of support.

In a small observational study, SiPAP provided better gas exchange than did standard CPAP in preterm infants.⁷¹ Ancora et al⁷² retrospectively evaluated whether SiPAP following surfactant administration and brief ventilation would prevent re-intubation and mechanical ventilation in

preterm neonates. Neonates in the historical control group ($n = 22$) were supported with 4–6 cm H₂O CPAP, and neonates in the SiPAP group ($n = 38$) were managed using primary CPAP at 4–6 cm H₂O and secondary CPAP at 5–8 cm H₂O; time high was 0.5–0.6 second, and the respiratory rate was 10–30 cycles/min. The need for mechanical ventilation was greater in the historical control group than in the infants supported with SiPAP (27% vs 0%, $P = .001$). The mothers of the infants in the SiPAP group had received antenatal steroids more frequently than had the historical control infants ($P = .003$), which may help explain why re-intubation was not needed in the SiPAP infants. Nonetheless, SiPAP, combined with antenatal steroids and surfactant, appears to be an attractive initial clinical approach for preterm neonates.

In a prospective RCT, Lista et al⁷³ compared outcomes in preterm neonates who received either CPAP ($n = 20$) or SiPAP ($n = 20$) as the initial form of support in the acute phase of RDS. All the infants received sustained lung inflations in the delivery room and surfactant (as needed), with immediate extubation. Neonates in the CPAP group were supported with CPAP 6 cm H₂O, and the settings in the SiPAP group were adjusted to provide similar mean airway pressure. Infants supported by SiPAP had shorter duration of mechanical ventilation ($P = .03$), less O₂ dependence ($P = .03$), and were discharged sooner ($P = .02$) with similar serum levels of pro-inflammatory cytokines (interleukin 6, interleukin 8, tumor necrosis factor alpha), as did the infants supported initially with CPAP. The study suggests that SiPAP is a more beneficial form of noninvasive support than is nasal CPAP at similar mean airway pressure, without increasing lung injury.

Nasal High-Frequency Ventilation

Invasive high-frequency ventilation is a form of lung-protective ventilation that is commonly used in neonates with lung disease, as an initial ventilation strategy or as a rescue intervention if a neonate fails conventional ventilation. In a premature baboon model, long-term HFOV resulted in better pulmonary mechanics, consistently more uniform lung inflation, and less pulmonary inflammation than did conventional ventilation with a low- V_T strategy.⁷⁴

In a recent meta-analysis⁷⁵ of RCTs that compared outcomes in neonates supported by different forms of high-frequency ventilation or conventional ventilation, there were no differences in infant chronic lung disease, mortality, or neurological insult. However, when randomization occurred earlier (1–4 h), HFOV was associated with less death or BPD than was conventional ventilation ($P = .01$).

Over the last 5 years, nasal high-frequency ventilation (HFV) has been used more commonly in clinical practice as a form of NIV. Unlike nasal IMV and SiPAP, nasal

HFV uses lower pressure and smaller volume at higher frequency, and may be more lung-protective than are other higher-pressure NIV modes. The most common ventilator used to apply nasal HFV is the Infrasonics Infant Star. Nasal HFV is applied via either nasopharyngeal ETT or bi-nasal prongs with fixation.

The physiologic mechanism through which nasal HFV supports spontaneously breathing neonates with RDS is unclear. Nasal HFV may improve gas exchange by providing higher mean airway pressure and pneumatic stenting of the laryngeal structures. The effects of high-frequency, small-amplitude pressure oscillations applied via nasal mask have been observed in healthy adults and in adults with obstructive sleep apnea.⁷⁶ The most important finding from that study was that pressure oscillations were associated with a partial or complete reversal of the upper-airway obstruction and V_T increase. Those authors concluded that upper-airway receptors were responding to the low-pressure, high-frequency oscillations, with input to the genioglossus and other muscles of respiration. These responses may be important for improving ventilation and reducing the adverse effects of obstructive apnea during nasal HFV in neonates.

In a case study, Hoehn et al⁷⁷ described the first successful application of nasal HFV in an extremely-low-birth-weight (760 g) preterm (27 weeks gestational age) neonate with severe CO₂ retention, acidemia, and respiratory distress. Re-intubation was avoided and P_{aCO_2} and pH dramatically improved. The improvements in alveolar ventilation were probably related to the high-frequency pressure oscillations, which may enhance gas mixing in the upper airways through the process of facilitated augmented diffusion. Other proposed gas-exchange mechanisms have been described during nasal HFV that may not be present during conventional ventilation.⁷⁸

In a recent animal study, Reyburn et al⁷⁹ tested the hypothesis that nasal HFV would result in less lung injury and better alveolar development than are observed with conventional invasive IMV. Two groups of premature lambs were administered surfactant, randomized to nasal HFV or invasive conventional ventilation, and supported for a 3-day period. The invasive conventional ventilation group was managed with a respiratory rate of 60 cycles/min, inspiratory time of 0.3 s, V_T of 7 mL/kg, and PEEP of 8 cm H₂O. The nasal HFV group was managed with high-frequency percussive ventilation (VDR3, Percussionaire, Bird Technologies, Sandpoint, Idaho) attached to a nasopharyngeal tube placed into a single nare. The initial settings were amplitude 20–25 cm H₂O, mean airway pressure 8–12 cm H₂O, and frequency 10 Hz. The 2 groups had similar gas-exchange goals, which guided subsequent ventilator adjustments and weaning over the study period. Nasal HFV resulted in smaller and more uniformly inflated terminal respiratory units and distal air spaces, lon-

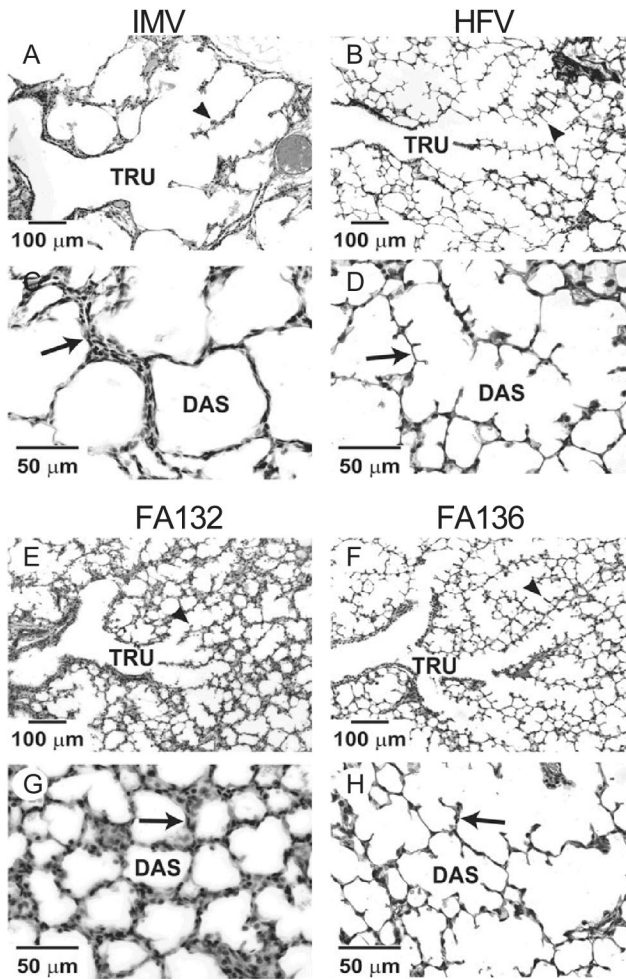


Fig. 7. Histology of lung tissue from preterm lambs ventilated for 3 days with invasive intermittent mandatory ventilation (IMV) (A and C) or noninvasively with nasal high-frequency ventilation (HFV) (B and D). Each row of panels has the same magnification (see scale bars). The gestation control fetal lambs were (1) delivered at the gestation age that the preterm lambs were delivered (FA132) or (2) delivered at the gestation age when the preterm lamb studies were completed (FA136). The terminal respiratory unit (TRUs) in the preterm lambs that received nasal HFV (B and D) have smaller and more uniform distal air spaces (DASs), more and thinner alveolar secondary septa (arrowhead in A and B), and thinner distal air-space walls (arrow in C and D) than the TRUs in the preterm lambs that received IMV (A and C). The TRUs in the preterm lambs that received nasal HFV are structurally similar to the TRUs in the FA136 gestation control lambs (F and H). On the other hand, the TRUs in the preterm lambs that received IMV (A and C) are structurally similar to the TRUs in the FA132 gestation control lambs (E and G). (From Reference 79, with permission.)

ger alveolar secondary septae, and thinner distal air-space walls than did invasive conventional ventilation ($P = .005$, Fig. 7). This implies that short-term nasal HFV may optimize lung recruitment and promote normal alveolarization in preterm lungs better than does a “gentle” invasive ventilation strategy. Additionally, at days 2 and 3, lower F_{IO_2} was required during nasal HFV than during invasive ventilation ($P = .005$).

Of particular interest was the fact that the investigators measured intratracheal pressure in the animals receiving nasal HFV, and the delivered pressure averaged only 0.37 ± 0.23 cm H_2O . These data imply a large leak at the nasal airway interface with the nasopharyngeal ETT. Whether bi-nasal prongs are more effective in providing ventilation is not resolved by these data. Conversely, it is unclear whether using bi-nasal prongs during HFV results in greater volutrauma, gas trapping, and lung injury and less favorable alveolarization than does HFV via nasopharyngeal ETT.

Unfortunately, nasal HFV is such a new form of NIV that very few data are available to suggest a long-term management strategy in neonatal patients. Short-term observational studies have suggested initial mean airway pressure set to equal the previous CPAP, frequency set at 10 Hz, amplitude adjusted to obtain visible chest-wall vibration and increased every 30 min by 4–6 units, if necessary, to maintain clinically appropriate chest-wall vibration, transcutaneous CO_2 , or blood gas values.^{80,81}

Clinical responses to HFV in preterm neonates in 2 small studies have been reported. Van der Hoeven et al⁷⁹ placed 21 preterm and term infants with moderate respiratory insufficiency on nasal HFV following CPAP. A nasopharyngeal ETT was placed 3–4 cm into a single nare, and HFV was provided with the Infant Star ventilator in the high-frequency flow-interrupter mode, with mean airway pressure settings similar to or higher than the previous CPAP setting, frequency of 10 Hz; amplitude was increased until chest-wall oscillations were observed. Initiation of HFV following CPAP resulted in a small reduction in P_{aCO_2} ($P = .001$) but no significant change in pH. Five (23%) of the patients failed nasal HFV and required invasive ventilation related to severe RDS, sepsis, and apnea.

Colaizy et al⁸¹ performed a similar observational study to compare the clinical effects of nasal HFV to CPAP in neonates with mild to moderate lung disease. All 14 subjects were very-low-birth-weight infants ($< 1,500$ g) who were transitioned from CPAP to HFV via nasopharyngeal ETT, with the Infant Star ventilator in the high-frequency, flow-interrupter mode. The investigators used an approach similar to that of van der Hoeven et al,⁸⁰ for 2 hours. After 2 hours of nasal HFV, capillary blood gases were measured and the subjects were returned to their pre-study CPAP settings. Nasal HFV decreased mean transcutaneous P_{CO_2} from 50 mm Hg to 45 mm Hg ($P = .01$) and increased pH from 7.40 to 7.37 ($P = .04$). In all the infants, chest radiograph obtained 1 hour after nasal HFV provided no evidence of hyperinflation.

Dumas de la Roque et al⁸² performed a prospective RCT of nasal CPAP versus nasal HFV in 40 term neonates with respiratory distress shortly after cesarean section. This was the first short-term prospective study to describe nasal HFV as an initial form of noninvasive respiratory support

in neonates. Neonates randomized to CPAP were supported with 5 cm of CPAP, and neonates in the nasal HFV group were supported with the VDR3 high-frequency percussion device, with an initial mean airway pressure of 5 cm H₂O and a frequency of 5 Hz. The groups had similar oxygenation goals, and the settings were not changed throughout the study period. Lung disease resolved in all the neonates within 10 hours, but the nasal HFV group had shorter duration of respiratory distress, lower oxygen therapy level, and shorter oxygen therapy duration ($P < .001$) than did the CPAP group.

Some clinicians are concerned that pressure oscillations delivered out of phase with the neonate's spontaneous breathing efforts may impose high WOB. Although the complex interplay between spontaneous breathing and HFV has not been described in the literature, van Heerde et al⁸³ found a low imposed WOB during invasive HFOV, with the 3100A HFOV ventilator (Carefusion, Yorba Linda, California) in a simulated spontaneously breathing neonate. How these data would compare to bi-nasal prongs or a nasopharyngeal ETT is unclear, but the effects are not likely to be similar due to the inherently leaky nature and lower imposed resistances of these nasal airway interfaces. Carlo⁸⁴ has suggested that a potential advantage of nasal HFV over IMV is that synchronization is not necessary, due to the relatively high frequencies. However, studies to test this hypothesis in neonates are needed.

The widespread use of nasal HFV in neonates with broadly different lung diseases cannot be suggested at this time, but HFV appears to be an NIV mode that will be evaluated in future clinical trials. The majority of the aforementioned studies were in animals and humans and used high-frequency flow-interrupter or high-frequency percussive ventilation strategies, and the most frequently used of those devices, the Infant Star ventilator, is now obsolete. As such, there is interest in using nasal HFV with the widely used 3100A HFOV ventilator. Whether this ventilator has been used off-label to provide HFV in neonates is unclear. The ventilator circuit is more rigid than are standard ventilator circuits, which creates difficulties in interfacing with nasal prongs without causing unnecessary torque on the neonate's airway. Further, the 3100A has a pressure-relief ("dump") valve that is activated by electronic and pneumatic controls that open the patient circuit to ambient air when the measured mean airway pressure reaches $< 20\%$ of the maximum set mean airway pressure. This factor may be a limitation in spontaneously breathing neonates using mean airway pressure (approximately 5 cm H₂O) similar to those previously described in short-term human neonatal HFV studies.

De Luca et al⁸⁵ evaluated the effect of ventilation parameters during nasal HFOV in a bench study with the 3100A HFOV ventilator. Nasal HFOV was applied to a neonatal test lung with a prototype adapter/circuit and bi-

nasal short prongs (Argyle CPAP nasal cannula, Sherwood Medical, St Louis, Missouri) of 2 different diameters (large and small), without a leak. Oscillatory volume, \dot{V}_E , and mean airway pressure were measured at several mean airway pressures and Hz settings. The power level was adjusted to obtain an amplitude of 45 cm H₂O for the entire study. Data from HFV were compared to a "control circuit" invasive HFOV simulation, wherein the HFOV circuit was attached directly to the neonatal lung model (without prongs or an ETT). The pressure drops between the nasal airway and test lung were calculated as $38.5 \pm 10.9\%$, $35.3 \pm 10.1\%$, and $22.1 \pm 10.4\%$, for the small prongs, large prongs, and control circuit, respectively. V_T was 0.4 ± 0.1 , 0.9 ± 0.3 , and 1.5 ± 0.5 for small prong, large prong, and the control circuit, respectively. The pressure delivered to the neonatal lung via the bi-nasal prongs in that study are much larger than those observed by Reyburn et al,⁷⁹ when tracheal pressure was measured in preterm lambs. Conversely, data from the bench study were obtained in the absence of a leak. These differences warrant further investigation, to compare the effects of gas trapping and lung injury between nasopharyngeal ETT and short bi-nasal prong interfaces during HFV.

Based on these small, short-term studies, nasal HFV appears to be technically possible in preterm neonates. However, more bench and animal studies are needed, using different nasal airway interfaces with the available high-frequency ventilators, before long-term studies are performed in human neonates with severe lung disease.

Bubble CPAP is a form of noninvasive respiratory support that is being called "inexpensive nasal HFV," because the bubbling in the water-seal creates small-amplitude, high-frequency oscillations that are transmitted to the nasal airway interface of spontaneously breathing neonates. Animal studies^{86,87} and studies in human neonates⁸⁸ have shown that bubble CPAP may result in better alveolar ventilation and lung recruitment than conventional (ventilator-derived) CPAP. However, those studies were conducted in subjects who were endotracheally intubated, and no studies have evaluated these physiologic effects in subjects with a leaky nasal airway interface. In a recent bench test, bubble CPAP, applied with leaky bi-nasal short prongs, resulted in measureable volume oscillations (approximately 0.5–0.6 mL) delivered to a neonatal nasal airway/test lung.⁸⁹ Clinicians often increase the bias flow to increase the amplitude and frequency of airway pressure oscillations during bubble CPAP, but this practice has not been shown to enhance gas exchange or lung recruitment.⁹⁰

In 2010, 2 reports appeared^{91,92} of a novel high-amplitude bubble-CPAP system that can provide a greater level of NIV support than conventional bubble CPAP alone. Controlling the angle through which gas exits, the bubble-CPAP water-seal column was reported to enhance greatly the airway-pressure oscillations at the nasal airway inter-

face, thus providing flexibility to meet the differing requirements of patients with differing levels of respiratory distress. In a neonatal lung model with leaky nasal prongs, the high-amplitude bubble-CPAP device adjusted with the outlet tubing at 135°, in relation to the water surface level, delivered V_T similar to that previously measured during HFOV in infants.⁹³ In addition, high-amplitude bubble CPAP provided noninvasive support, via bi-nasal prongs, to spontaneously breathing, lung-lavaged juvenile rabbits with lower WOB ($P < .001$) and higher P_{aO_2} ($P = .007$) than were observed in the same animals supported with bubble CPAP at identical mean airway pressures.⁹¹ Two rabbits supported by high-amplitude bubble CPAP became apneic, with normal P_{aCO_2} and vital signs. High-amplitude bubble CPAP may represent a relatively simple new strategy for supporting a greater fraction of neonates who would otherwise fail CPAP and require invasive ventilation. Neonatal clinical trials are needed to test this hypothesis.

Summary

The prevailing message from this comprehensive review suggests that there is a large population of neonatal patients who cannot be supported by CPAP, and the clinical consensus is that invasive ventilation should be avoided at “all cost” to the patient. The advent of neonatal airway interfaces has ushered in a whole new generation of NIV strategies for neonatal patients, specifically those affected by RDS. In the not so distant future, clinicians may rely more on IMV, SiPAP, NAVA, and HFV as the established initial NIV approach for supporting infants at risk for developing most forms of neonatal respiratory distress. It is unlikely that these strategies will completely obviate invasive ventilation, but they may reduce the need for repeated intubation and prolonged ventilation, and so may reduce the numerous complications that affect this sensitive patient population. While still early in its inception, clinicians will need further clinical research to determine the “best” form of NIV that satisfies their patient population and embraces development of disease-specific management strategies.

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Discussion

Willson: Would you say more about the nasal cannula you invented? I think the interface is a big issue for NIV, not only in newborns but in our population as well, and we've not had anybody address that. It's fascinating to me that with just a small design change it looks like you're a lot more successful.

DiBlasi: The RAM nasal cannula [NeoTech Products, Valencia, California] was invented by Drs Heyman and Ramanathan. I was involved with some of the design work and research. It will be commercially available in October 2011. It differs from standard oxygen cannula and high-flow nasal cannula in having wider-bore tubing and soft silicone bi-nasal prongs that are similar in size to those used during nasal CPAP. The advantage is that more pressure can be transmitted to the lungs with this cannula during nasal IMV than with standard high-flow nasal cannula, and without the cumbersome fixation techniques that are often required with nasal CPAP prongs.

My concern with developing larger-bore prongs for larger infants or small children is that they would have to be made quite large to transmit pressure to the child's airways, and therefore might not be light enough to interface as a "simple" nasal cannula and would probably require a cap or straps. I believe that folks have already begun working on such devices for toddlers and small children. I am also concerned by the resistance that may be imposed when higher V_T and flow are applied with these interfaces as the patient gets larger.

Willson: Is it going to be available for older kids?

DiBlasi: To my knowledge these will only be available for neonates at this time.

Brown: I know you're primarily NICU, Rob, I think what Doug was getting at is that in the PICU [pediatric

ICU] it's bronchiolitis patients who are on that support. So it's not a stretch to think that something that's infant-sized would work for what they want to use it for.

DiBlasi: My research is focused on neonates, but I also work in the PICU and understand the need for noninvasive interfaces for larger infants and small pediatric patients. In the PICU I would use this new cannula on an 8-kg infant who was doing poorly on high-flow or nasal CPAP to avoid intubation, for sure. Some folks are desperate and would use an adult nasal cannula, but I do not advocate that.

Wiswell: Rob, a worry with nasal cannula ventilation is the variability of intrathoracic pressure generated. In some trials in which they measured thoracic pressure there was an inverse relationship: the smaller the infant, the higher the intrathoracic pressure. A smaller premature baby—say, 750–900 g—may develop an intrathoracic pressure of 28 cm H₂O or more. This worries a lot of people, as we do not routinely measure intrathoracic pressure. I'm intrigued by the RAM cannula. NeoTech's medical director told me they're developing a nasal cannula that has a pressure-relief system once a pressure of 10 cm H₂O is generated. Are you familiar with that? High intrathoracic pressure worries me. Nasal cannula for ventilation is intriguing, but are we sure it's safe for babies?

DiBlasi: I don't know much about the high-flow nasal cannula situation, other than that its use is widespread across the United States. But that's a separate issue. In babies on nasal IMV, tracheal pressure measurements have indicated that 30–60% of the peak airway pressure is transmitted to the trachea. I would be more willing to use a nasal cannula to provide nasal IMV than high-flow therapy, because there is an exhalation valve regulating the pressure. We don't know what kind of intrathoracic pressure will be generated with a high-flow cannula system, because flow

is monophasic and the delivered pressure is dependent on the patient leak. There is no pressure-relief valve in the RAM cannula, but I believe NeoTech is working on a separate cannula design, Adina, for high-flow therapy, which records proximal flow and limits pressure to around 10 cm H₂O.

Wiswell: I look at the nasal IMV story as being similar to how people jumped on the bandwagon with high-frequency ventilation in the NICU. Similarly, there has been a widespread increase in using nasal CPAP. Unfortunately, we have minimal supportive data on efficacy for all of these types of respiratory support. In the RCTs there has been minimal to no improvement in the major outcomes, including mortality, duration of ventilation, BPD, and chronic lung disease. But despite the scant supportive data, many in neonatology are using these therapies in everyday practice. Neonatologists are "gizmo-ologists." We like playing around with new technology. This worries me. I see you had some of Robertson's pictures from the babies' nostrils,¹ of damage we can see. New therapies may cause damage we are unaware of. Before jumping on the bandwagon we need to do good clinical trials and make sure therapies are safe and improve patient outcomes.

1. Robertson NJ, McCarthy LS, Hamilton PA, Moss AL. Nasal deformities resulting from flow driver continuous positive airway pressure. *Arch Dis Child Fetal Neonatal Ed* 1996;75(3):F209-F212.

DiBlasi: Absolutely.

Branson: This low-cost ventilator that you guys in Seattle have been working on is very interesting. A lot of us in academia have developed technology, but what happens when you need to manufacture it, and you have to get an ISO [International Organization for Standardization] facility to make the device, and then you need to meet FDA requirements for alarms and validation? For a company I'm aware of it took 7 years to

get FDA approval for a bubble-CPAP system. With regard to this low-cost ventilator, essentially the engineers developed a Baby Bird. It's inexpensive, but it's 30 years behind current devices.

DiBlasi: The IMV device is separate from the high-amplitude bubble-CPAP device I showed you. Interestingly, these devices can be combined to provide the continuum of respiratory care to critically ill infants with respiratory failure. Nonetheless, the requirements and regulatory approach for any of these devices will be determined by stakeholders in the country where they'll be manufactured and used. We have involved neonatologists and pediatricians from all over India to provide feedback on the design of this ventilator. We're pursuing FDA approval, but this device may or may not be used in the United States. We are looking to use these devices where they do not have access to simple respiratory-support devices, so thousands of babies die every day. They have nothing. I saw this first-hand on a recent trip to India and Vietnam. The good news is that we have engaged stakeholders in India and we have begun discussing strategies for manufacturing these devices and conducting the necessary research in India.

Branson: What are the rules if you make it in the United States and ship it overseas?

Rogers:* The FDA does impose export regulations on mechanical respiratory devices. Unless the company is wholly outside the United States, there are a lot of export regulations to go through to get it out of the United States.

DiBlasi: Thanks Mark. That's interesting information because it conflicts a little bit with what we've been told in some of these countries. At this point our goal is to manufacture these devices

in India, conduct the necessary clinical research, and then pursue FDA approval. Luckily, we have some donors who want to fund this project. Many of these types of projects fizzle out and never go anywhere.

Gentile: That's great, because neonatology is practiced differently in those countries. The device you showed might help. Another consideration is the ability to put other gases through the system, so it has multiple purposes. Regarding NAVA, this is great science, but it's interesting that you presented a bunch of studies in which they used the Infant Star ventilator. We'd all bring the Infant Star back, because the world didn't really know how good it was until it was gone. So far no studies have justified the cost of NAVA. I'm all for patient/ventilator synchrony and spontaneous breathing, but there's limited space in the esophagus, especially in tiny patients, for a nasogastric tube *and* the NAVA catheter.

DiBlasi: I think NAVA is a wonderful innovation and has a lot of potential, but I'm a little concerned because NAVA is invasive. Having placed many esophageal balloons in my time, I know that catheters can change position and the signal can be lost, so I've wondered if that happens during NAVA. Folks who use NAVA feel that, since you are placing an orogastric or nasogastric tube anyway, that negates the invasiveness of NAVA. But a standard nasogastric tube doesn't cost \$500 or \$600, so the cost of NAVA is a concern.

Is there going to be a large RCT with the 1,000-plus patients that would prove or disprove NAVA's clinical benefit? Who's going to fund that study? And will the benefits justify the cost of the software and catheters? So far, more papers have been published on NAVA than on pressure-regulated volume control in neonates, and that's a great start. I think 8 or 9 abstracts of NAVA studies have been submitted to the AARC [American Association for Respiratory Care] OPEN FORUM this year.

Gentile: Esophageal balloon for PEEP and transpulmonary pressure measurement are becoming common in all patient populations, and these catheters are combined with a nasogastric, so one tube has multiple purposes. If we can get it outside the body, similar to a Graseby capsule, I think that's where we should be headed. Simply put the patient on a little PEEP and let them determine their own respiratory rate and V_T , unless they require more assistance.

Walsh: I struggle with the science, because I think we all know that NIV may be beneficial because you transfer more of the work of breathing to the patient. We tend to over-ventilate intubated patients, even though we think we're not. What would be the ideal clinical trial that would show whether bubble CPAP is better?

DiBlasi: For our device?

Walsh: Any noninvasive device: high-frequency, NAVA, et cetera. To me, intubation doesn't seem to be it.

DiBlasi: Several investigators have started that process, and some studies have been submitted to peer-reviewed journals. Trying to design the perfect study, especially in premature neonates, is very difficult, because the practice differs so much from one institution to the next. There are such disparities in practice, we don't know if we should be giving surfactant or supporting them with CPAP initially. If we can figure out how we're going to give the CPAP and surfactant, then we can go from there in designing trials with NIV.

Curley: In your bubble-CPAP device, why does angling the bubble tube in the water affect the oscillations?

DiBlasi: With small modifications in the distal tubing submerged in a simple CPAP water column, we developed a flow-interrupter device to increase the

* Mark Rogers RRT, CareFusion San Diego, California.

magnitude of high-frequency pressure oscillations delivered to the nasal airway of infants who would otherwise fail bubble nasal CPAP. By moving the bubbler angle from conventional bubble nasal CPAP (0 degrees) to 135 degrees in the water-column, we found that when a bubble breaks off, the airway pressure is at its lowest point; water rushes into the tubing and occludes it; gas flow is directed toward the nasal airway and pressure rises; gas then drives water out of the tubing, a bubble forms, and pressure decreases. These pressure oscillations produce enough energy to provide gas exchange similar to that from a conventional mechanical ventilator in paralyzed juvenile rabbits.¹

This device, which we have termed high-amplitude bubble CPAP, has a lower bubbling frequency than conventional bubble nasal CPAP. The lower frequency provides more time for the airway pressure to equilibrate with the lung pressure, to displace a larger volume of gas. The frequency of conventional bubble CPAP is 10–20 Hz with an amplitude of 2 cm H₂O. The pressure change with the bubbler at 135 degrees is around 8 cm H₂O. So the angle changes the way that the water interacts with the gas, which reduces the frequency.

We studied this with high-speed video. We are able to allow the airway pressure to equilibrate with the lung or

get closer to equilibrating, and that drives gas in and out of the lung. If you want me to go on about the complex interplay of the gases and the water, we can do that over a drink later.

1. DiBlasi RM, Zignego JC, Smith CV, Hansen TN, Richardson CP. Effective gas exchange in paralyzed juvenile rabbits using simple, inexpensive respiratory support devices. *Pediatr Res* 2010;68(6):526-530.

Curley: How are you going to evaluate the device in India? Have you asked the Gates Foundation for support in this? If anyone would be interested in improving outcomes in developing countries, it would be them.

DiBlasi: We are identifying manufacturers and potential research sites in India. The goal is to conduct multiple studies of the device over the next 5 years. We have submitted a grant proposal to the Gates Foundation, and others. You are correct: the Gates Foundation could have a huge impact in resource-limited settings.

Eiserman:[†] Regarding nasal cannulas, I would say “everything old is new again.” We’re looking at creative new uses for nasal cannulas that have a lot

[†] Jeri E Eiserman MBA RRT FAARC, Teleflex Medical, Research Triangle Park, North Carolina.

of potential. We should be looking at the limitations and opportunities that are posed by an occlusive cannula such as Rob is talking about for infant nasal CPAP, versus a non-occlusive cannula, which is what’s typically used in high-flow nasal cannula therapy.

We hear concerns from physicians using high-flow nasal cannula that they want to know the pressures created in the upper airways and the alveoli. I think one paper looked at oropharyngeal pressure in an adult at flows up to 40 L/min and found very low oropharyngeal pressure, but perhaps enough to support the upper airways. We should determine what’s really happening.

One of the disadvantages, from a research standpoint, of looking at something old in a new way is that we’ve been using nasal cannula therapy for so long that we think it’s safe therapy. We’re seeing evidence—mostly anecdotal—that high-flow nasal cannula is safe in most instances. Most of them have a pressure-relief valve, which is really getting at system pressure, because it’s a high-back-pressure system, as opposed to what’s necessarily going on in the baby’s lungs. I think it’s exciting to look at the use of nasal cannulas in the ways you’ve talked about, but it begs for additional research that takes a close and careful look at what we’re doing with them.

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