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Ventilation strategies in transition from neonatal respiratory distress to chronic lung disease

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ABSTRACT

Despite the advance in neonatal care over the past few decades, preventing preterm infants with respiratory distress syndrome progress to bronchopulmonary dysplasia remained challenging. In this review, we will discuss the respiratory support strategies in preterm infants with RDS evolving into BPD based on the changes in pulmonary mechanics and pathophysiology as well as currently available evidence.

1. Introduction

The advance in neonatal intensive care has enabled the survival of very premature infants with extremely low birth weight. However, bronchopulmonary dysplasia (BPD) remained as one of the most common complications leading to both short and longer term mortality and morbidities. Survivors of BPD often face chronic cardiopulmonary impairment, growth failure, and poor neurodevelopmental outcomes, which brings a major burden to the babies, their families, the health care system and the society. Prevention of BPD has therefore been the focus of research for the recent years. However, most of the studies concentrated on the first few days of life and few have examined the factors that may affect the transition from early respiratory insufficiency due to respiratory distress syndrome (RDS) to established BPD, and the best strategies to support a preterm infant in this stage to prevent the advance to BPD.

This review attempts to summarize the current available evidence that focuses on the respiratory support strategies to support infants in transition from RDS to BPD. Although other managements such as medication use, PDA management and others are also important in preventing BPD, they are beyond the scope of this review.

2. Changes in pathophysiologic and pulmonary mechanics from RDS to BPD

Both RDS and BPD can be considered developmental diseases that start off with infants born prematurely in the late canalicular or saccular phases of lung development. Multiple characteristics of the premature respiratory system contribute to the pathophysiology and clinical presentation of RDS (Fig. 1). Of these, the developmental deficiency of surfactant is the most important, which contributes to not only the pathological findings of RDS but also to the decrease host defense mechanisms in preterm infants. All four components of surfactant proteins are developmentally and hormonally regulated and increase markedly in the first few days after preterm birth [1,2]. However, their levels can be modulated by the pathogens, toxins and reactive oxygen species in the local microenvironment [3]. In addition to surfactant deficiency, all the other factors that contribute to the pathophysiology of RDS can also increase the preterm infant's susceptibility to injury and poor lung growth. Therefore maintaining a healthy local microenvironment would have critical importance for preterm infants to improve from RDS and enter into a phase of injury repair and healthy lung growth to prevent the progression to BPD.

Unfortunately, this healthy microenvironment is hard to establish or maintain for some of the infants. A variety of prenatal and post-natal factors will influence postnatal lung growth and contribute to lung injury. Genetic and prenatal factors set the stage for increased susceptibility to inflammation and growth failure. Postnatal factors directly or indirectly result in lung injury and poor growth and repair. As a result, pathophysiology of BPD in the current era is characterized by an arrest or delay in alveolar/pulmonary vascular development and various degrees of lung injury. However, depending on the status of lung development at the time of postnatal insults and the interaction between the predisposed susceptibility and the injury, infants with BPD will have

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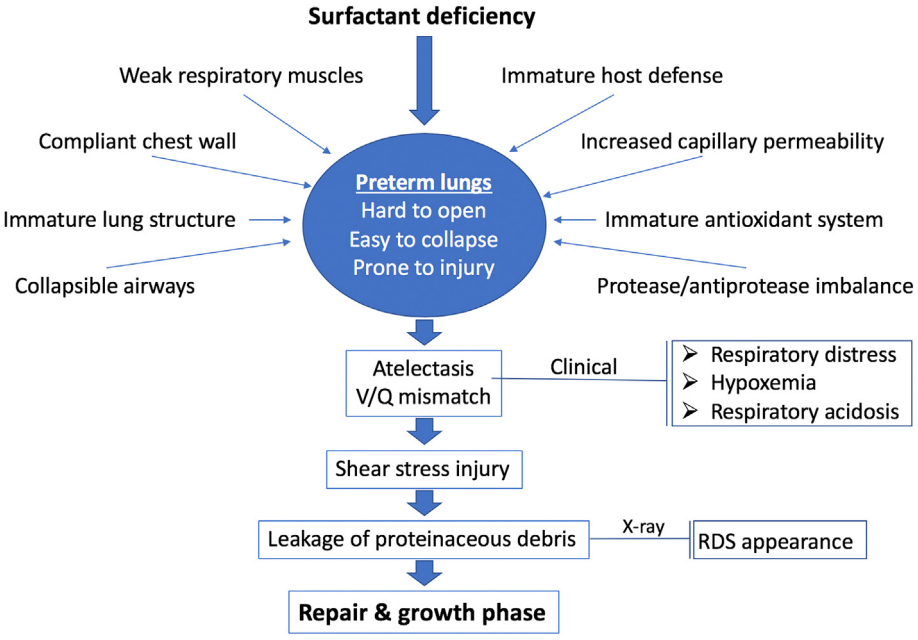

Fig. 1. Characteristics of the premature respiratory system contribute to the pathophysiology and clinical presentation of RDS.

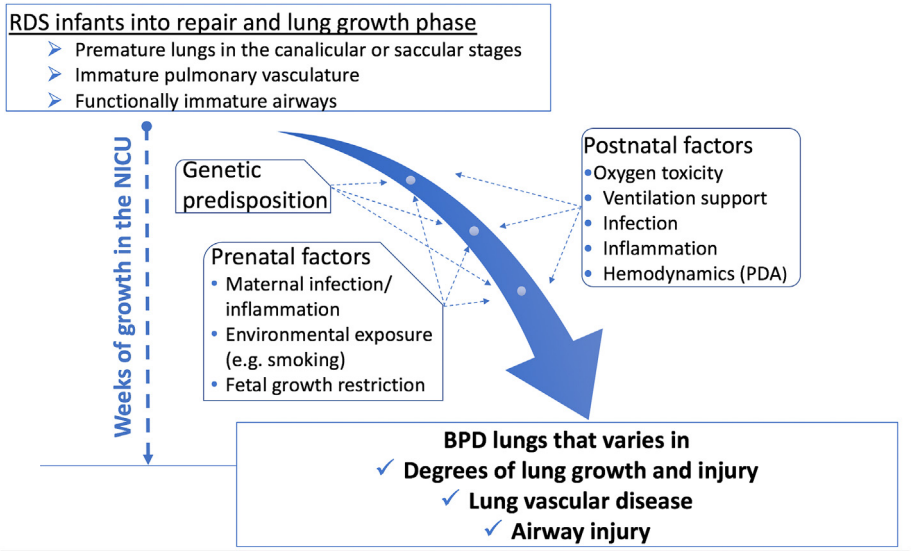

Fig. 2. Interactions of pre-postnatal factors and lung developmental stages resulting in variations in BPD pathophysiology.

variation in the degrees of lung parenchymal disease, pulmonary vascular disease and airway problems (Fig. 2).

The pulmonary mechanics of an infant with RDS is characterized by stiff lungs, i.e. hard to open and easy to collapse, due to decreased lung compliance and high elastance. Without anatomical obstruction, the airway resistance is usually normal in these infants and hence the time constant (the product of compliance times resistance) is usually short, which means that the alveoli of these infant are fast to inflate and deflate. The lung mechanics of a BPD infant, however, is hard to determine as ventilation in these lungs is often uneven with areas of atelectasis and areas of hyperinflation or cystic changes. Therefore, the lung compliance may be high in some areas but low in others. The airway resistance is often high due to hyperplasia of the airway smooth muscles, air trapping, airway malacia or secretions. In these lungs with heterogenous ventilation, some parts of the lung has very long time constant and therefore require much longer time inspiration time to inflate and longer expiration time to deflate [4].

3. Respiratory support strategies to prevent BPD

3.1. Goals of respiratory support

Since lung injury plays an important role in the development of BPD, much of research efforts has focused on finding proper respiratory support strategies that avoid or minimize lung injury. However, we need to keep in our minds that the ultimate goal of respiratory support is to promote healthy life, and avoiding lung injury is only one aspect helping to reach this goal. It is important to remember we are trying to support a whole person, not just a pair of lungs as the lung health will affect the well-being of the other organ systems and vice versa. Take nutritional status and the development of BPD for example, poor nutrition will lead to difficulties with proper lung development, which is the key aspect of pathogenesis of BPD. Meanwhile, chronic respiratory insufficiency in infants with evolving or established BPD will also create challenges for the infant to grow properly (Fig. 3). Therefore the goal of respiratory support for a preterm infant transitioning from RDS to BPD

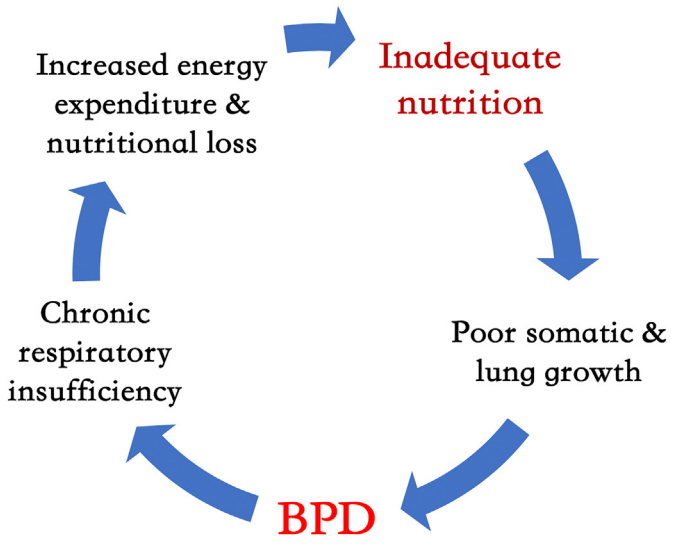

Fig. 3. Interaction of nutrition and BPD.

should not be aimed solely at keeping PCO_2 and SPO_2 in acceptable ranges, but rather providing adequate but not too much support that will adequately support proper growth and injury repair while avoiding or minimizing further lung injury.

The concept of lung protective ventilation has been introduced in an attempt to minimize lung injury. The main goals of lung protective ventilation strategies are avoiding volutrauma, atelectotrauma and biotrauma (e.g. oxygen toxicity). We will discuss some of the most commonly used approaches in this section.

3.2. Permissive hypercarbia

Permissive hypercarbia is a commonly used lung protective ventilation strategy in the treatment of premature infants. With several studies suggesting the strong association of hypocarbia with poor outcomes in preterm infants, including increased risk of BPD, severe intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), and cerebral palsy (CP) [5–8], this approach was quickly and widely adapted worldwide as a method of BPD prevention, before high quality evidence in terms of the efficacy and safety of this approach was available.

The main theoretical benefits of permissive hypercarbia include that through intentional hypoventilation and tolerance of higher pCO_2 levels, we can: 1) Avoid hypocapnia, and its related complications; 2) decrease the level of mechanical ventilation and allow early extubation, thus avoid ventilator associated lung injury; 3) potentially dampen the systemic pro-inflammatory response [9–11] and 4) increased oxygen delivery to tissues and cerebral blood flow preventing cerebral ischemia [12]. Early randomized, controlled trials testing the effect of mild hypercarbia (i.e. $PaCO_2$ 45–55 mmHg as compared to a normocapnia target of 35–45 mmHg), found a trend towards shortened extent of mechanical ventilation and decreased need for ventilator assistance at 36 weeks postmenstrual age (PMA), without increasing adverse neurodevelopmental effects in the mild hypercarbia group [13,14]. However, a meta-analysis of the early trials did not show a significant benefit of permissive hypercapnia in the prevention of death or BPD at 36 weeks [15].

In recent years, data from several randomized trials and observational cohort studies continue to fail to demonstrate the efficacy of this approach in the reduction of BPD but raised more concerns for its safety (Table 1). Furthermore, several other studies provided data demonstrating potential detrimental effects of persistent high pCO_2 levels in a developing preterm infant. Kaiser et al. investigated the effects of pCO_2 levels on cerebral autoregulation and found a progressive loss of autoregulation with increasing pCO_2 beyond 45 mmHg [16]. Victor et al. studied weekly EEG recordings of 25 babies born between 23 and 32 weeks from 48 h of age till 4 weeks of age. They found that compensated respiratory acidosis may be associated with EEG activity changes in preterm infants over 48 h of age, which may help explain previous finding of reduction in the percentage of active sleep in babies with BPD [17,18]. In a small subset of infants in the PHELBI trail, infants randomized to high pCO_2 target group was found to have significantly and progressively reduced functional vessel density in the skin suggesting impaired peripheral microcirculation in these infants.

Although permissive hypercarbia is theoretically plausible, the current evidence questions that it is a safe and effective way of reducing the risk of BPD. In addition, most of the trials focused on the effects of mild to moderate hypercapnia (i.e. < 55–60 mmHg) in the first couple of weeks of life. The timing and the range of pCO_2 that may provide benefit, without increasing the adverse outcomes, are not known. We therefore caution the liberal use of permissive hypercarbia to much higher pCO_2 level and well beyond the first weeks of life.

3.3. Non-invasive ventilation

Although mechanical ventilation through endotracheal tubes (ETT) is an effective life-saving therapy for infants with severe respiratory failure, it has been linked to ventilator associated lung injury and increased risk of BPD [19,20]. These injures can result from over or under-expansion of the lungs leading to mechanical injury from sheer stress and inflammation, or increased risk for infection including ventilator-associated pneumonia and late onset sepsis causing biotrauma [21], and/or free radical damage from oxygen toxicity. Therefore, tremendous efforts have been spend on finding ways to avoid endotracheal intubation (i.e. invasive ventilation) and various modes of non-invasive ventilation have been developed and quickly applied in clinical practice world-wide. Some commonly used modes include nasal continuous positive airway pressure (nCPAP), Bi-level CPAP (BiPAP), nasal intermittent positive pressure ventilation (NIPPV), heated and humidified high flow nasal cannula (HHHFNC). In a meta-analysis comparing ventilation strategies with or without ETT in infants < 30 weeks of gestational age, Fischer et al. showed that avoiding the use of a tube had significant benefit in preventing BPD (OR 0.83; 95% CI 0.71–096) [22].

nCPAP, providing continuous positive airway pressure through nasal masks or prongs, is the most studied non-invasive method. Data from RCTs has consistently showed a trend towards benefit in early CPAP use and meta-analysis of the trials showed a small but a statistically significant reduction in the risk of death or BPD with a relative risk (RR) of 0.90 (CI 0.83–0.98), and number need to treat to benefit (NNTB) of 25 (CI 13–244) [23]. Early use of CPAP with subsequent selective use of surfactant, is therefore considered an evidence-based strategy to reduce BPD and is endorsed by the American Academy of Pediatrics Committee on Fetus and Newborn [24].

NIPPV has been used as a non-invasive respiratory method for newborns since the 1970s. It combines CPAP with intermittent pressure increases applied through a nasal interface. This intermittent pressure increase may (synchronized NIPPV or sNIPPV) or may not (non-synchronized NIPPV or nsNIPPV) be synchronized with baby's breathing. BiPAP is often included in the NIPPV umbrella. Previous meta-analysis of trials did not provide convincing evidence that NIPPV is advantageous over CPAP as a primary mode of respiratory support, as more than half of the trials found no reduction in the need of intubation [25,26]. When used as a post-extubation support mode, NIPPV may be able to reduce extubation failure, especially when synchronized with patient's breathing and delivered by a ventilator [25,27]. A new meta-analysis by Ekhaguere et al. included more trials since the 2016 and 2017 Cochrane reviews and found that NIPPV was superior to nCPAP in both reducing respiratory failure as the primary support mode after birth (RR 0.55, 95% CI 0.46–0.65; NNT8), and preventing post

Table 1
Recent studies raising concerns of lack of efficacy and potential adverse effects of permissive hypercarbia.

Study	Study group and design	pCO2 related observations	Findings and comments
Subramanian 2011	N = 425, BW 500–1499 g, multicenter observational study	pCO2 > 50 mmHg in the first 6 days of life compared to normocapnia	Hypercapnia in the first 6 days of life associated with higher incidence of BPD (p = 0.024)
Thome 2015 (PHELBI trial)	N = 359, BW 400–1000 g, GA 23–28^{+6} weeks, multicenter RCT	3 increasing levels in the first 14 days of life (pCO2 high target group 55–65 mmHg vs. control group 40–50 mmHg in the first 3 days of life)	- No difference in death or BPD - Trial was stopped early for no benefit and trend towards benefiting controls - High-target group had lower ventilator pressures but it did not translate into better outcomes - Higher NEC and death in infants with severe disease in the high target group - No difference in NDI/death at 2 year follow up
Ambalvanan 2015	N = 1316, GA 24–27^{+6} weeks, secondary data analysis of SUPPORT trial	Blood gas in the first 14 days of life	Higher pCO2 is an independent predictor of BPD/death, severe IVH/death or NDI/death
Brown 2018	N = 147, GA < 32 weeks, secondary data analysis of a delayed cord clamping trial	Blood gas in the first 72 h of life	- Routine practice of permissive hypercarbia led to low incidence of hypocarbia (2%) but without a significant improvement in BPD or pneumothorax - High mean pCO2, higher variability of pCO2 and lower minimum pH were associated with death/severe IVH

extubation failure (RR 0.60, 95% CI 0.45–0.81; NNT 7) [28]. However, despite these beneficial effects, meta-analysis of the trails was not able to show a reduction in BPD with NIPPV, although several small trials suggest synchronized NIPPV may be effective (RR 0.64,95% CI 0.44–0.95, NNTB 7 (95% CI 4–42) [27]. In recent years, neutrally adjusted ventilatory assist (NAVA) that utilizes the detection of diaphragm electrical activity as the triggering mechanism has been introduced and can be used non-invasively. Some studies has shown that when compared to the traditional NIPPV, non-invasive ventilation NAVA (NIV-NAVA) improves patient-ventilator synchrony during non-invasive nasal ventilation, even in the presence of large air leaks [29]. In a small retrospective study, Lee et al. reported that NIV-NAVA may be promising in reducing extubation failure in preterm infants compared to nCPAP [30]. However, this technique requires a specific ventilator and an expensive esophageal catheter, which hinders the accumulation of high level evidence for its use.

HHHFNC, with its advantages of easy to use, better tolerance and less nasal trauma, has gained popularity as an alternative method of respiratory support to nCPAP or NIPPV. Three meta-analysis published in 2019 compared the effects of HFNC to NCPAP as primary respiratory support or post-extubation support, all concentrating on the need of intubation as the primary outcome [28,31,32]. Their results were not consistent as the studies included in each meta-analysis varied. As primary respiratory support, Ekhaguere et al. found that nCPAP is superior to HFNC in preventing respiratory failure, while the other two analysis found no significant difference. When used following extubation, Hong et al. reported nCPAP is associated with fewer extubation failure as compared to HFNC, whereas Fleeman et al. did not and Ekhaguere only described that most of the trials did not see difference. Both Hong and Fleeman reported reduced nasal trauma and air leak post extubation with HFNC use. Despite the difference in the reported primary outcomes, all three reports pointed out that few preterm infants born at < 28 weeks' gestation or < 1000 g were included in the analyzed trials and routine use of HFNC in these extremely premature infants is not supported by the current evidence. Manley et al. reported that birth gestational age ≥30 weeks and pre-randomization FiO2 < 0.30 were independent predictors of treatment success in infants randomized to HFNC in their trial [33].

Nasal high frequency ventilation (nHFV), especially in the form of nasal high frequency oscillatory ventilation (nHFOV), is a relatively new mode of non-invasive ventilation but gaining popularity despite scarce evidence. One recently published meta-analysis included 8 small randomized trials with a total of 463 preterm infants, 6 compared nHFOV to nCPAP (359 patients) and 2 compared nHFOV to BiPAP (104 infants) [34]. Sample size of each trial varied from 26 to 126 and most of infants studied were more than 30 weeks' gestation and over 1500 g at birth. Meta-analysis of these 8 trial data showed that the use of nHFOV was more beneficial in enhancing CO_2 elimination and reduce the risk of intubation. However, the author also reported moderate to high risk of bias in all trials and appropriately pointed out that data from these trial was not sufficient to provide information regarding the appropriate parameter settings of nHFOV, the effect of nHFOV on extremely preterm infants, or the longer term outcomes of nHFOV including risks of BPD, IVH and neurodevelopmental outcomes. In one new single center trial not included in the above meta-analysis, Chen et al. reported that as post extubation support, nHFOV reduced the reintubation rate (OR 0.35, 95% CI 0.18–0.70) and post extubation pCO_2 (MD -7.15, 95% CI -9.95 to −4.80) as compared to nCPAP, especially in infants less than 32 weeks [35]. However, the infants included in this trial were relatively older (30–35 weeks' gestation) and bigger (birth weight 1290–2395 g) and the study was not powered to examine if nHFOV can help reduce BPD. Potential complications found in the trials include nasal trauma and abdominal distention as well as a trend toward higher incidence of NEC in the 32–36 + 6 week group (19.3% vs.8.6%, p = 0.06). In summary, current data suggests that nHFOV may be effective in preventing intubation. However, the optimal ventilator and ventilator settings, its effects on extremely preterm infants, its role in BPD prevention, as well as its safety profile (including short term effects on IVH and NEC, and long term neurodevelopmental outcomes) will need to be further studies before it can be widely adapted in clinical practice.

3.4. Invasive mechanical ventilation

In the last few decades, mechanical ventilation (MV) has advanced greatly with more sophisticated ventilators that are more suitable for the small newborns. Ventilators in the modern era can provide better synchronization with infants' breathing, compensate for air leak and also with better monitoring capabilities. However, these improvements in the ventilators may not translate into better outcomes of mechanical ventilation unless the clinicians use these tools appropriately. As discussed earlier, the goal of mechanical ventilation is to provide adequate but not too much support. To achieve this goal, the clinician need to have a good understanding of the pulmonary pathophysiology and mechanics, the advantages and disadvantages of different modes of ventilation and the characteristics of different ventilators. Given the limited space, we will concentrate our discussion on some key concepts and recent developments in the MV strategies for infants evolving from RDS to BPD.

3.4.1. The "open lung" concept

The RDS pathophysiology and lung mechanics decided that the RDS lungs are hard to open, and easy to collapse. Therefore applying CPAP or PEEP either via non-invasive support or intubated MV is important and effective in recruiting the lungs and maintain the FRC [36,37]. Once the lungs in a RDS infant are successfully recruited, maintaining an "open lung" is an important lung protective ventilation concept to prevent the evolvement of RDS into BPD. The open lung strategy helps to distribute the tidal ventilation during traditional MV evenly throughout the lungs and avoid the sheer stress from repeated collapse and reopening of the alveoli.

In MV, the "open lung" is mainly achieved through applying adequate PEEP or utilizing mean airway pressure (MAP) in high frequency oscillatory ventilation (HFOV) [38,39]. Unfortunately, many clinician are afraid of PEEP. Some NICUs even have a set policy that will not allow the PEEP to be set above 6 cmH_2O. Unfortunately, there are very limited data to help guide the selection of optimum PEEP. A recent Cochrane review only identified 4 trials of a total of 72 patients and suggested that using an oxygenation-guided lung recruitment maneuver might be helpful in selecting PEEP levels [40].

3.4.2. Conventional mechanical ventilation (CMV) vs. high frequency ventilation (HFV)

CMV, generally referred as positive pressure ventilation targeting the physiological range of tidal breathing, has been the standard MV method for infants with RDS. In comparison, HFV utilizes supra-physiological frequencies with much smaller tidal volumes (V_T) that is close to the airway dead-space volume and much lower inflation pressure at the alveolar level. Although initially introduced as potential strategy to reduce ventilator induced lung injury, HFOV has mainly been used as a rescue mode in the neonates and young infants. Data from recent years suggest that HFOV is an effective way of lung recruitment and early use of HFOV as a primary mode, rather than a rescue mode of MV, in preterm infants with RDS may result in a small reduction in the risk of BPD when compared with CMV [41]. However, as the authors of the 2014 Cochrane review pointed out, this evidence is weakened by the inconsistency of this effect across trials and counteracted by an increased risk of acute air leak (fixed-effect model summary RR 1.19, 95% CI 1.05 to 1.34; summary RD 0.04, 95%CI 0.01 to 0.07; NNTH25, 95%CI 14 to 100). Most of the studies reported similar short and long-term neurodevelopmental outcome of HFOV as compared to CMV. However, few trials showed an increase in severe intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL) in the HFOV groups [42,43] while some others showed a reduction in the risk of cerebral palsy [44]. It is also hard to compare the effects of HFOV with CMV on short and long-term pulmonary and neurodevelopmental outcomes when the open lung strategy is utilized. Even less data exist that compare the use of HFOV and CMV in infants with evolving BPD or compare the other commonly used HFV, the high frequency Jet Ventilation (HFJV) with CMV in terms of BPD prevention. Therefore, the selection of CMV vs. HFV in infants with RDS and evolving BPD remained at the discretion of the clinicians at the present time.

3.4.3. Modes of MV in infants with RDS and evolving BPD

There are various kinds of ventilators and mode of ventilation currently available to the clinicians to choose from. However, high quality data to guide this choice in this patient population are limited. Many physicians would like to have a "cookbook" recipe of best ventilator settings for these infants. Unfortunately, as we have discussed earlier, due to the complex interaction between lung developmental stages at birth and the timing of various post-natal influences and injuries, these infants' lung pathology and pulmonary mechanics are constantly changing and at different pace. Therefore the choice of best ventilator modality and settings needs to be individualized and also adapt to the change in each patient. In this section, we will discuss some key features of MV that need to be considered when providing MV support to preterm infants with RDS that are evolving into BPD.

3.4.3.1. Non-synchronized vs. synchronized support. Modern neonatal ventilators are capable of synchronize positive pressure support from the ventilator with patient's spontaneous breathing efforts. Synchronized MV provides several advantages that is very important for this patient population: 1) improve ventilation efficiency by utilizing patient's own breathing efforts, and avoid the ventilator breath and patient's breath to go against each other; 2) minimize sedation and muscle paralysis need by improving patient's comforts; 3) reduce air leak and duration of MV [45]. There are several triggering mechanisms available in the modern ventilators. Currently, most neonatal ventilators use flow triggering mechanism. To best deliver synchronized breath in a preterm infants, clinicians need to pay attention to several details: 1) best to use a ventilator with a proximal flow sensor to ensure easy sensing and quick response time; 2) meticulous care of the flow sensor with timely cleaning and re-calibration to avoid malfunctioning of the flow sensor; 3) Choose the appropriate triggering sensitivity. In a rapidly breathing premature infant, decreasing triggering sensitivity to reduce respiratory rate is not recommended as this will only increase the infant's work of breathing without addressing the underlying cause leading to tachypnea.

3.4.3.2. Modes of synchronized ventilation. There are several modes of synchronized ventilation that clinicians can choose from. Some commonly used modes in the neonates include synchronized intermittent mandatory ventilation (SIMV), Assist control (AC), Pressure support ventilation (PSV) or a combination of SIMV + PSV or CPAP + PSV. Table 2 summaries the features of SIMV, AC and PSV as the primary support mode and listed the advantages and disadvantages of each mode. It is important to set appropriate triggering sensitivity when using these synchronized ventilation modes. Inappropriately set low triggering sensitivity can lead to under detect of patient's spontaneous breathing and ventilators will deliver mandatory IMV breath without synchronization. Patient-ventilator asynchrony will result in increased work of breathing (WOB), agitation, and uneven/inefficient ventilation. On the contrary, inappropriately set high triggering sensitivity, especially in the presence of ETT leak, may lead to auto-triggering of the ventilator and as a result, over ventilation.

As previously discussed, the lung pathology and pulmonary mechanics changes over time from RDS to BPD. Therefore the ventilator mode of choice and the settings needs to adapt to patient's change. For example, the AC mode may be appropriate for a preterm infant with RDS in the early postnatal days when the baby has a more homogenous lung disease. However, when the lung disease evolve towards BPD with heterogenous aeration (i.e. areas of atelectasis and areas of hyperinflation or cystic changes), AC mode with a fixed short Ti may not be adequate to ventilate the areas with a long time constant. PSV mode may also have similar problems in an infant with heterogeneous lung disease or when higher P_{AW} is required to maintain an open lung. As a result, the combination mode of SIMV + PSV is frequently utilized. However, the ventilator settings needs to be adjusted over time. In the early postnatal days, a faster rate (30–40 times/minute) with a shorter Ti (0.3–0.4s), V_T of 4–6 ml/kg and PEEP of 5–8 CM are usually appropriate to ventilate an infant with RDS. The pressure support level can initially be set at slightly lower than the PIP required to deliver the targeted V_T. Later, when the lung pathology changes towards heterogenous lung disease, longer inspiratory and expiratory time may be needed to ventilator the areas with long time constant and higher V_T as well as PEEP maybe necessary to compensate for increased dead-space, overcome airway malacia and maintain FRC. Therefore, a strategy with lower SIMV rate (10–25 times/minute), longer Ti (0.5–0.8s) with higher V_T and PEEP might be more appropriate [4].

3.4.3.3. Volume-targeted ventilation vs. pressure-limited ventilation. Pressure-limited ventilation has been the main state of

Table 2
Features of SIMV, AC and PSV as the primary support modes.

	SIMV	AC	PSV
Cycling mechanism	Time-cycled based on preset Ti and RR	Time-cycled based on preset Ti	Flow-cycled based on preset % peak inspiratory flow
Preset settings	PIP or V_T, Ti, rate and PEEP, triggering level	PIP or V_T, Ti, PEEP, triggering level, and backup rate	PIP or V_T, PEEP, triggering level, and backup rate
Spontaneous breath	- Ventilator synchronize with detected spontaneous efforts to deliver preset number of breath; - Spontaneous breath in excess of the set rate supported only by PEEP	- Every detected spontaneous breath supported according to preset PIP or target V_T - Every inspiration controlled by a fixed Ti	- Every detected spontaneous breath supported according to preset PIP or target V_T - Variable Ti
Mandatory breath	Given when no spontaneous effort is detected during a triggering window based on the preset rate	Given when no spontaneous effort is detected during a triggering window based on the preset minimum backup rate	Given when no spontaneous effort is detected during a triggering window based on the preset minimum backup rate
Weaning	Gradual decrease of rate and inflation pressure	Gradual decrease of inflation pressure to reduce the level of support	Gradual decrease of inflation pressure to reduce the level of support
Advantage	Improve patient comfort as compared to no synchronization	All spontaneous breath supported leading to more consistent V_T and lowered WOB as compared to SIMV	- Patient determined Ti allows complete synchrony - Automatically adjust Ti with lung mechanics changes
Disadvantage	Uneven support of spontaneous breaths may result in variable V_T and high WOB in small preterms	- Under support if infant becomes apneic and backup rate set too low (usually set at 30–40 for small preterms) - Over ventilation if infant breathing too fast - Fixed Ti may worsen uneven ventilation in different lung areas	- Patient determined Ti is usually short, which may lead to low mean airway pressure (P_{AW}) and atelectasis unless PEEP is appropriately adjusted - Substantial leak from ETT may affect triggering

WOB: work of breathing, Ti: inspiration time, V_T: tidal volume, PIP: peak inspiratory pressure, PEEP: positive end expiratory pressure.

conventional MV in the neonates for many years. However, with the rapid change in lung compliance in an infant with RDS pre and post surfactant and over the course of the first few days and weeks after birth, volume-targeted ventilation (VTV) may be more appropriate. VTV aims to produce a stable tidal volume and thus avoid volutrauma due to lung overdistension and decrease the incidence of hypocapnia. A Cochrane meta-analysis that included 16 parallel studies and 4 cross-over trials demonstrated that infants ventilated with VTV modes had reduced rates of death or BPD, pneumothoraces, hypocarbia, severe cranial ultrasound pathologies and duration of ventilation compared with infants ventilated with PLV modes [46].

One mode of VTV is Volume Guarantee (VG) in which the microprocessor compares exhaled tidal volume of the previous breath to the desired target V_T set by the operator, and adjusts the inspiratory pressure up or down to achieve that V_T. The choice of an appropriate V_T level is crucial and based on weight, postnatal age and underlying diseases. The most appropriate V_T level for preterm infants with RDS has not been determined, mostly 4–6 ml/kg. The smallest infants usually require a higher tidal volume (5.5–6 ml/kg for infants < 750 g) than bigger infants due to proportional larger instrumental dead spaces [47,48]. It has been shown that preterm infants with RDS who were ventilated with low V_T of 3 ml/kg, as compared to 5 ml/kg, had increased levels of pro-inflammatory cytokines and required longer duration of MV [49]. A several week-old preterm infants with evolving BPD may also need larger TV (5.5–6.5 ml/kg) for a combination of increased anatomical and alveolar dead space [48]. In a randomized crossover study, Hunt et al. compared the WOB under different V_T levels of 4 ml/kg to 7 ml/kg in 18 preterm infants born at < 32 weeks' gestation that remained ventilated beyond the 1st weeks of life (7–60 days of age). They found that only a V_T target of 7 ml/kg were able to reduce WOB below baseline in this group of infants with evolving BPD or established BPD [50].

Other than conventional ventilation mode, HFOV mode can work with volume guarantee as well. However, it has not been proven whether HFOV + VG offers short and long-term advantages over HFOV alone or CMV + VG. Further studies are needed to demonstrate the long-term neurodevelopmental effects of VTV and identify which VTV strategy offers the best long-term outcomes for preterm infants with RDS.

3.4.3.4. Neurally adjusted ventilatory assist (NAVA). NAVA provides synchronized respiratory support by detecting the electrical activity of the diaphragm instead of the traditional flow or pressure triggering mechanism. It provides inspiration assist in proportion to the strength of the electrical signal captured from the diaphragm. There are some evidence that NAVA improves patient-ventilator synchrony and short-term oxygenation [51,52]. In a retrospective study of 29 preterm infants who were on MV for over 4 weeks, Jung et al. reported improved oxygen saturation, significantly lower FiO2 requirements, lower ventilator support settings with improved blood gas values after transition from SIMV to NAVA [53]. In another retrospective study, the same group reported that NAVA can facilitate reduction in sedative use and decrease the frequency of cyanotic episodes in preterm infants on chronic MV [54]. However, data on longer term outcomes are lacking. A recent Cochrane review only included one RCT, which compared NAVA to patient-triggered time-cycled pressure-limited ventilation and found no significant difference in the duration of MV or incidence of BPD, pneumothorax or IVH [51].

4. Conclusion

The goal of respiratory support in a preterm with RDS and evolving into BPD is to provide adequate support for growth and development while avoiding or minimizing lung injury. Both non-invasive and invasive respiratory support can be utilized. However the selection of proper mode of support and the support settings will vary based on each patient's pathophysiology and pulmonary mechanics, and needed to be weighed against the potential risks.

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