2019 Year in Review: Neonatal Respiratory Support

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Respiratory support of the critically ill neonate has steadily shifted from invasive to noninvasive forms of support. There have recently been a number of important advances in our understanding of the changes to neonatal resuscitation practices as they pertain to clinically important outcomes, mechanisms of gas exchange for high-flow nasal cannula, and best use of noninvasive ventilation and predicting response. Although the proportion of infants requiring intubation and mechanical ventilation has decreased, the most severely ill often still require intubation and ventilation. Recently, volume-targeted ventilation, high-frequency ventilation, and different methods of assessing weaning and extubation have been investigated. This review summarizes a number of important advances that have been made in the management of prematurity and neonatal respiratory distress syndrome. [Respir Care 2020;65(5):693–704. © 2020 Daedalus Enterprises]

Introduction

Current recommendations promote primary use of noninvasive modes of ventilation in spontaneously breathing premature infants with the aim of avoiding intubation and exposure to invasive mechanical ventilation, which have been associated with increased mortality and morbidities.[1] Despite increased utilization of noninvasive ventilation

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The authors have disclosed no conflicts of interest.

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DOI: 10.4187/respcare.07720

(NIV), a significant proportion of infants < 28 weeks gestational age require intubation in the delivery room or after failing NIV. The avoidance of endotracheal intubation may defer or limit the use of conventional methods of surfactant replacement therapy. This review summarizes a multitude of important discoveries and advances that have been made in the management of prematurity and neonatal respiratory distress syndrome in 2019.

Neonatal Resuscitation

Suctioning Infants With Meconium-Stained Amniotic Fluid

Approximately 10–15% of all infants are born in the presence of meconium-stained amniotic fluid.[2] Of these, 3–9% go on to develop meconium aspiration syndrome.[2] It has been known for some time that routine intubation and tracheal suctioning of all neonates with meconium-stained amniotic fluid does not result in a decreased incidence of meconium aspiration syndrome.[3] Because there is insufficient evidence to support the routine practice of tracheal suctioning in nonvigorous infants (defined as having depressed respiration and poor muscle tone) born with meconium-stained amniotic fluid, suctioning is not recommended.[2] Positive-pressure ventilation is recommended by the American Heart Association and the American Academy of Pediatrics for nonvigorous infants born with meconium stained amniotic fluid, but only if the infant is apneic or the heart rate fell to < 100 beats/min.[4] Edwards et al[5] conducted a retrospective database review of 301,150 infants from United States centers participating in the Vermont Oxford Network admitted to the neonatal ICU before the guideline change (2013–2015) and after the change (2017). Overall, neonatal ICU admissions for meconium aspiration syndrome decreased from 1.8% to 1.5% of total admissions (relative risk [RR] 0.82, 95% CI 0.68–0.97). In the delivery room, endotracheal tube suctioning decreased from 57.0% to 28.9% from before the guideline change to the current era (RR 0.51, 95% CI 0.41–0.62). Adjunct therapies, including high-frequency ventilation, inhaled nitric oxide (INO), and extracorporeal membrane oxygenation, were unchanged between the groups. The authors note that the use of surfactant in patients with meconium aspiration syndrome increased from 24.6% to 30.0% (RR 0.82, 95% CI 1.01–1.48) in 2017. Although the authors state that mortality increased from 2.6% to 2.9% (RR 1.12, 95% CI .74–1.69) and moderate to severe hypoxic-ischemic encephalopathy increased from 5.4% to 6.8% (RR 1.24, 95% CI 0.91–1.69). Importantly, the confidence intervals are wide, and it is unknown what interventions or clinical features may have confounded this retrospective study. Indeed, the current guidelines do not recommend routine suctioning, but clinicians may feel inclined to offer suctioning in certain cases. Edwards et al[5] were unable to comment about this rate because further work is needed before a concrete conclusion can be made.

Kumar et al[6] conducted a randomized controlled trial (RCT) of endotracheal suctioning for the prevention of meconium aspiration syndrome. They enrolled 132 nonvigorous neonates with meconium-stained fluid to receive either endotracheal suctioning or no suctioning. No differences were observed in the incidence of meconium aspiration syndrome (31.8% vs 22.7%, RR 1.4, 95% CI 0.793–2.470), mortality (13.6% vs 7.5%, $P > .05$), or duration of hospital stay (54 vs 44 h, $P > .05$) in the endotracheal suctioning or no suctioning groups. Routine suctioning in the moments following birth with meconium-stained amniotic fluid was not found to be useful in preventing meconium aspiration syndrome.

Supplemental Oxygen

Over the last quarter century, the overall survival in extremely premature babies has improved.[7,8] Because more infants are surviving, there is an increased incidence of intraventricular hemorrhage, necrotizing enterocolitis, patent ductus arteriosus, developmental delay, bronchopulmonary dysplasia (BPD), and retinopathy of prematurity.[8] Supplemental oxygen and mechanical ventilation are important risk factors for the development of BPD and retinopathy of prematurity.[9,10] Certainly, supplemental oxygen is an essential component of the overall life-sustaining care that is provided to premature babies as part of resuscitation, but are there ways to facilitate pulmonary vasodilation and support adequate oxygenation without high levels of oxygen? Sekar et al[11] investigated the use of INO as an additional therapy during neonatal resuscitation with a double-blind, RCT of 28 infants during positive-pressure ventilation. Half were randomized to receive oxygen ($F_{IO_2} = 0.3$) and INO at 20 ppm (the INO group), and the other half were randomized to receive oxygen and placebo (the control group). The authors noted that cumulative oxygen exposure was significantly lower in the INO group compared to the control group ($P = .001$). The proportion of hyperoxia was also lower in the INO group compared to the control group ($P < .001$). There were no differences in the measured physiologic parameters, nor was there a need for invasive mechanical ventilation. Although use of INO is understood to be safe when used at levels ≤ 20 ppm, it is not clear from the current data that adding INO to reduce F_{IO_2} has an important effect on the risk of BPD and retinopathy of prematurity. However, it will be interesting to see this work grow in the coming years as more work will be done.

A number of large RCTs have sought to determine the effect of low (85–89%) and high (91–95%) S_{PO_2} targets in

extremely premature infants.[12-14] Lower saturation ranges are associated with an increased risk of death but with a reduced risk of retinopathy of prematurity.[12-14] As such, the optimal saturation range continues to be debated. Foglia et al[15] sought to investigate the association between oxygen saturation alarm policy changes and neonatal morbidity and mortality. They conducted a retrospective review of 3,809 subjects in 10 hospitals with a change in S_{PO_2} alarm policy and 3,685 neonates from 9 hospitals with no changes in their policy between 2006 and 2014. In hospitals with a policy change, differences in morbidity and mortality were compared in the period before and after the policy change. The policy change primarily included tightening the upper and lower S_{PO_2} alarm limits. Mortality was similar in hospitals that did have a policy change over the study period (adjusted odds ratio 0.94, 95% CI 0.75–1.18), but it decreased in hospitals who did not institute a policy change (adjusted odds ratio 0.63, 95% CI 0.5–0.8). Stated more simply, hospitals that enacted tight S_{PO_2} alarm targets did not see an improvement in mortality, and those that ignored this initiative tended to see a decrease in mortality. Although these data are retrospective, the findings suggest that tight S_{PO_2} alarm limits are not associated with reduced mortality or incidence of retinopathy of prematurity, as one may suspect.

Heated Humidified High-Flow Nasal Cannula

Because life-saving invasive mechanical ventilation may induce lung injury in premature infants with delicate, immature lungs, noninvasive respiratory support is therefore an important part of treating a premature baby. CPAP applied using a nasal interface has be shown to be beneficial in infants with apnea and parenchymal lung disease.[16,17] However, CPAP use is associated with an increased risk of nasal trauma from the interface, permanent changes to the nasal anatomy in severe cases of trauma, abdominal distention, and pneumothorax.

Comparing High-Flow Nasal Cannula and Nasal CPAP

Recently, Guimarães et al[18] conducted a retrospective analysis of 135 premature infants whose birthweight was < 1,500 g. Nasal trauma was reported in 65% of subjects receiving CPAP, 26% of whom had skin breakdown of grade 2 or worse. Therefore, many groups have sought alternative treatment modalities. Heated, humidified, high-flow nasal cannula (HFNC) therapy has exhibited efficacy and safety similar to CPAP when applied as a primary approach to mild and moderate respiratory distress in premature babies and may reduce the likelihood of nasal trauma and pneumothorax.[19] Hong et al[20] conducted a meta-analysis of RCTs comparing the effectiveness and side effects of HFNC and CPAP that included data from 21 RCTs and 2,886 premature infants. Overall, treatment failure was similar between HFNC and CPAP (RR 1.03, 95% CI 0.79–1.33). HFNC was associated with a reduced risk of nasal trauma ($P < .001$) and pneumothorax ($P = .03$) versus CPAP. In the case of providing respiratory support following extubation, CPAP was associated with a lower chance of treatment failure (RR 1.23, 95% CI 1.01–1.50). In babies with primary respiratory support, there were no differences in the time to reach full feeds between HFNC and CPAP. On the surface, this finding is perplexing because one would think that increased comfort and reduced abdominal distention during HFNC would allow a quicker advance on feedings. However, many trials do not protocolize the feeding regimen when comparing respiratory support devices, and the similarities in time to full feeds may be due to practice. Trials specifically designed to assess the advancement and tolerance of full feeds between respiratory support modalities are warranted.

Physiologic Effects of HFNC

Overall, HFNC continues to be a safe and mostly effective tool to provide respiratory support to premature infants. The mechanisms of action are not well understood, however, although they are thought to include a reduction in dead-space, generation of end-expiratory pressure, and possibly even agitation.[21] During HFNC, a number of factors influence the relative effectiveness of the therapy. Degree of leak around the nares, mouth open or closed, degree of spontaneous breathing, and flow settings have important effects on the degree of pressure generation and therefore on support.[21,22]

Liew et al[23] conducted a prospective randomized crossover study to assess the effects of HFNC on respiratory physiology. Among 44 infants whose birthweight was < 2,000 g, increasing flows from 2 to 8 L/min led to a mean increase in end-expiratory pressure of 2.3–6.1 cm H_2O as measured with nasopharyngeal airway pressure monitoring. However, the variance among subjects and in subjects when the mouth was closed or open was great. In some cases, the end-expiratory pressure exceeded 12 cm H_2O. In Figure 1, the variance in nasopharyngeal pressure as a function of set flow on the HFNC is depicted.

Charles et al[24] conducted a prospective, randomized, crossover study of HFNC and NIV to compare the work of breathing for premature infants following extubation. To assess work of breathing, catheters were placed to measure esophageal and gastric pressures, and the transdiaphragmatic pressure was calculated to obtain an estimate of the work of breathing. By virtue of the crossover design, each subject served as their own control and received 2 h of

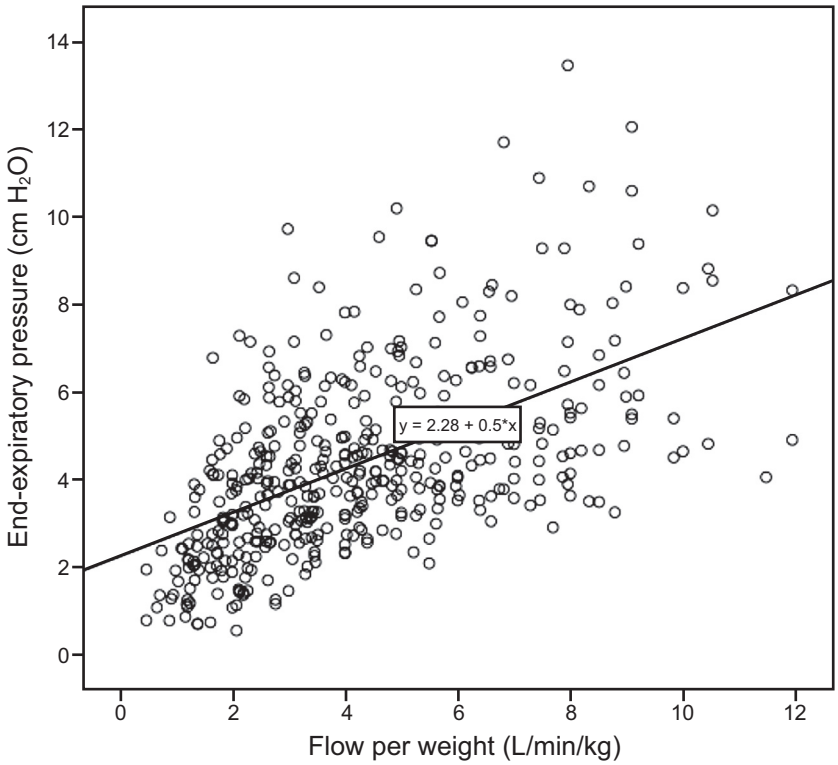

Fig. 1. Scatter plot of relationship between nasopharyngeal end-expiratory pressure and weight-adjusted flow. There is large variability of end-expiratory pressure measured > 6 L/min/kg, with some measurements measuring up to 8–13 cm H_2O. From Reference 23, with permission.

either HFNC or NIV followed by 2 h of the opposing therapy in a randomized fashion. Although 21 subjects were enrolled, only 9 completed the study and were therefore included in the analysis. The pressure-time product of the transdiaphragmatic pressure was lower during NIV than HFNC (232 vs 365 cm $H_2O \times$ s/min; $P = .008$). Applying these findings to other patient populations is tricky. First, the NIV was set to deliver a peak pressure of 14–16 cm H_2O and an expiratory pressure of 5 cm H_2O. Because there is no increase in support during the inspiratory phase of the breath cycle with HFNC, it is not surprising that NIV provides more support and therefore decreases the total pressure-time product of the transdiaphragmatic pressure. Although the authors concluded that the lower estimated work of breathing during NIV is advantageous, that may not always be the case. Indeed, the essential question to answer is what the target work of breathing for a premature infant in the ICU actually is. Certainly, in the context of acute decompensation and limited respiratory effort, NIV may be indicated, but if a patient is supported without distress on HFNC, why would one select a therapy that offers a reduced work of breathing? This study offers a reasonable comparison of NIV and HFNC, but larger RCTs are required to determine which is most effective.

Noninvasive Ventilation

Respiratory distress syndrome (RDS) is the primary cause of respiratory failure in premature infants as result of inadequate lung development and surfactant deficiency.[25] Mounting evidence from multi-center RCTs and subsequent meta-analyses indicate that nasal CPAP is an effective alternative to intubation and prophylactic surfactant administration.[26-28] These data were incorporated into the American Academy of Pediatrics recommendation to utilize CPAP immediately after birth for spontaneously breathing infants, with selective surfactant administration being reserved for infants who subsequently require intubation and mechanical ventilation.[1] Current care includes early utilization of CPAP to reduce respiratory distress, ventilator-induced lung injury, and risk of BPD.[1,29] Despite increased utilization of CPAP as the primary mode of respiratory support, failure rates approach 50% in infants < 28 weeks gestational age, with progressively higher rates of intubation in babies with lower gestational age.[30-33] However, it remains unclear what proportion of infants at lower gestational ages can be successfully supported with CPAP alone. In a large, multi-center, prospective, observational study, Moya et al[34] sought to compare the initial respiratory management of premature infants, with a focus on

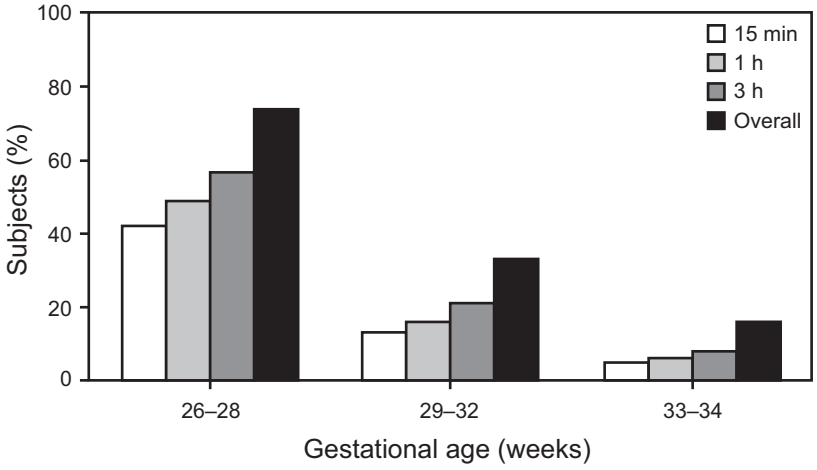

Fig. 2. Rates and timing of endotracheal intubation stratified by gestational age. Nearly 75% of infants between 26 and 28 weeks gestational age were intubated within 3 h after delivery. From Reference 34, with permission.

identifying indications for and timing of endotracheal intubation. These authors stratified subjects according to gestational age (ie, 26–28 weeks, 29–31 weeks, and 33–34 weeks) and found corresponding CPAP failure rates of 50%, 26%, and 20%, respectively. Rates of intubation were progressively higher at lower gestational age: 76% of infants 26–28 weeks; 33% of infants 29–32 weeks, and 16% of those 33–34 weeks gestational age. Nearly 75% of subjects < 28 weeks gestational age were intubated within 3 h after delivery. Rates and timing of endotracheal intubation are displayed in Figure 2.

Although surfactant deficiency is often considered the primary cause of CPAP failure, other etiologies of failure including lung immaturity, chest wall instability, upper airway obstruction, poor respiratory drive, apnea, bradycardia, and type of equipment may also impact effectiveness. Therefore, early identification of treatment failure is paramount because it is associated with adverse outcomes including BPD, prolonged duration of mechanical ventilation, and death.[30,35] As such, several investigators have sought to identify risk factors associated with failure and to create prediction models with clinically relevant cut-points to aid clinicians in more efficient management. In a multicenter prospective study of infants < 30 weeks gestational age who received CPAP within 15 min of birth, Gulczyńska and colleagues[36] aimed to assess prognostic factors to define CPAP failure and facilitate timely identification of infants requiring surfactant replacement therapy (SRT). These authors described an overall failure rate of ~28% with increased frequency at lower gestational ages: 50% for infants 23–24 weeks versus 23% for infants 29 weeks. Moreover, birthweight (odds ratio 1.06, 95% CI 1.04–1.09, $P < .001$) and $F_{IO_2} > .29$ (odds ratio 0.84, 95% CI 0.77–0.92, $P < .001$) in the second hour of life were independent predictors of CPAP failure. Importantly, CPAP failure was associated with a 20-fold higher risk of death or pneumothorax and 2–5-fold increased risk for BPD and intraventricular hemorrhage. Consistent with these findings, Kakkilaya et al[37] reported a 50% failure rate in subjects < 29 weeks gestational age and identified $F_{IO_2} > 0.30$ at 2 h of life and radiographic severe RDS (assessed via Downes score) as independent predictors of CPAP failure. Collectively, these data suggest that $F_{IO_2} > 0.3$ at 2 h of life is a useful metric to identify infants who are at risk of failing CPAP, thereby allowing clinicians to consider interventions that may prevent or limit exposure to invasive mechanical ventilation (eg, escalation of CPAP level, NIV, or SRT).

The utilization of NIV has gained traction as an alternative to CPAP for both primary and postextubation respiratory support.[38,39] NIV provides similar baseline distending pressures as CPAP with the addition of superimposed PIP and either time-cycled or synchronized ventilator breaths. The potential advantages of NIV include reductions in work of breathing, increased tidal volume (V_T), minute volume, and mean airway pressure, with reported improvements in S_{PO_2} and carbon dioxide removal. Ekhaguere and colleagues[40] pooled data from 16 trials ($n = 2{,}014$ subjects) comparing NIV to CPAP and reported a significant reduction in respiratory failure (RR 0.55, 95% CI 0.46–0.65) in premature infants. Additionally, the aggregate data from 4 trials comparing synchronized NIV to CPAP suggest synchronization may further improve effectiveness (RR 0.40, 95% CI 0.26–0.62).[40] Importantly, some trials included in the meta-analysis contained subjects who received intubation and SRT, which limits the ability to generalize these findings to extremely low birthweight (ELBW) infants who are naïve to early intubation and SRT.[38] In a secondary analysis of RCT data, Bourque and associates[41]

restricted inclusion criteria to ELBW infants who were never intubated prior to randomization. The primary outcome assessed was noninvasive respiratory support (CPAP vs NIV) failure, defined as the need for intubation in the first 7 d. Of the 142 included subjects, 28% in the NIV group and 30% of the CPAP group experienced treatment failure (RR 0.91, 95% CI 0.54–1.53). Consistent with previous trials and meta-analyses, there was no difference in the composite outcome of death or in BPD at 36 weeks, and time until failure between CPAP and NIV groups was similar. Similarly, Armanian et al[42] randomized infants < 1,500 g to HFNC, NIV, or CPAP and noted that treatment failure occurred most frequently in HFNC (54%), followed by CPAP (35%) and then NIV (22%). Based on these findings, the authors concluded that NIV and CPAP had similar outcomes, whereas HFNC was associated with a 9-fold increase in failure rate and therefore should not be used as early support. Using similar criteria, Gharehbaghi and colleagues[43] randomized 61 subjects (28–32 weeks gestational age) to either CPAP or NIV and reported that either mode was equally effective as initial support. Lastly, Kallio et al[44] randomized preterm subjects (28–36 weeks gestational age) to either noninvasive neurally adjusted ventilator assist ventilation (NIV-NAVA) or CPAP and found no significant effect on the need for invasive ventilation or oxygen requirements. Collectively, these finding suggest that either CPAP or NIV (synchronized or time-cycled) are effective as primary support; however, available evidence suggests that NIV is superior to CPAP.

NIV had also demonstrated superiority over CPAP in the reduction of respiratory failure (RR 0.60, 95% CI 0.45–0.81) in the setting of postextubation respiratory support.[40] Despite the potential advantages of NIV over CPAP on reducing the need for re-intubation, there is no conclusive evidence that NIV is superior insofar as reducing BPD.[39,45] In contrast, retrospective studies comparing extubation to CPAP or NIV in ELBW infants < 28 weeks gestational age have suggested that NIV may be associated with a higher incidence of BPD.[46,47]After adjusting for birthweight and gestational age, Abu-Shaweesh et al[46] reported that NIV continued to be associated with a higher incidence of BPD (odds ratio 5.9, 95% CI 1.2–29.1, $P = .03$). Moreover, prolonged usage of NIV demonstrated a higher incidence of moderate to severe BPD (84% vs 66%, $P = .044$) and death or severe BPD (75% vs 48%, $P = .003$) compared with subjects treated with CPAP.[47] After adjustment for days on oxygen, ventilator duration, and days on respiratory support, the odds of developing moderate to severe BPD increased by 5% for each additional week on NIV (95% CI 2.1–7.7%, $P < .001$). Although these findings require further prospective validation, these data underscore the need for more research to assess the effects of varied NIV pressures, develop standardized guidelines, and weaning criteria.

Other modalities, including NIV-NAVA and noninvasive high-frequency ventilation have been utilized as both primary support and to prevent re-intubation in preterm infants.[48] NAVA has received considerable research interest based on the potential benefits of synchronizing noninvasive support with an infant's spontaneous breaths. NAVA is unique because it uses a proprietary nasogastric catheter to measure the electrical activity of the diaphragm and proportionally augment respiratory support according to diaphragmatic signal activity.[49] Yagui and associates[50] retrospectively compared NIV-NAVA to CPAP in a cohort of subjects who were considered at high risk for re-intubation, operationally defined as birthweight < 1,000 g, on invasive ventilation for > 7 d, or previous extubation failure. These authors found that the re-intubation rate was significantly lower in the NIV-NAVA group (12% vs 50%, $P = .02$) despite a significantly longer duration of invasive ventilation (5.5 vs 12.4 d, $P = .04$). Consistent with these findings, Lee and colleagues[51] reported a reduction in extubation failure for infants < 30 weeks gestational age who received NIV compared with CPAP (6% vs 38%, $P = .041$). Although these results are encouraging, both studies were retrospective by design and had a limited sample size.

Noninvasive high-frequency oscillatory ventilation (HFOV) has also been investigated for primary and postextubation support. Similar to invasive HFOV, noninvasive HFOV is not dependent on synchronization, and set parameters include mean airway pressure, pressure amplitude, and frequency.[40] Whereas smaller observational studies in premature infants suggest that noninvasive HFOV is capable of enhancing carbon dioxide elimination,[52,53] a larger randomized crossover trial including preterm infants < 32 weeks gestational age following SRT found no difference.[54] Iranpour et al[55] randomized older subjects (30–36 weeks gestational age) to either noninvasive HFOV or CPAP and reported duration of noninvasive support was shorter in the noninvasive HFOV group (20 h vs 26.5 h) with no difference in P_{CO_2} after 1 h. A recent meta-analysis of 8 RCTs comparing noninvasive HFOV to CPAP or NIV reported a lower risk of intubation (RR 0.50, 95% CI 0.36–0.70) and more effective carbon dioxide clearance (weighted mean difference = −4.61, 95% CI −7.94 to 1.28) in the noninvasive HFOV group.[56] Importantly, evidence is inconsistent due to methodological heterogeneity in subject characteristics such as age, weight, receipt of SRT, ventilator type, and set parameters. As such, noninvasive HFOV is feasible in preterm infants, although further investigation is needed to evaluate strategies, efficacy, and safety before adoption into practice. Currently, a large, international, multi-center RCT (NCT03181958) consisting of 3 arms (ie, CPAP, NIV, or noninvasive HFOV) is enrolling

subjects (25–32 weeks gestational age) with the aim of evaluating both superiority and safety in the setting of postextubation support[57] (https://clinicaltrials.gov/ct2/show/NCT03181958, *Accessed February 7, 2020*).

Surfactant Replacement Therapy

Historically, surfactant was administered to preterm infants via an endotracheal tube in combination with mechanical ventilation. Although invasive mechanical ventilation is a life-saving intervention in premature infants with respiratory failure, it has been associated with ventilator-induced lung injury and increased risk for the development of BPD.[58] Therefore, to minimize exposure to endotracheal intubation and the negative aspects of mechanical ventilation, several methods of less invasive surfactant replacement have been developed.[59]

INSURE Technique

The INtubation-SURfactant-Extubate (INSURE) technique is one of the most commonly used methods to provide SRT to preterm infants with RDS. The INSURE technique requires a brief exposure to invasive mechanical ventilation with the aim of extubation to noninvasive support; however, a subset of infants cannot be extubated successfully, many of whom were previously stable on CPAP.[16,30,60] De Bisschop and colleagues[61] performed a systematic review with the aim of identifying early predictive risk factors for INSURE failure in preterm subjects with RDS. These authors found a median INSURE failure rate of 33% (9.3–52%) and identified ELBW (ie, 750–1,000 g), lower gestational age, and severe RDS as risk factors for failure. Due the methodological heterogeneity of included studies, it was not possible to create a clinical tool to distinguish infants who could be successfully extubated after the INSURE technique from those who may benefit from continued mechanical ventilation. Similarly, Awaysheh et al[62] described a failure rate of 25% in subjects < 30 weeks gestational age who were treated with the INSURE technique and mechanical ventilation for < 2 h. They reported that gestational age < 28 weeks, birthweight $< 1{,}000$ g, and pH < 7.0 were risk factors for INSURE failure.

Novel Delivery Approaches

The high failure rate of the INSURE technique and perceived benefits of avoiding intubation and mechanical ventilation altogether have led to the development of less invasive methods of SRT, including pharyngeal or laryngeal delivery, inhalation, and thin catheter administration (TCA), which is synonymously described as minimally invasive surfactant therapy or less invasive surfactant administration. Of these methods, TCA via feeding tube, flexible angiocatheter, or specialty introducer tubes has been most extensively investigated.[59] The TCA procedure requires direct or video-assisted laryngoscopy, followed by the insertion of a catheter into the trachea and through the vocal cords of spontaneously breathing infants.[63] Although methods vary slightly, surfactant can be delivered while the infant continues to receive noninvasive support. A recent meta-analysis of RCTs directly comparing TCA and INSURE have reported a reduction in BPD or death composite (RR 0.66, 95% CI 0.46–0.93) and a decrease in the need for mechanical ventilation in the first 72 h (RR 0.72, 95% CI 0.53–0.97), with marginal or no difference in pneumothorax and mortality, respectively.[59] These finding are consistent with previous meta-analyses that reported improved survival without adverse events for infants treated with TCA.[64-68] These data contribute to the growing body of evidence supporting the benefits of less invasive surfactant administration, which has been adopted in Europe as the preferred method of SRT for spontaneously breathing infants.[69] It is important to note that TCA is more commonly practiced in Europe and Australia. In the United States, only 15% of surveyed neonatologists reported using TCA (8% as routine care and 7% for research).[70] Additionally, the procedure requires training, and there are several areas that require further investigation, including the establishment of specific treatment thresholds according to gestational age, timing of treatment, and whether analgesia or sedation is required.[63]

Nebulized Surfactant

Inhaled surfactant represents the least invasive method of SRT and has received considerable research interest. However, due to technical difficulties, including the high viscosity of surfactant, the ability to reproducibly aerosolize particles 1–5 μm in diameter without protein denaturation, and the uncertainty of optimal concentration or dosing, have hampered adoption into clinical practice.[59,71] A recent, single-center, blinded RCT stratified subjects by 29–31 or 32–33 weeks gestational age and compared the efficacy of CPAP alone to CPAP with nebulized surfactant, with the primary outcomes being intubation and the requirement of mechanical ventilation at 72 h.[72] Surfactant nebulization reduced the requirement for intubation compared with CPAP alone (RR 0.53, 95% CI 0.29–0.95). However, this reduction was limited to the 32–33 weeks gestational age stratum, and there were no differences in the proportion of subjects who remained intubated after 24 h, 72 h, or 7 d. This was the first study to provide evidence of successful noninvasive SRT using the eFlow vibrating mesh nebulizer (Pari, Starnberg, Germany). In vitro evaluations of the eFlow nebulizer have reported favorable aerosol

characteristics (mass median particle diameter = 3 μm).[73] These authors also evaluated dose-response in spontaneously breathing rabbits with severe respiratory distress and noted that surfactant doses of 200–400 mg/kg significantly improved oxygenation, respiratory indices, and compliance, achieving a similar response to animals treated with an intratracheal bolus of 200 mg/kg. This nebulization strategy is currently being evaluated in a multi-center phase 2 clinical trial including preterm subjects with mild to moderate RDS (https://www.clinicaltrialsregister.eu/ctr-search/search?query=2016-004547-36, *Accessed February 7, 2020*).

Invasive Mechanical Ventilation

Despite increased utilization of NIV for primary respiratory support, approximately 50% of infants < 28 weeks gestational age go on to require intubation and mechanical ventilation, with risk increasing inversely to gestational age. Moreover, 70% of infants receive invasive mechanical ventilation preceding initiation of CPAP in the delivery room.[30,34] As such, invasive mechanical ventilation continues to be the mainstay of respiratory support for premature infants with RDS. Therefore, it is important to distinguish infants who require SRT and continued mechanical ventilation from those who can be successfully managed on NIV.

Predicted Need for Invasive Ventilation

In a secondary analysis of RCT data, Roberts and colleageues[74,75] sought to identify predictors of both early intubation and short duration respiratory support (≤ 1 d) in subjects born at 28–36 weeks gestational age. Subjects < 30 weeks gestational age with $F_{IO_2} \geq 0.3$ were independent predictors of intubation within 72 h with a corresponding likelihood ratio of 9.1. Conversely, subjects ≥ 34 weeks getstational age with $F_{IO_2} = 0.21$ were 5 times more likely to require only brief respiratory support. These data corroborate the findings of previous studies evaluating NIV failure and suggest that a subset of older infants > 34 weeks gestational age may receive noninvasive support unnecessarily.

Volume-Targeted Ventilation

The greatest need for intubation and mechanical ventilation is observed in the smallest and most premature infants. The use of volume-targeted ventilation over pressure-limited ventilation confers a reduction of BPD, hypocapnia, grade III–IV intraventricular hemorrhage, pneumothorax, and ventilator duration.[76] Despite high-level evidence in support of volume-targeted ventilation, acceptance into clinical practice has occurred slowly because this represents a major paradigm shift away from decades of mostly pressure-limited ventilation use. Several barriers have hampered the diffusion of volume-targeted ventilation, including provider experience level, lack of established V_T targets based upon disease state, large endotracheal tube leaks (eg, > 50%), and a ventilator's ability to deliver and accurately measure V_T.[77-79]

Wong and colleagues[80] prospectively studied very low birthweight and ELBW subjects who underwent volume-targeted ventilation with the aim of describing breath-to-breath variation in expired V_T. The authors analyzed 6 h of continuous ventilator data and found no significant variations in expired V_T between cohorts, despite the ELBW cohort having significantly lower set V_T (4.6 vs 7.2 mL, $P < .001$). This study evaluated volume-targeted ventilation delivery in a single ventilator type because previous bench and animal studies have suggested considerable variability in ventilator performance, with variations in V_T becoming more pronounced with increased leak or lower V_T targets.[79,81] Future studies should evaluate V_T target ranges for specific disease conditions, such as evolving RDS, congenital diaphragmatic hernia, meconium aspiration syndrome, and BPD, and incorporate performance data respective to different ventilators.

High-Frequency Ventilation

A subset of infants are managed with high-frequency ventilation (HFV) as the primary mode of ventilation. In many cases, HFV is implemented primarily as a rescue modality in babies who exhibit persistent respiratory failure despite maximum conventional lung-protective ventilation strategies. Overall, studies comparing the use of HFOV and high-frequency jet ventilation to conventional mechanical ventilation have not reported significant improvement in outcomes for elective or rescue usage.[82,83] A recent, single-center, retrospective cohort of actively managed extremely premature infants were separated in 2 groups: 22–23 gestational age and 24–25 weeks gestational age.[84] The investigators assessed survival and neurological outcomes at 18–22 months of corrected age. Both groups received antenatal steroids, intubation, SRT, and high-frequency jet ventilation as the primary mode of ventilation. Survival to discharge for subjects 22–23 weeks gestational age was 78% (95% CI 0.69–0.88) compared to 89% (95% CI 0.84–0.93) for subjects 24–25 weeks gestational age. In surviving infants, no or mild neurologic impairment was present in 64% (95% CI 0.50–0.77) and 76% (95% CI 0.68–0.83) for the 22–23 and 24–25 weeks groups, respectively. Although the study was conducted over a 10-y period, the results suggest favorable survival and neurodevelopmental outcomes for infants who are often perceived as being on the fringe of viability. In addition, extremely premature infants were not included in previous RCTs evaluating primary use of HFV.

The role of primary HFV in extremely premature infants warrants further prospective investigation.

The Rescue-HFOV Trial Group prospectively evaluated factors affecting the response of 372 subjects who underwent rescue HFOV after failing conventional ventilation.[85] Subjects were separated into 2 groups: survivors and nonsurvivors or those who received extracorporeal membrane oxygenation ($n = 8$). All subjects initially underwent volume-controlled ventilation with $V_T < 7$ mL/kg and were managed with a permissive hypercapnia strategy to maintain a pH > 7.25. HFOV was initiated when the oxygen requirement exceeded 0.6 to achieve $S_{PO_2} > 90\%$. Overall survival to discharge was 58%; subjects who died had lower birthweight (1,655 ± 1,091 g vs 1,858 ± 1,027 g, $P < .006$), higher initial F_{IO_2} (0.83 vs 0.72, $P < .001$), and higher rate of INO exposure (29% vs 11%, $P = .004$). Gestational age was similar between groups; however, in a subgroup analysis of lower gestational age was associated with non survivors (28.6 ± 3.6 vs 29.8 ± 3.6 weeks, $P = .006$). The Rescue-HFOV study included a large multi-center cohort using an open-lung approach during HFOV and used several ventilators that are not commercially available in the United States. These data afford a unique perspective because extracorporeal membrane oxygenation was only available in 1 out of 23 sites, which underscores the importance of early identification of HFOV failure.

Liberation From Mechanical Ventilation

Given the relationship between exposure to mechanical ventilation and BPD, it is prudent to routinely evaluate extubation readiness, provided there are no other indications for continued invasive mechanical ventilation. The decision to extubate is generally based on a review of overall clinical stability, trajectory, gas exchange, and level of ventilatory support. However, approximately one third of premature infants require re-intubation within 7 d.[86] Gupta and colleagues[87] sought to develop a clinical tool to predict successful extubation in preterm infants. In a retrospective cohort of 312 subjects with a birthweight ≤ 1,250 g, perinatal factors and characteristics were compared between successful (defined as ≥ 5 d without requiring re-intubation) and failed extubation. Subjects were considered for extubation if the following criteria were met: ventilator rate of 16–20 breaths/min, mean airway pressure < 8 cm H_2O, $F_{IO_2} < 0.4$, pH > 7.25, and $P_{CO_2} < 60$ mm Hg. Extubation success was reported in 73% of subjects; in the 27% subjects who failed extubation, 89% were reintubated within 72 h. Adjusted analysis indicated that successful extubation was independently associated with higher gestational age, chronologic age at time of extubation, pH, lower pre-extubation F_{IO_2}, and lower respiratory severity score (ie, F_{IO_2} × mean airway pressure). The area under the receiver operator curve was 0.77, which indicated a reasonable predictive performance. Sensitivity analysis was repeated using an alternative definition of successful extubation (ie, ≥ 72 h without requiring re-intubation), and the same covariates were identified, suggesting that the resultant estimator is useful for either definition.

The Automated Prediction of Extubation Readiness (APEX) study prospectively enrolled subjects with birthweight < 1,250 g who were considered ready to extubate and underwent a 5-min spontaneous breathing trial (SBT) on endotracheal tube CPAP prior to extubation.[88] APEX utilized machine learning tools to characterize clinical variables and quantitative measures of cardiorespiratory events, including apnea requiring stimulation, bradycardia, desaturation, and requirement for increased F_{IO_2}. Of the 259 subjects who met inclusion criteria, 71% were successfully extubated (ie, defined as not requiring intubation within 7 d). Subjects who extubated successfully had fewer clinical events, shorter duration of bradycardia, desaturation, and fewer instances of oxygen requirement compared to their counterparts who failed extubation. Multiple receiver operating characteristic curves were constructed to evaluate the diagnostic performance of clinical events and > 40,000 combinations of SBT definitions. Based on these data, the Youden index was used to identify combinations of clinical events with maximum sensitivity and specificity. The SBT with highest Youden index, which defined SBT pass as not demonstrating apnea and desaturation necessitating a 15% increase in F_{IO_2}, yielded a sensitivity of 93% and specificity of 39%. Explained another way, the SBT accurately predicted extubation success for the majority of subjects; however, 61% of subjects who failed extubation would have passed the extubation readiness test, and 7% who failed the extubation readiness test could have been extubated successfully. Systematic review and meta-analysis evaluating predictors of extubation further indicate that commonly used SBT procedures have poor specificity, meaning a significant proportion of those who pass the SBT subsequently fail extubation.[89] Collectively, these findings suggest that there is limited clinical value in assessing extubation readiness via SBT.

Summary

Respiratory support of the premature infant is essential to ensuring the effectiveness of spontaneous breathing and adequate gas exchange. There have been a number of recent and important advances in the field of neonatal respiratory support that have helped improve our understanding of how they work, when one therapy should be selected over others, and the challenges that remain in assessing readiness for weaning and extubation. Aerosolized surfactant and noninvasive high-frequency ventilation are currently being investigated, and it will very interesting to see

the results. Improved methods of predicting extubation failures are warranted.

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