# Novel Ventilation Strategies to Reduce Adverse Pulmonary Outcomes

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**KEYWORDS**

• Mechanical ventilation • Lung injury • Bronchopulmonary dysplasia
• Noninvasive respiratory support • Less invasive surfactant administration
• Volutrauma • Volume-targeted ventilation

**KEY POINTS**

- The pathogenesis of chronic lung disease is multifactorial and consequently strategies to prevent bronchopulmonary dysplasia must be equally comprehensive.
- Less invasive approaches to initial stabilization and surfactant administration are based on sound evidence and generally accepted. Various modalities of noninvasive respiratory support are widely practiced, but evidence of superiority of one over another is incomplete.
- Optimal lung aeration and avoidance of atelectrauma is an essential element of any lung-protective ventilation strategy.
- Volume-targeted ventilation is the most evidence-based approach to invasive mechanical ventilation; other novel modalities are potentially attractive, but insufficiently studied.

Advances in obstetric and neonatal intensive care have led to the survival of smaller and more immature infants born at earlier stages of lung development. Although the survival of very premature infants improved, the rate of bronchopulmonary dysplasia (BPD) has remained the same, or even increased.[1,2] Extremely premature survivors who are most likely to develop BPD after a prolonged hospitalization suffer from chronic cardiopulmonary impairment, growth failure, neurodevelopmental impairment, and difficulties with social functioning, all of which can have a profound impact on the entire family, financially and emotionally.[3,4] Efforts to prevent or mitigate the severity of BPD must take into account the multifactorial nature of the condition and the substantial individual differences in susceptibility. Well known factors that increase the risk of BPD include intrauterine factors, such as chorioamnionitis, maternal smoking, and intrauterine growth restriction; perinatal factors, the most prominent of which

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is prematurity; and postnatal factors including exposure to relative hyperoxia and mechanical ventilation.[5–7] Suboptimal initial stabilization and postnatal infections further increase the risk. Some of the postnatal factors are within control, but most of the intrauterine factors are not easily modifiable. Gestational age remains the most important risk factor for BPD and prevention of prematurity remains an elusive goal. Impairment of normal pulmonary development is likely unavoidable when a fetus in the early saccular stage of lung development finds himself or herself in the hyperoxic environment (relative to the intrauterine oxygen level) and is required to support his or her gas exchange with lungs that are inadequately developed. Nonetheless, the substantial variation in the incidence of BPD among different institutions not explainable by differences in patient population strongly suggests that postnatal management can influence the degree of lung injury.[2,8]

Detailed discussion of the mechanisms of ventilator-associated lung injury (VALI) and cause of BPD is beyond the scope of this article, but is discussed elsewhere.[9–11] In this article, we briefly discuss the mechanisms of lung injury and review the available evidence for possible benefits of various newer strategies of respiratory support.

## VENTILATOR-ASSOCIATED LUNG INJURY

Lung injury and subsequent repair that ultimately leads to BPD is a complex process with no single element being able to fully account for its development. However, several aspects are generally believed to be central to its development. (1) Excessive tissue stretch (volutrauma) is the key determinant of VALI. Inflation pressure by itself, without generating an excessively large tidal volume ($V_T$), has been shown to not result in acute lung injury.[12,13] (2) Positive-pressure ventilation in lungs that are partially atelectatic predisposes to VALI by a variety of mechanisms collectively known as atelectrauma. Maintenance of alveolar stability at end-expiration by using adequate positive end-expiratory pressure (PEEP) mitigates lung injury.[9,14] (3) Both antenatal and postnatal infection can initiate the cascade of lung injury and repair,[15] a process sometimes referred to as biotrauma.

## INITIAL STABILIZATION AND STRATEGIES TO OPTIMIZE LUNG AERATION AT BIRTH

Avoidance of practices that can potentiate lung injury must start during initial stabilization of the preterm infant during the "golden first hour."[16] Even a brief period of manual ventilation with excessive $V_T$ can rapidly injure the immature lung in the delivery room.[17] The best strategy aimed at helping the preterm infant with insufficient chest wall rigidity to establish functional residual capacity (FRC) and facilitating lung fluid clearance is the subject of ongoing studies. There is strong physiologic rationale and substantial preclinical data to support the use of PEEP in the delivery room, but paucity of clinical evidence from randomized trials. Sustained inflation became widespread in Europe based on encouraging preclinical studies and several modest-sized clinical trials,[18–20] but the largest study to date, the Sustained Aeration of Infant Lungs (SAIL) trial, failed to substantiate its presumed benefit.[21] Although there was no overall difference in the primary outcome of death or BPD, there was a signal of increased early mortality in this highly vulnerable population of infants less than 27 weeks gestational age and no hint of benefit. An updated meta-analysis clearly indicates caution, because the cumulative evidence shows a strong, although not statistically significant trend to higher mortality with sustained inflation (**Fig. 1**).[22] A large multicenter trial to explore a titrated PEEP strategy that seeks to tailor the level of distending pressure to each infant's need based on initial response is underway (Australian New Zealand Clinical Trials Registry ACTRN12618001686291).

Current evidence, although incomplete, suggests that sustained inflation should be avoided in favor of sufficient PEEP, and gentle positive-pressure inflations, if needed, and early application of continuous positive airway pressure (CPAP). A T-piece resuscitator is preferred to self-inflating bag, because it achieves more consistent inflation pressure and effective PEEP delivery.[23,24] Estimation of $V_T$ by observation of chest wall movement is inaccurate and tends to substantially underestimate the actual $V_T$.[25] Therefore the goal is to use just enough pressure to achieve a barely perceptible chest rise. $V_T$ measurement during manual ventilation is feasible, but seldom used clinically. A prototype volume-targeted resuscitation device has been developed,[26] a tool that is highly desirable, because of sound evidence that volutrauma is the key factor in lung injury and that respiratory system compliance changes rapidly soon after birth. Clinical studies are needed to determine if this device results in reduction of lung injury.

Neonatal Resuscitation Program (NRP) recommends that the initial fraction of inspired oxygen ($F_{IO_2}$) should be between 0.21 and 0.30 for preterm infants and 0.21 for term infants.[27] However, all preterm infants who were started with $F_{IO_2}$ of 0.21 required increased $F_{IO_2}$ to reach adequate saturation levels[28]; therefore, most clinicians begin with $F_{IO_2}$ around 0.30. Avoidance of excessive oxygen exposure should be part of any lung-protective ventilation strategy. $F_{IO_2}$ should be promptly titrated to maintain target saturation according to published nomograms.[29] Intubation solely for the purpose of administering prophylactic surfactant is no longer recommended, but if intubation is required for initial stabilization, surfactant should be administered promptly, once the endotracheal tube (ETT) position has been confirmed.[30]

## NONINVASIVE RESPIRATORY SUPPORT/LESS INVASIVE SURFACTANT ADMINISTRATION

Noninvasive support with CPAP is successful in most infants greater than 26 weeks gestation.[31] Although the effect on BPD seen in a series of large randomized controlled trials comparing CPAP with routine intubation and surfactant administration was smaller than anticipated, the cumulative evidence clearly supports the role of CPAP in reducing the need for mechanical ventilation and the risk of BPD.[32,33] Less invasive approaches to surfactant administration via a thin catheter or laryngeal mask airway are gaining acceptance based on accumulating evidence of the potential benefit of surfactant administration without the need for mechanical ventilation.[34–36] Until recently, the use of laryngeal mask airway was limited by lack of sufficiently small devices, but newer laryngeal mask airways are adequate down to 1000-g infants. Nebulized surfactant administration, the only truly noninvasive strategy, is another attractive option, but its use remains investigational.[37,38]

In the absence of adequately powered prospective trials controversy persists regarding relative merits of various forms of CPAP. A preclinical study in preterm lambs showed that bubble CPAP improved gas exchange and decreased markers of lung injury.[39] Clinical data are limited to a series of small single-center studies, but a recent meta-analysis indicated that bubble CPAP reduced the incidence of CPAP failure compared with ventilator CPAP.[40]

Bilevel CPAP was touted as a better approach than static CPAP, but the cyclic pressure swings do not produce a measurable $V_T$[41,42] and when applied at equivalent mean airway pressure (MAP), bilevel CPAP did not seem to offer any advantage over constant pressure CPAP.[43,44]

Nasal intermittent positive-pressure ventilation (NIPPV) has rapidly gained acceptance as an effective modality of noninvasive support based on a handful of

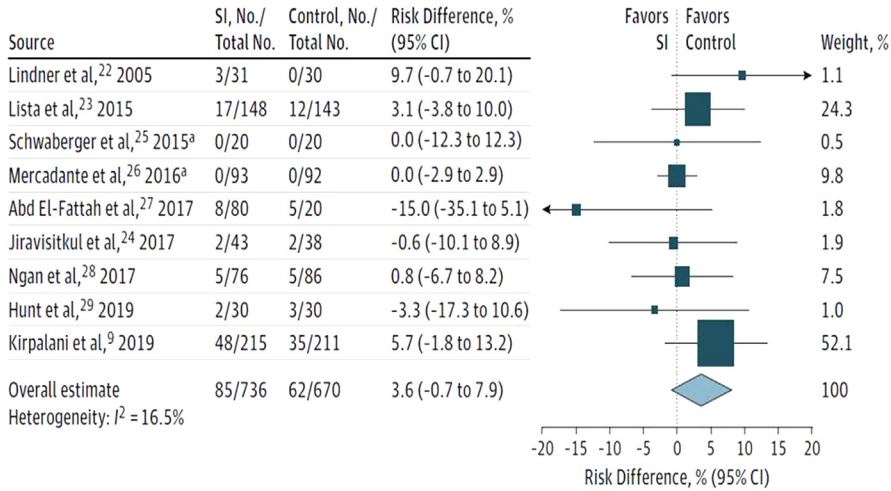


**Fig. 1.** Updated meta-analysis of available randomized controlled trials of sustained inflation (SI) for in-hospital mortality. The size of each trial is reflected by the size of the *box* representing the point estimate. The total number of subjects included is 1406 with an overall mortality risk difference, represented by the *diamond*, of +3.6% (95% confidence interval [CI], −0.7 to 7.9). (*From* Foglia EE, Te Pas AB, Kirpalani H, Davis PG, Owen LS, van Kaam AH, et al. Sustained Inflation vs Standard Resuscitation for Preterm Infants: A Systematic Review and Meta-analysis. *JAMA Pediatr.* 2020;174(4):e195897.)

randomized trials, whereas the largest randomized trial did not show any benefit.[45,46] The widely held belief that NIPPV is able to provide effective ventilation via a nasal interface is not supported by evidence. Only a fraction of ventilator inflations achieve a measurable $V_T$ with unsynchronized NIPPV (the only kind currently available in the United States) because in newborn infants the glottis is closed unless the infant is actively inspiring.[47,48] Thus, the benefit of NIPPV, primarily in reducing postextubation failure documented in the most recent Cochrane review,[45] seems to derive from the higher MAP used with NIPPV, compared with CPAP in most of the published studies. Buzzella and colleagues[49] demonstrated that the use of higher, as opposed to lower CPAP level following extubation significantly reduced CPAP failure, providing the plausible explanation for the apparent superiority of NIPPV over CPAP. Studies are underway to test the hypothesis that CPAP and NIPPV are equivalent when used at the same MAP (ClinicalTrials.gov Identifier: NCT03512158 and NCT03670732).

The importance of patient interface has not received adequate attention until recently. The RAM cannula (Neotech, Valencia, CA) was designed and approved by the Food and Drug Administration as a nasal cannula for delivery of low- or high-flow oxygen, but has been promoted for off-label use as a device to deliver CPAP and NIPPV. The cannula rapidly gained popularity because of the ease of application and less need for skilled nursing attention. However, it has become clear that such off-label use is problematic. Extensive evidence indicates that short binasal prongs are superior to the RAM cannula for delivery of CPAP and NIPPV, because of the large loss of pressure across the high resistance of the RAM cannula (**Fig. 2**).[50–55]

## NOVEL APPROACHES TO NONINVASIVE RESPIRATORY SUPPORT

A proprietary variant of NIPPV known as noninvasive neurally adjusted ventilatory assist (NIV NAVA) seems to overcome the limitations of nonsynchronized NIPPV.

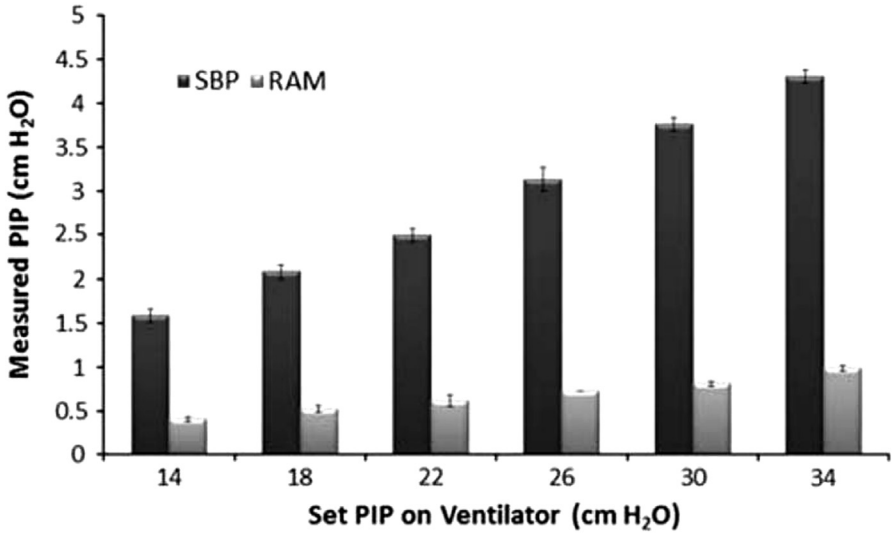


**Fig. 2.** Transmitted peak inflation pressure (measured at the distal airway) during NIPPV via small RAM cannula, compared with small binasal prongs (SBP) in a bench study. There is a large drop across both interfaces, with minimal pressure being transmitted via the RAM cannula. PIP, peak inflation pressure. (*From* Mukerji A, Beli, k J. Neonatal nasal intermittent positive pressure ventilation efficacy and lung pressure transmission. *Journal of perinatology : official journal of the California Perinatal Association*. 2015;35(9):716-719.)

This unique method of noninvasive ventilation uses the electrical activity of the diaphragm (EAdi) to synchronize inflation with the infant's respiratory effort and therefore is able to synchronize effectively with the open interface of NIV. The evidence for superiority of NIV NAVA is limited to a few small single-center studies demonstrating improved synchrony, lower peak pressures, greater patient comfort, and lower rate of extubation failure.[56–60] A large National Institutes of Health–funded multicenter trial, the Diaphragmatic Initiated Ventilatory Assist (DIVA) trial (Clinicaltrials.gov registration pending) seeks to provide more definitive evidence of benefit of this promising approach. Currently NIV NAVA is only available on the Maquet SERVO ventilators (Getinge, Solna, Sweden). A prototype of NIV NAVA-dedicated device termed "NeuroPAP" that not only supports spontaneous respiratory effort of the infant with inflation pressure proportional to the magnitude of the EAdi like regular NIV NAVA, but also uses the resting tonic activity of the diaphragm to actively modulate the PEEP, performed well in a small crossover trial in preterm infants. Despite being actively modulated, the average PEEP was similar as the set PEEP during NIPPV.[61]

Interest in improving noninvasive respiratory support by using high-frequency oscillatory ventilation (HFOV) via the nasal route dates back a couple of decades.[62] More recently, several small and medium-sized single-center randomized studies reported encouraging findings when comparing nasal HFOV with biphasic CPAP,[63] or static nasal CPAP.[64–67] These studies varied widely in terms of the population and the specific settings. Some studies did not match the MAP between the groups. Two meta-analysis sum up the findings and acknowledge the heterogeneity; nonetheless, the overall effect was a significant reduction in the need for invasive mechanical ventilation.[68,69] Some of the studies also reported lower $P_{CO_2}$ in the nasal HFOV arm. Larger randomized trials are needed to establish the safety and effectiveness of nasal HFOV

and two such studies are planned.[70,71] It would also be important to elucidate the mechanism of action and effect of different nasal/nasopharyngeal interfaces. Although anecdotally clinicians report observing detectable chest wall vibration with this technique, there is substantial reduction in the transmission of oscillatory amplitude through narrow prongs.[72] For this reason some studies used a single nasopharyngeal tube as the interface.[62,73,74] Frequency of 6 to 8 Hz was found to result in optimal $CO_2$ clearance in a bench study.[75] It is also possible that there is an increase in distal pressure leading to more effective lung recruitment and perhaps better maintenance of an open airway.

High-frequency percussive ventilation has been used in laboratory on preterm sheep using the VDR4 and on neonatal transport using the Bronchotron ventilators (both Percussionaire, Sand Point, ID) with good results.[76] Shorter duration of respiratory support and supplemental oxygen requirement was also reported using high-frequency percussive ventilation, compared with nasal CPAP in term infants with transient tachypnea of the newborn,[77] but larger trials in preterm infants with significant respiratory distress are lacking.

A recent paper described a small retrospective series of infants ventilated by high-frequency jet ventilation (HFJV) combined with NIPPV at a rate of 40 inflations/min via a RAM cannula.[78] Given the very high resistance of the long, narrow tubing of RAM cannula, it is questionable whether this approach could result in anything but a substantially increased (and unmeasured) distending airway pressure as the high gas flow from the jet ventilator acts like a very high-flow nasal cannula. In the laboratory setting nasal HFJV is effective when applied via a nasopharyngeal tube in preterm lambs (K. Albertine, personal communication). Clearly, more data are needed regarding nasal HFJV safety and efficacy of nasal HFJV and the pressure and flow transmission through various interfaces. A prospective trial has been registered in ClinicalTrials.gov (NCT03558737) proposing to use a nasopharyngeal interface for the delivery of nasal HFJV.

It remains to be seen if any of these noninvasive high-frequency modalities can improve overall outcome when compared with bubble CPAP at similar distending pressures.

## INCREASED DURATION OF CONTINUOUS POSITIVE AIRWAY PRESSURE

It is well known that the distending pressure exerted on fetal lungs in utero is critical for normal lung growth and that prolonged oligohydramnios is associated with lung hypoplasia. Animal models have demonstrated that lung growth is induced by continuous distending pressure.[79,80] Occlusion of fetal trachea in fetuses with congenital diaphragmatic hernia results in significant lung growth.[81,82] Therefore, it is conceivable that infants born extremely preterm might benefit from continuation of distending airway pressure until lung development is near-complete. Continuation of CPAP beyond the traditional criteria has long been the practice at Morgan Stanley Children's Hospital in New York and seems to be associated with a remarkably low incidence of BPD.[83] However, this approach has never been subjected to a randomized controlled trial. The first evidence supporting the concept that prolonged CPAP use may improve lung function in preterm infants was a clinical trial that randomly assigned infants less than 32 weeks gestation who reached traditional criteria for discontinuation of CPAP to be weaned to room air or to continue on CPAP for 2 additional weeks.[84] Infants randomized to extended CPAP had a significantly greater increase in FRC from baseline through 2 weeks of treatment (12.6 mL vs 6.4 mL; $P = 0.03$) and this benefit was still evident at discharge (FRC, 27.2 mL vs 17.1 mL; $P = 0.01$). The longer duration of

CPAP did not affect initiation of oral feeding or prolong hospitalization. These data are certainly encouraging but whether this increased lung growth translates into a reduction in the rate of BPD or long-term respiratory morbidity in the most vulnerable infants requires a larger randomized trial with important clinical outcomes. It is unlikely that this intervention alone could affect the rate of type II severe BPD, because these infants generally receive positive-pressure support throughout their hospitalization,[85-] but less severe degrees of BPD may well be preventable.

## PREVENTION OF ATELECTRAUMA

Prevention of atelectrauma is not a new concept, but is not rigorously applied in neonatal respiratory support. Reluctance to use sufficiently high PEEP, known as "PEEP-o-phobia," remains pervasive, despite evidence that sufficient PEEP mitigates lung injury.[86–88] Ventilation of injured lungs using insufficient PEEP results in repeated alveolar collapse and expansion with each inflation, leading rapidly to injury of the immature lung. When the lungs remain partially atelectatic, the gas that enters the lungs preferentially distends the more compliant aerated portion of the lung, whereas the atelectatic portion with its high critical opening pressure remains collapsed. This fact is evident from Laplace's law and is corroborated by experimental evidence, showing that the most injured portion of the lung was the aerated, nondependent lung.[89] Because of this maldistribution of $V_T$, volutrauma can occur even with normal physiologic $V_T$ and this may explain why high oxygen requirement in infants on CPAP, a marker of ventilation/perfusion mismatch (i.e., atelectasis), was associated with increased risk of pneumothorax.[90] Studies exploring the use of substantially higher PEEP suggest that this approach is safe and effective, but more data are needed from larger studies.[91]

Thus the key elements in minimizing lung injury include: (1) minimizing alveolar overdistention (volutrauma), (2) optimizing end-expiratory lung volume by reversing atelectasis by means of some form of lung recruitment, and (3) stabilizing lung units throughout the ventilatory cycle (avoiding repeated collapse and re-expansion). Applying this strategy also improves ventilation/perfusion matching and thus oxygenation, allowing reduction of supplemental oxygen concentration (less oxygen toxicity). This lung-protective ventilation strategy is referred to as an open lung strategy.[14,92]

Lung volume recruitment seems to be more easily achieved with HFOV,[93] but is also feasible with conventional ventilation.[94] With either approach, the critical opening pressure of the atelectatic saccules needs to be reached and then maintained with sufficiently high end-expiratory pressure.[95] With HFOV, lung volume recruitment is performed by inflating the lungs to close to their maximum volume with stepwise increases in MAP. Electrical impedance tomography is a promising tool to visualize lung aeration in real time, but is not yet widely available.[96,97] Therefore, oxygen requirement as a reflection of ventilation/perfusion matching is used to guide this strategy. The lungs are considered to be fully inflated when $F_{IO_2}$ is weaned to less than 0.30. The lungs are then deflated to the closing volume that is indicated by deterioration in oxygen saturation on pulse oximetry. The lungs are subsequently reinflated and the final MAP is set at a point just above closing volume.[93] This technique allows ventilation to move from the inspiratory limb of the pressure-volume curve to the expiratory limb, allowing effective ventilation and oxygenation at lower pressures.[98] Surfactant distribution is improved when it is administered into an adequately aerated lung.[99] Aggressive lung recruitment is seldom necessary in infants with uncomplicated respiratory distress syndrome after surfactant treatment, but if high oxygen requirement persists, optimization of lung volume should be attempted. However, not all lungs

are recruitable; some infants may have neonatal pneumonia or other conditions that preclude effective recruitment. Consequently, if two consecutive increases in MAP fail to produce an improvement in oxygenation, further efforts should be abandoned. It is important to recognize that once the lungs are adequately recruited, lung compliance improves and the pressure needed to maintain that recruitment is less than the pressure that was initially required to open the atelectatic portions of the lungs. Thus, it is important to reduce the distending pressure once lung volume is optimized. With conventional ventilation, recruitment is achieved by stepwise increases in PEEP, while maintaining adequate peak inflation pressure to avoid hypoventilation and reach the critical opening pressure of atelectatic saccules.[94]

## AVOIDANCE OF VOLUTRAUMA

Several meta-analyses have documented the benefits of volume-controlled and volume-targeted ventilation (VTV) in newborn infants, including significant decrease in the rate of BPD, pneumothorax, severe intraventricular hemorrhage, periventricular leukomalacia, less hypocapnia and shorter duration of mechanical ventilation (**Table 1**).[100,101] Volume-controlled ventilation, where a user-set volume of gas is injected into the proximal (ventilator) end of the circuit, is routinely used in pediatric and adult intensive care units, because direct control of minute ventilation and avoidance of volutrauma is recognized as an important goal. However, early attempts at volume-controlled ventilation in neonates using ventilators designed for large patients were a dismal failure because of loss of $V_T$ to compression of gas within the circuit and leak around uncuffed ETT. This experience resulted in the adoption of pressure-controlled ventilation in the neonatal intensive care unit, a situation that persists to a significant degree in the United States.[102] The major problem with pressure-controlled ventilation is that $V_T$ changes with changes in lung compliance, which can occur rapidly and often results in lung overexpansion, volutrauma, and hypocapnia.

Modern ventilators now make it possible to use volume-controlled ventilation in newborn infants by allowing for measurement of exhaled $V_T$ at the airway opening, so that manual adjustment of set $V_T$ at the ventilator end of the patient circuit is

**Table 1**
**Metaanalysis of studies comparing volume controlled/targeted ventilation modalities with pressure controlled ventilation.[101]**

| | Relative Risk or Mean Difference | 95% CI | NNTB (95% CI) |
|---|---|---|---|
| Death or BPD at 36 wk | 0.75 | 0.53 to 1.07 | NA |
| BPD at 36 wk PMA | 0.73 | 0.59 to 0.89 | 8 (5 to 20) |
| Grade 3-4 IVH | 0.53 | 0.37 to 0.77 | 11 (7 to 25) |
| PVL ± severe IVH | 0.47 | 0.27 to 0.80 | 11 (7 to 33) |
| Pneumothorax | 0.52 | 0.31 to 0.87 | 20 (11 to 100) |
| Hypocapnia | 0.49 | 0.33 to 0.72 | 3 (2 to 5) |
| Days of MV | −1.35 | −1.83 to −0.86 | |

*Abbreviations:* CI, confidence interval; IVH, intraventricular hemorrhage; MV, mechanical ventilation; PVL, periventricular leukomalacia; NA, not applicable; NNTB, number needed to benefit; PMA, postmenstrual age.

made to achieve a desired exhaled $V_T$.[103] More convenient are volume-targeted modes that are modifications of pressure-controlled ventilation that automatically adjust inflation pressure to achieve a target $V_T$.[104] With $V_T$ as the primary control variable, peak inflation pressure is automatically reduced as lung compliance and patient inspiratory effort improve, resulting in real-time weaning, in contrast to intermittent manual lowering of peak inflation pressure in response to blood gas measurement. Volume guarantee (VG) is the most extensively studied form of VTV and the basic control algorithm is increasingly being adopted by other ventilator manufacturers. The key to successful use of VTV is recognition of the importance of choosing the appropriate $V_T$ target. A series of observational studies defined the typical $V_T$ requirement in various conditions and patient categories.[105–108] However, it is important to recognize that these values are population means, which are a good starting point, but clinical assessment of the patient's response to these initial settings should be promptly assessed and adjustments made as indicated based on patient's respiratory effort (tachypnea, retractions, or apnea) and of ventilator waveforms.[109] VG ventilation has been clinically available for more than 20 years, but despite strong evidence of benefit, it has not been universally accepted. Reasons for this include simple inertia, but also lack of suitable equipment in many neonatal intensive care units and a lack of understanding of the complexities of the approach.[102] For more detailed discussion of VTV the interested reader is referred to the latest article on the subject.[110]

## HIGH-FREQUENCY VENTILATION WITH VOLUME TARGETING

High-frequency ventilation is not novel and the evidence for its benefit as first-line therapy for infants with uncomplicated RDS is weak.[111] HFOV facilitates lung volume recruitment and HFJV is an effective rescue therapy for air leak.[112] The novel aspect of HFOV, which is already widely available in the rest of the world and may soon become available in the United States, is the ability to combine VG with HFOV.[113–115] The volume-targeting concept is similar to conventional VG, but because of the high frequency, $V_T$ is averaged over several cycles to guide automatic adjustment of pressure amplitude within user-preset limits. This technological advance should reduce the risk of inadvertent overventilation that readily occurs with high-frequency ventilation because even modest change in $V_T$ has a large impact on $CO_2$ elimination because of the geometric relationship between $V_T$ and ventilation efficiency. A multicenter clinical trial to document safety and efficacy of HFOV combined with VG has been completed (ClinicalTrials.gov Identifier: NCT02445040) with the goal of obtaining Food and Drug Administration approval.

## PROPORTIONAL ASSIST MODALITIES

Giving the patient more complete control of the entire respiratory cycle is an attractive concept that has the potential to achieve more complete synchrony, greater patient comfort, improved gas exchange, and lower ventilator pressures.[116] Two such approaches have been available for more than a decade, although their use remains limited, in part because they are both proprietary technologies. Proportional assist ventilation (PAV) is available on the Stephanie ventilator (Stephan, Gackenbach, Germany) and is not available in the United States. The NAVA modality is only available on the Maquet SERVO ventilators (Getinge, Solna, Sweden).

PAV is a sophisticated modality that senses the patient's effort throughout the respiratory cycle by means of a high-fidelity pneumotachograph with a rapid sampling rate and generates inflation pressure in proportion to the inspired volume and flow. The gain applied to the patient's effort is designed to keep the inspiratory effort

needed to generate a given volume stable to the preset degree of unloading of the total respiratory system elastance, including the ventilator and circuit. This is referred to as elastic unloading and the gain is denominated in cm $H_2O$/mL of $V_T$ measured at the airway opening. The resistance is unloaded in a similar fashion by keeping the effort needed to generate a given airflow constant, a process known as resistive unloading and is denominated in cm $H_2O$/mL/s. The estimated ETT resistance is usually included in the calculation.

PAV has been evaluated in animal models[117] and a handful of small clinical studies with short-term outcomes, demonstrating lower work of breathing, lower MAPs, and no apparent complications.[118–121] There are several impediments to widespread acceptance of PAV. The technique is complex and presents several unique challenges. The choice of appropriate gain setting for elastic and resistive unloading is not intuitive and normative data are not readily available for different patient conditions. Excessive gain setting can result in oscillation of the system, lack of respiratory muscle training, and prolonged ventilator dependence. The method requires the use of inspiratory flow and volume measurement, which presents a problem if there is a substantial leak around the uncuffed ETT. Water condensation in the pneumotachograph can affect performance and lead to oversupport or undersupport. Finally, the immature respiratory control in very preterm infants requires a backup ventilation mode and appropriate pressure limits to deal with periodic breathing and apnea, and brief bursts of vigorous respiratory effort with handling or stimulation. Larger randomized trials with important clinical outcomes are needed to determine if the effort of mastering this modality is warranted.

NAVA is a modality developed for use in adult patients but now more widely used in newborn infants. As with PAV, the goal is to give the patient full control of the respiratory cycle, including onset of inflation, peak inflation pressure, and onset of exhalation. EAdi is measured by an array of electrodes mounted on a special catheter that can simultaneously serve as a feeding tube. When the infant initiates inspiration by activating his or her phrenic nerve, the EAdi is sensed by the EAdi catheter and this signal triggers inflation pressures in proportion to the voltage (measured in $\mu$V), and multiplied by the "NAVA level," measured in cm $H_2O/\mu V$, which is the gain, or degree of unloading of the patient's respiratory work. The ventilator displays the maximal EAdi and the minimal EAdi, the former being the maximal EAdi reached at peak inspiration and the latter being the EAdi at end-expiration and represents the tonic activity of the diaphragm activity. Monitoring the peak EAdi lets the clinician monitor how much work of breathing the infant is generating. High or rising peak EAdi suggests a need for increasing the NAVA level. Patients with significant lung disease and intact respiratory control typically generate strong inspiratory effort, but are unable to achieve adequate $V_T$. With progressive increases in the NAVA level, the EAdi initially remains stable while the inflation pressure and resulting $V_T$ increase. At some point, the degree of unloading becomes sufficient to achieve adequate minute ventilation and the infant's respiratory effort, as measured by the EAdi, comes down, indicating lower work of breathing. This point is referred to as the "break point" (**Fig. 3**).[122] Further increases in EAdi do not increase the $V_T$ or minute ventilation, but simply result in lower work of breathing for the infant. However, a recent study demonstrated that in premature infants, this response is not always reliable. They observed that as the NAVA level increased, a higher proportion of excessive $V_T$ was delivered, with 20% to 25% of $V_T$ greater than 10 mL/kg (measured at the airway opening) at NAVA level of 2.5 cm $H_2O/\mu V$ (**Fig. 4**).[123] This is likely because preterm infants often respond to external stimuli and may briefly generate large inspiratory effort, when disturbed, which is potentiated by the positive feedback of NAVA (**Fig. 5**).

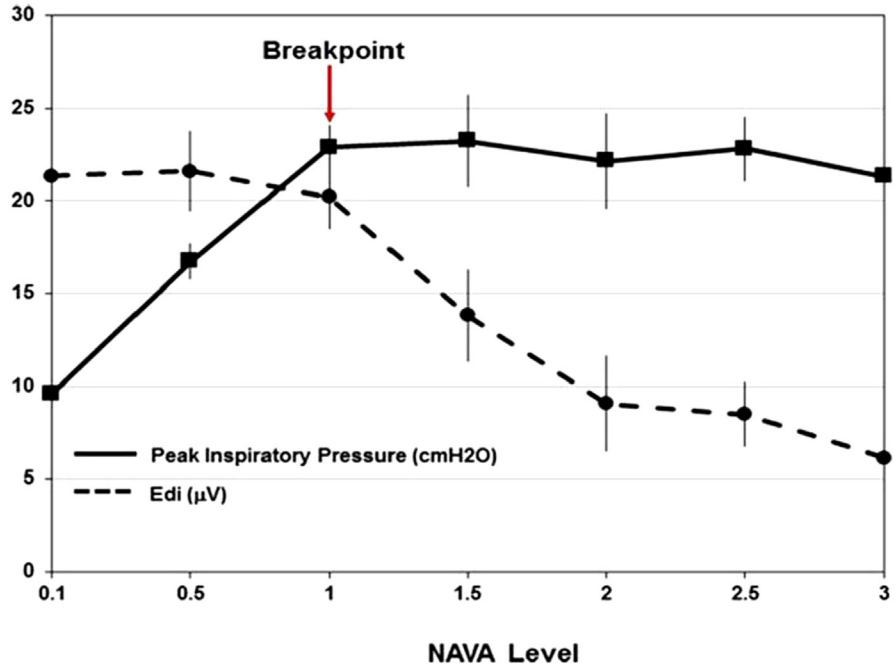


**Fig. 3.** The breakpoint in a subject with a mature respiratory pattern. Increasing the NAVA level, the gain applied to EAdi initially results in higher peak inflation pressure, but once the unloading of the diaphragm is sufficient, further increases in the NAVA level result in no further increase in peak inflation pressure, as the patient's respiratory effort decreases to maintain stable minute ventilation. (*From* Firestone KS, Fisher S, Reddy S, White DB, Stein HM. Effect of changing NAVA levels on peak inspiratory pressures and electrical activity of the diaphragm in premature neonates. *Journal of perinatology : official journal of the California Perinatal Association*. 2015;35(8):612-616.)

Elevated minimum EAdi level indicates tonic activity of the diaphragm is increased, which reflects the patient's effort to maintain FRC by not completely exhaling and suggests the need to increase PEEP, which is set manually, not controlled by the patient. The feedback available to the clinician is an attractive feature of NAVA and allows physiologic monitoring and appropriate adjustments of respiratory support. The EAdi signal has minimal trigger delay and is unaffected by movement, airflow artifacts, or air leak around uncuffed ETT. Unlike pneumatic triggers the EAdi signal is unaffected by leakage in an open system, making NAVA attractive for noninvasive ventilation with a high degree of synchrony.

The key disadvantage is that NAVA requires sustained spontaneous respiratory drive and thus is best suited for more physiologically mature subjects. For preterm infants with frequent apnea and periodic breathing the device provides flow or pressure-triggered pressure support ventilation mode and backup ventilation in case of inadequate EAdi signal. In some circumstances, the device switches in and out of backup ventilation frequently, which is undesirable. In addition to immature respiratory system, it is also important to consider the immaturity of other organs, such as the kidneys, which commonly leads to transient renal tubular acidosis in the first few days of life. Because respiratory control is driven by pH, not simply $P_{CO_2}$, clinicians must

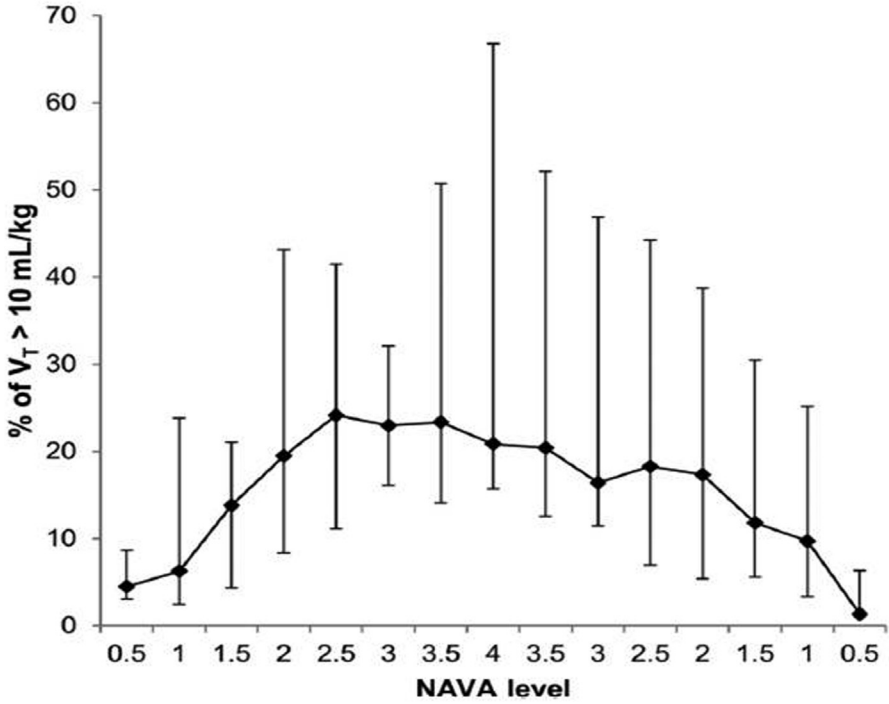


**Fig. 4.** In preterm infants with immature respiratory control, external stimuli often affect the immature respiratory pattern of the infant and result in a substantial proportion of potentially dangerous tidal volumes. Some 20% to 25% of tidal volumes were greater than 10 mL/kg at NAVA levels greater than or equal to 2.5 cm $H_2O$/mV. (*From* Nam SK, Lee J, Jun YH. Neural feedback is insufficient in preterm infants during neurally adjusted ventilatory assist. Pediatric pulmonology. 2019;54(8):1277-1283.)

not focus solely on $P_{CO_2}$ targets but rather evaluate the patient's respiratory drive in the context of pH.

Several small clinical studies of NAVA have compared NAVA with various modalities of synchronized ventilation and have demonstrated improved synchrony, lower peak pressure, and comparable gas exchange.[124–128] One study reported lower $V_T$ and lung compliance with NAVA, compared with pressure-support ventilation.[129] However, $V_T$ measurement with the SERVO-i in small infants is inaccurate (the reported values were barely above anatomic dead space) and lung compliance derived from the ventilator fails to take into account the patient's spontaneous respiratory effort. The single randomized trial failed to demonstrate any benefit of NAVA in terms of duration of ventilation, rate of pneumothorax, intraventricular hemorrhage, or BPD.[130] More recently, interest has shifted to using NAVA in olderinfants with evolving or established BPD, an application that may be better suited for NAVA. The findings were encouraging, but the studies were small and observational or crossover design in nature.[131–134]

The approach of positive feedback mechanism used by these proportional modalities would seem more appropriate for more mature subjects with reliable respiratory effort. There are limited data regarding the stability of $V_T$ delivered with these devices and the potential exists for inadequate support and potentially dangerously large $V_T$

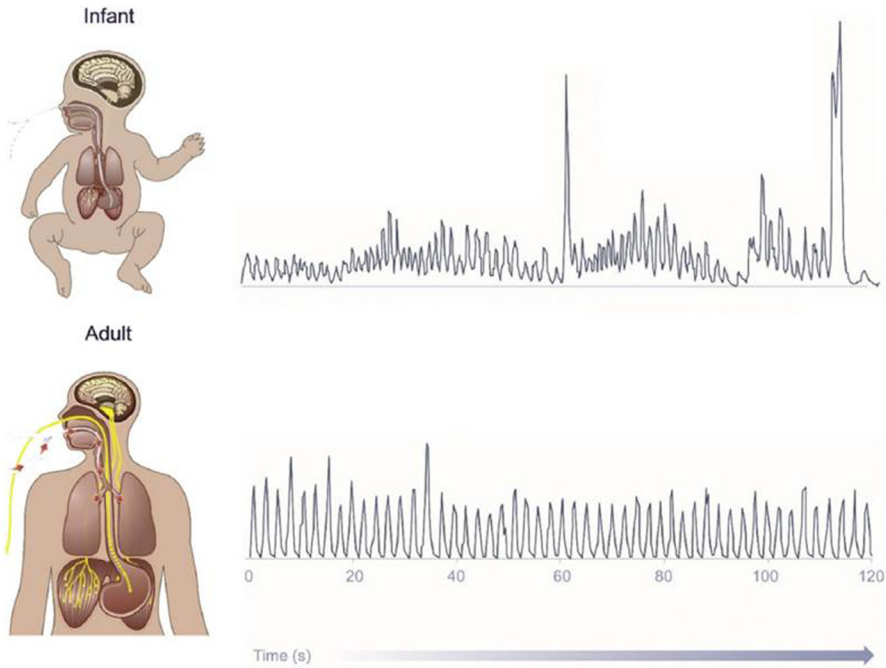


**Fig. 5.** In contrast to the adult or child with mature respiratory control (*bottom*), the preterm infant's breathing pattern, as reflected by the EAdi, is erratic with bursts of vigorous breathing interspersed with periods of hypoventilation and short apneas (*top*). (*From* Firestone KS, Fisher S, Reddy S, White DB, Stein HM. Effect of changing NAVA levels on peak inspiratory pressures and electrical activity of the diaphragm in premature neonates. *Journal of perinatology: official journal of the California Perinatal Association*. 2015;35(8):612-616.)

with the sometimes erratic respiratory effort of the preterm infant.[123] VG, a modality developed specifically for preterm infants is, by contrast, a negative feedback approach, which generates less inflation pressure when the $V_T$ exceeds the target and more when it is less than target, aiming to maintain a stable $V_T$ (**Fig. 6**). Although NAVA and PAV are interesting modalities with obvious potential benefits, larger randomized trials are needed to establish safety and efficacy in preterm infants with immature respiratory control.

## AIRWAY PRESSURE RELEASE VENTILATION

Airway pressure release ventilation is a technique designed to achieve lung volume recruitment and relies on patient's spontaneous breathing to achieve the bulk of minute ventilation. The ventilator maintains a high inflation pressure for most of each ventilator cycle with periodic "release" of this pressure for brief periods.[135] This alternating pattern of low and high airway pressure is, in essence, a form of extreme inverse ratio ventilation. Similar to biphasic CPAP it relies on spontaneous breathing and aims to optimize lung volume recruitment, but in a more extreme way. Airway pressure release ventilation is usually used as a rescue technique and in contrast to biphasic CPAP, the upper pressure level "P high" is maintained for most of the cycle "T high." The pressure to which the lungs are released is called "P low" and the release time is called

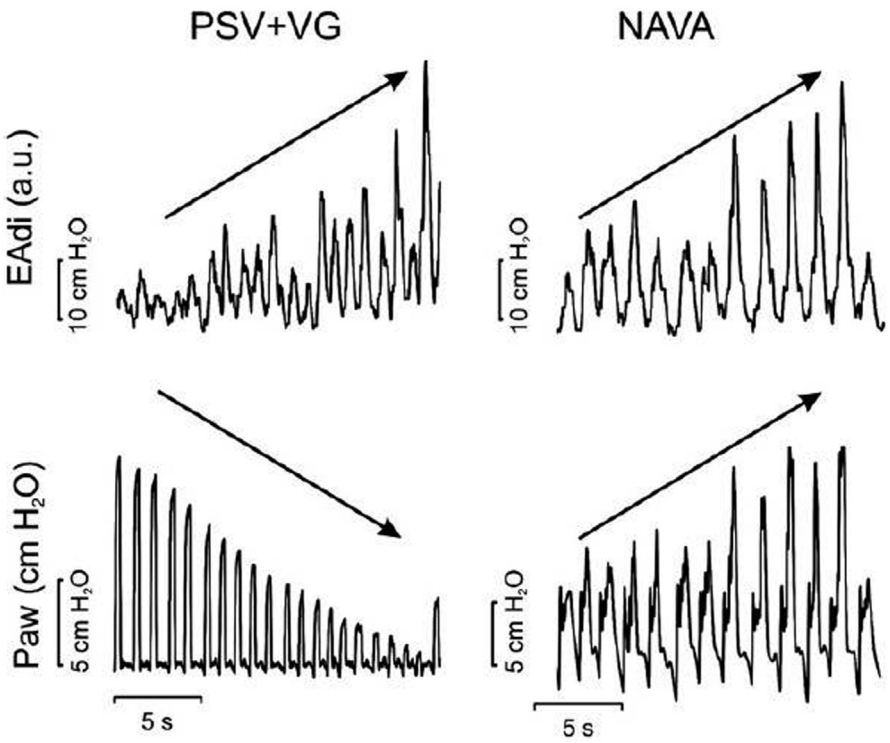


**Fig. 6.** The contrasting approaches to respiratory assist between VG ventilation (*left*) and NAVA (*right*). With VG, when the patient's respiratory effort, as indicated by the EAdi, is insufficient or absent, the ventilator generates a higher peak inflation pressure (PIP); when vigorous inspiratory effort generates excessive tidal volume, the ventilator pressure decreases to maintain a stable tidal volume. This is a negative feedback loop. With NAVA, mature respiratory control is assumed and the ventilator delivers PIP in direct proportion to the EAdi, a positive feedback mechanism. airway pressure (Paw); pressure support ventilation (PSV). (*From* Sinderby C, Beck J. Proportional assist ventilation and neurally adjusted ventilatory assist–better approaches to patient ventilator synchrony? Clin Chest Med. 2008;29(2):329-342, vii.)

"T low." The technique has primarily been used in adult patients with acute lung injury, where there is evidence for short-term benefits in terms of oxygenation but no demonstrable improvement in survival or reduction in complications.[135] There is insufficient evidence to assess the utility of this technique in newborn infants with only a handful of case reports available and no controlled trials, but it is concerning that a recent randomized trial in pediatric patients was terminated early because of increased mortality in the airway pressure release ventilation arm.[136]

## MANDATORY MINUTE VENTILATION

Mandatory minute ventilation may be useful in preterm infants who have inconsistent respiratory effort. Mandatory minute ventilation is a modification of SIMV with PS that maintains a low baseline rate of mandatory inflations as long as the patient's spontaneous effort, augmented by PS, is adequate to meet the user-selected mandatory

minute ventilation target. When the patient's respiratory rate falls, the device increases the SIMV rate in a proactive fashion if the projected minute ventilation is falling short.[137] Although conceptually attractive, the potential benefits of this approach have not been clearly demonstrated.[138] Other approaches, such as assist control with an appropriate backup rate combined with VG, can already achieve the same goal.

## ADAPTIVE SUPPORT VENTILATION

Adaptive support ventilation is modality of ventilation used in pediatric and adult patients that uses automatic adjustments to respiratory rate and $V_T$.[139] The clinician determines the desired minute ventilation, and the adaptive support ventilation algorithm determines the optimal respiratory rate/$V_T$ combination according to the patient's respiratory mechanics. The optimal respiratory rate and $V_T$ are reassessed on a breath-to-breath basis based on continuous measurement of lung mechanics. In periods during which the spontaneous breathing rate decreases, mandatory inflations are provided to maintain the desired respiratory rate. The modality is unlikely to be adapted to neonatal ventilation, because of its complexity, need for accurate measurement of lung mechanics and $V_T$, and the erratic respiratory pattern of preterm infants.

## AUTOMATED CONTROL OF FRACTION OF INSPIRED OXYGEN

Automated oxygen controllers reduce the percent of time infants spend outside target oxygen saturation as measured by pulse oximetry levels.[140,141] Both hyperoxemia and hypoxemia are reduced and thus this technology might reduce oxidative stress and proinflammatory stimuli in preterm infants at risk for BPD, a hypothesis being tested in a current multicenter trial.[142] Unfortunately, these devices have not yet received approval for clinical use by the Food and Drug Administration and are thus not available in the United States.

## SUMMARY

Prevention of lung injury remains an elusive goal of neonatal respiratory support. Careful delivery room stabilization with early application of distending pressure to facilitate establishment of FRC and clearance of lung fluid is an essential first step. CPAP remains the mainstay of noninvasive respiratory support, but a variety of other approaches to noninvasive ventilation are being explored with NIV NAVA potentially the most promising strategy. Less invasive means of surfactant administration have shown promising results, but evidence is still accumulating as to which approach is best. If mechanical ventilation is needed, optimization of lung inflation, avoidance of volutrauma, and atelectrauma are essential. Of the novel techniques of mechanical ventilation NAVA has been more extensively studied, but larger clinical trials with important clinical outcomes are needed. Clinicians should exercise caution regarding adoption of novel therapeutic interventions until more evidence of safety and efficacy are available.

## BEST PRACTICES

Current Practice: Large practice style variation persists in neonatal respiratory support, in part because of incomplete evidence to guide best practice. Lack of a consistent approach with

frequent changes in support based on individual clinician preference is common. Uncertainty remains about optimal delivery room stabilization of preterm infants. Pressure-controlled synchronized intermittent mandatory ventilation remains the most prevalent approach in the United States, despite evidence that alternate approaches lead to better outcomes. The open lung strategy is not often practiced with conventional ventilation. Adoption of less invasive surfactant administration, non-invasive support and advanced modalities of support remains uneven.

Steps that would improve outcome: Adoption of an evidence-based consistent approach to respiratory support is an important step toward improving outcome. The adopted strategies should start with initial stabilization and address surfactant administration, non-invasive support, criteria for escalation of support to invasive ventilation and for progression to novel strategies.

Best Practice: Gentle application of continuous positive airway pressure (CPAP) is appropriate in all preterm infants to facilitate lung aeration and clearance of lung fluid. The pressure used may need to be titrated to effect. Sustained inflation should be avoided. Positive pressure ventilation should be delivered via a T-piece resuscitator with care to use minimal pressures needed to achieve a chest rise and improved heart rate. Intubation and invasive ventilation should be reserved for infants with inadequate respiratory effort who fail to respond to initial non-invasive positive pressure ventilation. Intubation solely for the purpose of prophylactic surfactant is not indicated. Less invasive surfactant administration via a thin catheter or laryngeal mask airway appears to be the best option for avoiding the need for mechanical ventilation.Most infants born at 26 weeks and beyond are able to be supported, at least initially with non-invasive support. CPAP remains the gold standard and there is some evidence that bubble CPAP via short binasal prongs is superior to ventilator CPAP.The RAM cannula has very high resistance resulting in delivery of less pharyngeal pressure than the set value. It functions more lake a high flow cannula and is not the preferred interface for small preterm infants.High-flow nasal cannula therapy is a reasonable alternative in larger preterm infants, but less effective than CPAP in very low birth weight infants.Observational data and early randomized trials suggest that prolongation of CPAP use until 32 weeks promotes lung growth and may reduce the incidence of bronchopulmonary dysplasia.Nasal intermittent positive pressure ventilation (NIPPV) appears to be more effective than CPAP, but non-synchronized NIPPV does not generate a measurable tidal volume - its apparent benefits stem from the use of higher mean airway pressure, compared to CPAP. Synchronized NIPPV, only available outside of the United States, appears to be more effective than CPAP. Non-invasive neurally adjusted ventilatory assist (NIV NAVA) is a form of synchronized NIPPV that is available in the United States appears to be superior to CPAP or non-synchronized NIPPV, but current evidence is weak.Nasal high-frequency ventilation is a promising novel approach that needs further study before widespread use can be advocated.Volume-targeted ventilation is the preferred mode of invasive respiratory support, based on several meta-analyses, resulting in a significant reduction in most complications of respiratory support. It is best combined with assist-control or pressure support ventilation.The use of adequate distending pressure to achieve an open lung strategy is a key element in avoiding ventilator associated lung injury with all forms of non-invasive and invasive ventilation.High frequency ventilation may not be superior to state of the art conventional ventilation, but it does facilitate lung volume recruitment. When combined with optimal lung volume strategy and volume-targeting, as currently available outside the United States, it may provide the best lung-protective ventilation approach.Invasive neurally adjusted ventilatory assist (NAVA) support of very preterm infants has been widely embraced but lacks a solid evidence base. There are potential risks of this approach that provides inflation pressure in proportion to infant's effort in preterm infants with immature respiratory control and frequent periodic breathing, apnea and brief bursts of strong inspiratory effort when disturbed. For this reason, it cannot currently be recommended as best practice.

## DISCLOSURE

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