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REVIEW ARTICLE

Established severe BPD: is there a way out? Change of ventilatory paradigms

Richard Sindelar[1], Edward G. Shepherd[2], Johan Ågren[1], Howard B. Panitch[3], Steven H. Abman[4], Leif D. Nelin[1,2] and on behalf of the Bronchopulmonary Dysplasia Collaborative

Improved survival of extremely preterm newborn infants has increased the number of infants at risk for developing bronchopulmonary dysplasia (BPD). Despite efforts to prevent BPD, many of these infants still develop severe BPD (sBPD) and require long-term invasive mechanical ventilation. The focus of research and clinical management has been on the prevention of BPD, which has had only modest success. On the other hand, research on the management of the established sBPD patient has received minimal attention even though this condition poses large economic and health problems with extensive morbidities and late mortality. Patients with sBPD, however, have been shown to respond to treatments focused not only on ventilatory strategies but also on multidisciplinary approaches where neurodevelopmental support, growth promoting strategies, and aggressive treatment of pulmonary hypertension improve their long-term outcomes. In this review we will try to present a physiology-based ventilatory strategy for established sBPD, emphasizing a possible paradigm shift from acute efforts to wean infants at all costs to a more chronic approach of stabilizing the infant. This chronic approach, herein referred to as chronic phase ventilation, aims at allowing active patient engagement, reducing air trapping, and improving ventilation-perfusion matching, while providing sufficient support to optimize late outcomes.

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IMPACT:

- Based on pathophysiological aspects of evolving and established severe BPD in premature infants, this review presents some lung mechanical properties of the most severe phenotype and proposes a chronic phase ventilatory strategy that aims at reducing air trapping, improving ventilation-perfusion matching and optimizing late outcomes.

INTRODUCTION

Improved survival in the lower gestational ages has generated a higher incidence of bronchopulmonary dysplasia (BPD), but without increasing the rate of other major morbidities associated with prematurity.[1,2] Nonetheless, increased survival of preterm infants and especially extremely preterm infants presents the field of Neonatology with new challenges and hitherto unknown problems in respiratory support, and specifically in approaches to mechanical ventilation.[3–5] In the acute phase of neonatal lung injury, efforts are focused on reducing the potentially damaging effects of ventilator-induced injury to the developing lung. But in those patients who continue to need positive pressure ventilation and supplemental oxygen in the context of preterm birth, a chronic phase of established lung injury occurs that is currently defined as severe bronchopulmonary dysplasia (sBPD).[6,7] Established sBPD usually necessitates ventilatory strategies and treatment goals that are different from those used in the acute stage of respiratory distress. These different ventilatory approaches result from the need to maintain adequate respiratory support in response to the changed physiology and structure seen in chronic lung injury.[8]

The current approach to providing respiratory support during the acute phase of lung disease is characterized by "less is more" in preventing lung injury in preterm infants. Efforts are directed toward avoiding invasive positive pressure ventilation (IPPV) altogether, and if IPPV is needed, to have early and fast weaning strategies.[9] Current recommendations also include early surfactant administration to promote lung recruitment, achieve a more homogeneous distribution of ventilation, and reduce the risk for heterogeneous aeration of the lung.[9] However, these efforts to reduce acute lung injury and to promote lung development have only been modestly successful.[10] Indeed, rather than decreasing, the incidence of BPD is increasing and particularly in those born at periviable gestational ages.[11]

The pathophysiological changes leading to sBPD are multifactorial and remain incompletely understood.[12] The chronic lung injury cannot be explained solely by exposure to antenatal or postnatal adverse factors. Genetic, epigenetic, pharmacogenetic, or microbiomic influences are likely factors that further modulate the risk for developing sBPD. In this review we will discuss issues related to established sBPD, with a special emphasis on infants with the most severe phenotype, characterized by persistent need

[1]University Children's Hospital, Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden; [2]Nationwide Children's Hospital, Ohio State University, Columbus, OH, USA; [3]Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, PA, USA and [4]Children's Hospital Colorado, University of Colorado, Aurora, CO, USA

Correspondence: Richard Sindelar (richard.sindelar@kbh.uu.se)

A list of authors and their affiliations appears at the end of the paper

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for IPPV and high supplemental oxygen to treat hypoxemia and chronic respiratory failure. In these patients, ventilator strategies based on preventive measures used during the acute phase, such as low tidal volume and high-frequency ventilation, are less able to promote adequate $\dot{V}/\dot{Q}$ matching to maintain oxygenation.[7,13] We will also try to characterize the mechanical properties of the lung in sBPD and propose possible physiology-based approaches to strategies for mechanical ventilation to optimize $\dot{V}/\dot{Q}$ matching.

CLINICAL DEFINITIONS OF SEVERE BPD

BPD was first described by Northway in 1967,[14] as the chronic lung disease following hyaline membrane disease in preterm infants, and at that time BPD was characterized by fibrosis, atelectasis, and hyperinflation. However, as Neonatology evolved and preterm infants born at earlier and earlier gestational ages were surviving, a "new" BPD phenotype emerged that was characterized by aberrant alveolar development leading to larger alveoli and less surface area for gas exchange.[15] In 2000, the National Institutes of Health (NIH) held a workshop to develop a consensus definition of BPD.[16] This group defined BPD as a need for supplemental oxygen for 28 days or more, and then graded its severity as mild, moderate, or severe as based on supplemental oxygen need and respiratory support at 36 weeks post-menstrual age (PMA). The NIH workshop defined sBPD as a need for ≥30% oxygen with or without positive pressure respiratory support (nasal continuous positive airway pressure [nCPAP] or IPPV) at 36 weeks PMA, and this has become the standard definition of sBPD.

However, as the field of Neonatology has continued to evolve, patients born much earlier are now surviving and are more likely to have sBPD, with BPD rates approaching 100% for babies born at <24 weeks gestation.[17] Although the consensus definition for sBPD has helped to identify infants at high risk for mortality and morbidities, the definition of sBPD is very broad.[7] This has led to a growing recognition that new definitions for BPD are required, especially ones that more precisely identify patients with the most severe forms of BPD, while capturing important long-term outcomes.[18–20] In 2017, the BPD Collaborative suggested a modification of the 2000 consensus definition of sBPD to include type 1 and type 2 sBPD, where type 1 is defined as ≥30% oxygen and/or non-invasive positive pressure support at 36 weeks PMA, while type 2 is defined by the need for IPPV at 36 weeks PMA.[7] A workshop sponsored by the NIH in 2016 led to a suggested revised definition of BPD that included Grades I, II, and III based on a complex interaction between respiratory support and the fraction of inspired O_2 (FiO_2) at 36 weeks PMA.[12] This proposed definition included a Grade IIIA for patients with chronic lung disease who died before 36 weeks PMA, which represented the first attempt to try to include patients with evolving sBPD who died prior to 36 weeks PMA.[12] Recently, Jensen et al.[21] proposed a definition of BPD based solely on respiratory support at 36 weeks, wherein Grade 1 BPD requires low flow nasal cannula, Grade 2 BPD requires non-invasive positive pressure (nCPAP, high-flow nasal cannula, nasal IPPV), and Grade 3 BPD is need for invasive IPPV. This study reported that their Grade 3 definition identified those BPD patients who were at highest risk for mortality and/or morbidities. Interestingly, the Grade 3 definition from this report is essentially identical to the type 2 sBPD definition previously proposed by the BPD Collaborative.[7] Thus, this review is focused on those patients with *established sBPD*, defined as Type 2 sBPD or Grade 3 BPD.

LUNG PHYSIOLOGICAL CONSIDERATIONS RELATED TO VENTILATION IN SEVERE BPD

In contrast to milder forms of evolving BPD, in which lung compliance and resistance improve within days to weeks after birth,[22] infants with sBPD can have some early improvement in lung mechanics but fail to sustain or achieve sufficient respiratory stability to tolerate extubation for longer periods.[23] sBPD is common in infants born at 22–26 gestational weeks,[17] a time when the lung is in the late canalicular stage of development.[13] In a few patients, radiological signs of sBPD can be observed even at the end of the first week of life, as reflected by overexpansion, recurrent atelectasis, and heterogeneous regions of hyperinflation or densities (Fig. 1). Although unable to be classified formally as sBPD type 2 or Grade 3 BPD at these early time points, these patients show clear signs of *evolving sBPD*.

The acute phase of neonatal lung disease is characterized by relatively *homogeneous* lung disease, but as sBPD develops, the chronic phase progresses to a very *heterogeneous* lung disease.[7,24] In the early stage (i.e. prior to 36 weeks PMA), sBPD can be suspected and to some extent predicted by a combination of radiological findings and lung mechanics measurements.[25] Nevertheless, clinicians frequently continue efforts to wean support and endeavor to keep the infant off IPPV. This approach can result in atelectasis, which worsens $\dot{V}/\dot{Q}$ mismatch resulting in increasing FiO_2 requirements and work of breathing (WOB). There may be some patients at high risk of developing sBPD who may benefit from continued extubation with increased CPAP levels. A recent animal study demonstrated that CPAP attenuated hyperoxia-induced changes in lung structure and function.[26] Furthermore, impedance measurements using the forced oscillatory technique at different PEEP levels during the first week of life in extremely preterm infants have shown that optimal airway opening pressures were lower during the first days of life without compromising gas exchange or increasing resistance to airflow.[27] However, in many instances of evolving sBPD, respiratory support based on preventive strategies such as high rates and low tidal volumes may not adequately address the changing lung physiology in these infants.

Over time, most patients with evolving sBPD demonstrate a shift from tolerating periods of non-invasive respiratory support to requiring longer periods of invasive IPPV. Even though permissive hypercapnia is employed, high FiO_2 needs do not allow for the successful weaning strategies employed in the acute phase of

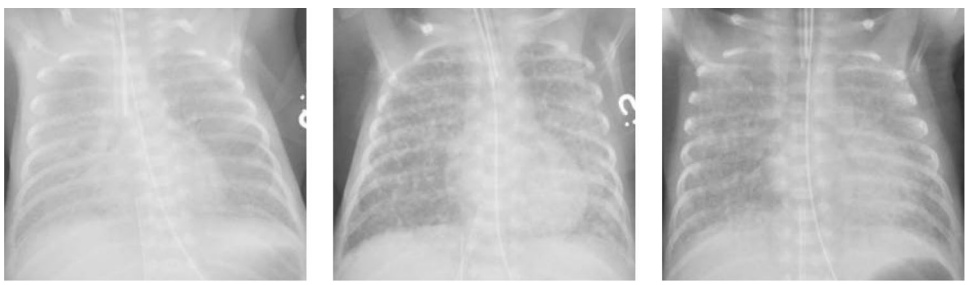

Fig. 1 Chest radiographic imaging of evolving sBPD during first week of life. Infant born after 22 + 2 weeks GA due to placental ablation and chorioamnionitis. Respiratory distress syndrome at 1½ hours age (left); first signs of barotrauma on day 2 (center); evolving sBPD on day 5 (right).

neonatal lung disease. At this stage the lungs are inhomogeneously ventilated with lung regions that are a combination of:[1] over expansion due to air trapping resulting in decreased ventilation (moderate to large $\dot{V}/\dot{Q}$ mismatch);[2] pneumatoceles resulting in no or decreased ventilation (moderate to large $\dot{V}/\dot{Q}$ mismatch);[3] atelectasis (large $\dot{V}/\dot{Q}$ mismatch); and/or[4] inadequate ventilation (mild $\dot{V}/\dot{Q}$ mismatch).[24] Most bedside measurements of lung mechanics assume that the entire lung can be a single compartment. However, in reality the heterogeneous lungs have many different compartments due to highly variable lung compliances (C_L) and lung resistances (R_L) within each compartment, but these differences are difficult to appreciate from the pressure–volume curves measured by the ventilator and even from pulmonary function measurements made at a later stage of sBPD.[28–30]

During the very early stages of BPD, C_L is mostly defined by surface tension forces at the air–liquid interface, i.e., the availability and/or function of surfactant, and less by the extracellular matrix composed of elastin and collagen whose levels are low in the extremely preterm lung.[31] The low levels of elastic elements likely play a role in the difficulties the extremely preterm infant has in maintaining an adequate functional residual capacity (FRC) for efficient gas exchange, accentuated by a highly compliant ribcage.[32–34] Interestingly, the pathophysiological changes in lung mechanics in evolving sBPD could be further affected by the imbalanced increase in collagen and elastin deposition during alveolar septation, lung injury, and lung inflammation; because of the intrinsic differences in the elastic properties of collagen and elastin, their contribution to compliance varies at different lung volumes, potentially accentuating the inhomogeneity of lung aeration during different ventilatory settings.[35–38]

The characteristic features of the *"new BPD"* with arrested alveolar development, increased size of alveoli, and reduced total surface area for gas exchange are likely established during the early stages of evolving sBPD, i.e., days to weeks.[16] Normally, the interaction between mechanical strain during inhalation and different transcription and growth factors guides the formation of new alveoli, where increased elastin and collagen play an important role in stabilizing the alveolar environment. But due to an imbalanced deposition and an altered cross-linking between elastin and collagen during the later stages of evolving sBPD, radiological and histological findings in established sBPD usually exhibit similarities to the *"old BPD"* with fibrosis and emphysema.[39–43] It should therefore be noted that these changes define a phenotype that occurs today in patients with sBPD and is a combination of the "new BPD" and the "old BPD".

Another aspect of early evolving sBPD is the relatively modest smooth muscle changes in the airways with initially a relatively low resistance; however, as elastin and collagen are laid down in the lung this progresses to marked expiratory flow limitations in established sBPD.[24] It is unclear if the increased resistance in sBPD is due to[1] increased airway reactivity;[2] peri-bronchial inflammation/edema;[3] secondary smooth muscle hypertrophy; and/or[4] failed airway tethering.[44] The finding that many sBPD patients are non-responsive to bronchodilators[45] could favor compromised airway tethering. Reduced airway tethering is also in line with the differently developed peripheral lung structures surrounding intra-parenchymal airways where the elastic elements do not provide adequate tension and stability to the bronchial elements,

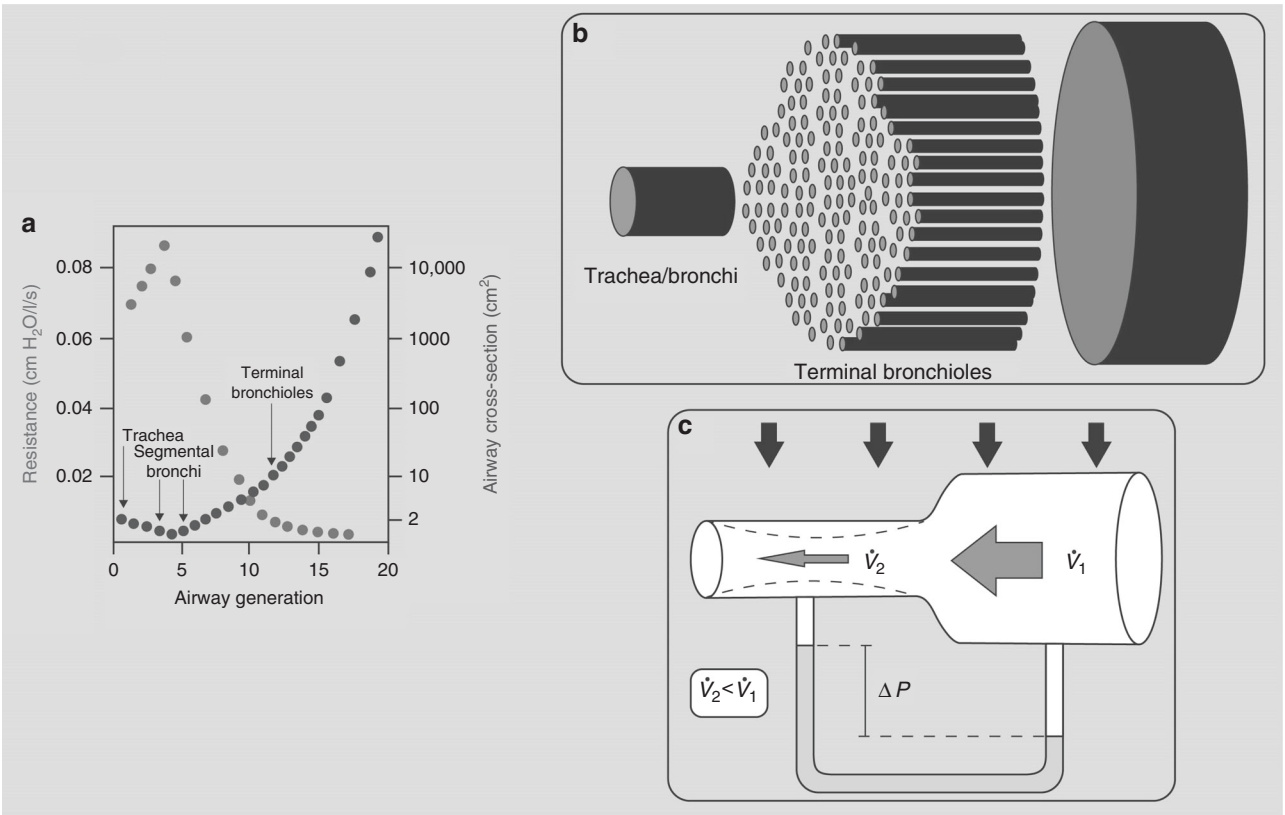

Fig. 2 Airway cross-sectional area related to airway generation and the Venturi effect during exhalation. a Airway cross-section (blue) and resistance (red) depending on airway generation showing the markedly reduced resistance after the fifth airway generation with increased cross-sectional area. **b** A simplified presentation of proximal and distal airway diameter showing the relative low cross-sectional area in trachea/bronchi compared to the high cross-sectional area in terminal bronchioles/airways. **c** The resulting compression of the proximal airways (dotted lines) during exhalation due to the Venturi effect, i.e. reduced inner pressure in the proximal airway compared to the distal airway (delta P) with decreased airway flow ($\dot{V}_2$); black arrows represent outer pressure.

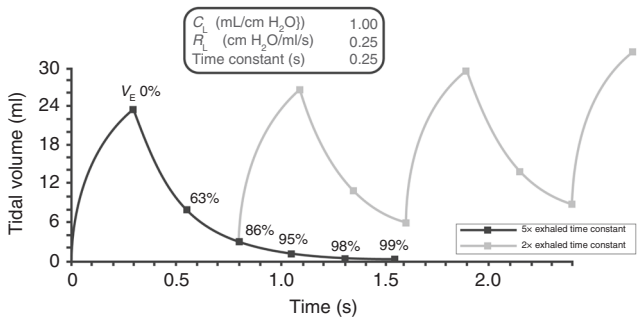

Fig. 3 Volume–time plot for one breath with tidal volume 24 ml. In this example, the time for complete exhalation is shown as the *black line* and is 5× the exhaled time constant ($\tau_E = 0.25$ s) or 1.25 s. If exhalation is stopped before 1.25 s by the next ventilator breath, then so-called "breath stacking" occurs and hyperinflation ensues as shown by the *gray line*.

resulting in intermittently reduced airway caliber and alveolar collapse.[46,47] Another structural factor that may be involved in the increased R_L seen in sBPD is the degree of airway dysanapsis, which is defined as the disproportional relationship between airway size and lung volume growth which will result in expiratory flow limitations if lung volume increases more in comparison to airway size.[48]

Interestingly, the well-known *Venturi effect*,[49] used in mixing gases in Venturi masks, during bronchoscopy, and in generating negative pressures during high-frequency oscillatory ventilation,[50–53] might affect the mechanics of the proximal airways during expiration. The rigidity of the first generation of bronchi is compromised and prone to compression by reduced intra-luminal airway pressures compared to the distal airways. The phenomenon of proximal airway collapse can be explained by the larger total cross-sectional diameter in the distal airways in relation to the smaller cross-sectional diameter of the first generation of the bronchi (Fig. 2a, b) creating a greater decrease in pressure across the airway, i.e., a relative reduction in intra-luminal pressure in the presence of a constant pressure surrounding the airway. The effect causes a further reduction of airway diameter with higher resistance, expiratory flow limitations, and distal air trapping (Fig. 2c). This can be counteracted by increasing the PEEP,[54] but one should bear in mind that if end-expiratory overexpansion occurs this could potentially reduce the expiratory flow and thereby promote an increased Venturi effect.[49]

For all the reasons outlined above the alterations in lung structure in sBPD result in a range of different lung mechanics, with lung regions having a relatively normal C_L and R_L, other regions having a low C_L with relatively normal R_L, while yet other regions having normal or high C_L with high R_L.[24] Air entry into the alveoli from the end of the endotracheal tube depends on C_L and R_L, which can be described in terms of the time constant (τ); the product of C_L and R_L ($\tau = C_L \times R_L$). In the lung one τ describes the time required for a compartment to fill or empty by ~63% following a step-change in pressure. The inspiratory time constant describes the time needed for the set tidal volume (V_T) to be delivered to the lung and the expiratory time constant gives the time needed for the inspired V_T to be completely exhaled, and in both inspiration and expiration it takes five time constants for the entire V_T to be delivered or exhaled (Fig. 3). In heterogeneous lung disease areas of normal C_L and R_L have relatively "fast time-constants", i.e. a short time to fill a set V_T, while areas of normal C_L and high R_L have relatively "slow time-constants", i.e., a long time to fill a set V_T. We have previously demonstrated that in sBPD the heterogeneity in lung regions can be modeled for inhalation and exhalation using a simplified model consisting of just two compartments: a "*fast compartment*" and a "*slow compartment*".[13] We previously found that the "slow compartment" in sBPD accounts for about two-thirds of the V_T.[55] Thus, in established sBPD the mechanical ventilation strategy should be centered on the "slow compartment" to deliver adequate V_T to achieve optimal $\dot{V}/\dot{Q}$ matching.

Acute neonatal lung disease is homogeneous and can be characterized as one lung compartment with low C_L and normal R_L, resulting in a "fast time-constant", where the air moves easily in and out of the lungs. A ventilation strategy with small V_T, short inspiratory times, and a fast rate is ideal for acute neonatal lung diseases. However, as sBPD evolves in the preterm infant the lung disease changes from the homogeneous, predominantly "fast time-constant" disorder to a heterogeneous, predominantly "slow time constant" (or obstructive) disease. If one continues to use a mechanical ventilation strategy appropriate for acute neonatal lung disease in established sBPD, then a majority of the lung will be under-ventilated or not ventilated at all, resulting in large areas of $\dot{V}/\dot{Q}$ mismatch and hypoxemia. This is often manifest clinically in the NICU as the preterm infant who advances beyond the acute phase of neonatal lung disease develops an increasing FiO_2 requirement just to maintain borderline SpO_2 values. In evolving sBPD this is usually due to increasingly larger $\dot{V}/\dot{Q}$ mismatch. Mechanical ventilation is used to improve $\dot{V}/\dot{Q}$ matching by enhancing ventilation to poorly ventilated areas of the lung. Thus, to ventilate this infant adequately a strategy aimed at the "slow compartment" should be employed. Given that the "slow compartment" is characterized by a normal (or even high) C_L and a high R_L that results in a long time constant, a strategy using longer inspiratory times (to get the V_T into the lung) and slower rates (to extend expiratory time and allow adequate emptying of the lung) would be wise to employ. And consequently, a slow rate would require higher V_T and longer inspiratory time to overcome the high resistance and to maintain adequate minute ventilation ($\dot{V}_E$).

CLINICAL PRACTICE OF CHRONIC PHASE VENTILATION IN SEVERE BPD

There is no high-quality evidence upon which to base strategies for ventilating infants with the most severe forms of BPD; no randomized, controlled trials have been done in this patient population and the evidence that exists is almost entirely observational. Therefore it is important to acknowledge that the following descriptions of our approach to ventilating infants with severe BPD is based on a combination of known physiological characteristics, comparative effectiveness research data, and expert consensus, but is not in the technical sense "evidence-based". We believe that the techniques described herein are based on sound physiology and are appropriate within the limitations of an understudied population, but we also hope that this discussion will lead the field of Neonatology to conduct rigorous studies of the optimal ventilatory approach to this high-risk, low-volume population.

Ventilating infants with established ventilator-dependent sBPD is challenging and rests on the foundation that BPD-prevention can no longer be the primary goal of therapy. These infants have established, severe lung injury, and therapies aimed solely at prevention of lung injury are likely not matched to the underlying physiology. Specifically, as mentioned previously, infants with the most severe forms of sBPD have a physiology that can be most accurately described as two distinct lung compartments, a relatively small compartment with normal C_L and R_L, and a relatively large compartment with near-normal C_L but significantly elevated R_L. This phenotype is characterized by lung over-inflation, $\dot{V}/\dot{Q}$ mismatch, and intrapulmonary right-to-left shunting of blood, which results in high oxygen demand, respiratory discomfort due to increased WOB, and/or frequent hypoxemic episodes. In practical terms this means that high-rate, low-tidal volume ventilatory strategies based on a homogeneous lung physiology

Table 1. Example of initial ventilator settings during acute phase ventilation (lung injury preventive strategy) and chronic phase ventilation (established sBPD).

Setting	Acute phase ventilation	Chronic phase ventilation[a]
Ventilator rate (bpm)	40–60	12–20
V_T (ml/kg)	4–6	10–15 (or as needed to achieve adequate chest rise)
Ti (seconds)	0.25–0.33	0.5–1.0
I:E ratio	1:2–1:4	1:5
PEEP (cm H_2O)	4–6	7–9 (may need higher PEEP depending on lung pathology)

[a]Synchronized intermittent mandatory ventilation (SIMV) with optional pressure support set at maximum 12 cm H_2O, SaO_2 target of 93–97%, and permissive hypercapnia. *V_T* tidal volume, *Ti* inspiratory time, *I:E ratio* inspiratory to expiratory ratio, *PEEP* positive end-expiratory pressure.

exacerbate the clinical features of this phenotype. Over time the hypoxemia contributes to progression of pulmonary hypertension, and pulmonary hypertensive crises, which are the leading cause of death in these infants.[56,57] Therefore, obtaining the best possible $\dot{V}/\dot{Q}$ match throughout the lung is the primary goal of ventilator care in established sBPD. The exact appropriate PMA for transitioning from "regular neonatal gentle ventilation strategies" (small V_T, high rate, often referred to as lung injury preventive ventilation) aimed at preventing BPD to the heterogeneous high R_L strategies (high V_T, low rate, which we refer to as *chronic phase ventilation; CPV*) suggested for established sBPD has not been determined. Although it is conceivable that these patients would benefit from a gradual transition to CPV settings, the timing of such a transition is difficult and most cases present when the regular small V_T/high rate ventilation strategy fails and no longer serves its purpose. While waiting for evidence, we suggest that infants who remain on mechanical ventilation for at least 4 weeks and/or are 32 weeks PMA and are not responding adequately to standard ventilatory approaches may be a reasonable time to initiate CPV. This is based on evidence in the literature that such infants are likely to have high R_L and thus prolonged exhalation times. In rare cases, this approach may be required prior to this age; however, it should be done carefully and only after other phenotypes and causes of respiratory deterioration have been excluded.

Optimizing *V/Q* matching in infants with severe BPD

The main goal of CPV is to improve $\dot{V}/\dot{Q}$ matching throughout a lung that is characterized by high resistance; this necessitates a focus on exhalation. Indeed, the exhalation time constant (τ_E) of the high-resistance compartment in the most severe forms of sBPD is likely to be 0.5 s or in some cases even longer, depending on the degree of lung injury, airway obstruction, and inter patient variability. The implication of this long time constant is clear—by definition it takes five time constants to achieve full exhalation (Fig. 3). Thus, for an infant with an exhalation time constant of 0.5 s, it will take 2.5 s for the lungs to empty fully. Assuming that the inspiratory time constant is shorter due to lung expansion than the expiratory time constant, we set the inspiratory time (Ti) between 0.5 and 0.8 s. To allow for full emptying the expiratory time (Te) is set at 2.5 s; with a Ti set at 0.75 s that results in a 3.25 s respiratory cycle (0.75 s Ti + 2.5 s Te). A 3.25 s respiratory cycle requires a set ventilator respiratory rate (RR) no greater than 18 breaths per minute (bpm). Thus, any set rate faster than 18 bpm will result in incomplete emptying leading to dynamic hyperinflation due to breath-stacking (Fig. 3). Ironically in sBPD, high-rate, low-tidal volume ventilator strategies (Table 1) will instead create even greater $\dot{V}/\dot{Q}$ mismatch leading to progressive hypoxemia.

Given that $\dot{V}_E$ equals RR times tidal volume (V_T) ($\dot{V}_E = RR \times V_T$), when we set a slow rate then V_T, by necessity, must be proportionally higher to maintain $\dot{V}_E$. For example, assuming a $\dot{V}_E$ of 250 ml/kg/min and a rate of 20 bpm, V_T must equal at least 12.5 ml/kg per breath to achieve adequate oxygenation and ventilation, and also to compensate for the initially increased dead space. Although it is possible to reduce $\dot{V}_E$ requirements by means of sedation, BPD is a long-term illness and prolonged sedation likely contributes to neurodevelopmental impairment.[58–62] Thus, an adequate $\dot{V}_E$ must be provided to the patient to reduce air hunger and avoid sedatives. Inspiratory pressures and Ti may need to be increased significantly in order to achieve adequate V_T, and to compensate for increased dead space. The long expiratory time constants require that the RR is lower than 20 bpm to accommodate exhalation. For example, for a RR of 12 bpm, V_T in the above example would need to be 21 ml/kg in order to provide a $\dot{V}_E$ of 250 ml/kg/min. Improved expiration reduces dead space, and eventually enables lower $\dot{V}_E$. Although limited to clinical experience and not subject to any prospective trials the *initial* ventilator settings for established sBPD used in our units are shown in Table 1.

We then increase the ventilator settings as needed, primarily to increase V_T by increasing the PIP or the set V_T, until the infant is comfortable (i.e. no air hunger and little if any increase in WOB) and the FiO_2 is able to be weaned. PEEP is typically set at the lowest pressure adequate to maintain FRC and normoxia while maintaining a mean airway pressure that is consistent with the possibility of eventual extubation to CPAP. In some cases, for instance in the presence of bronchomalacia, increased PEEP may be necessary and occasionally to fairly high levels (Table 1).

Serial assessments of ventilation and oxygenation

Historically, neonatologists have relied upon blood gas assessments by means of indwelling arterial catheters to determine the relative success or failure of mechanical ventilation. It is assumed that frequent blood gas sampling facilitates rapid weaning during the acute phase of neonatal lung disease and that the benefits of blood gas assessments outweigh their risks. While these assumptions may be true in rapidly changing physiological states like the immediate perinatal period, the trade-off is very different in chronic disease states such as sBPD. Infants with chronic sBPD typically do not have indwelling arterial catheters, and thus each blood gas assessment requires skin-breaking. Moreover, the more painful procedures infants undergo during their NICU hospitalizations, the worse their neurodevelopmental outcomes[62,63]. Thus, there is a real risk to the sBPD patient associated with each blood draw, and therefore we recommend minimizing skin-breaking.

We argue, therefore, that serial physical examination and the use of non-invasive respiratory parameters (e.g. pulmonary function data from the ventilator, transcutaneous CO_2, capnography) are adequate to determine ventilatory success in infants with sBPD.[64] Specifically, infants with sBPD supported by mechanical ventilation should be free of air hunger, pink, well-perfused, and able to interact comfortably with their caregivers and their environment. In addition, they should always be able to maintain adequate oxygenation as measured by pulse oximetry. We believe that comfortable, well-saturated, and interactive infants are by definition adequately ventilated and that this does

not need confirmation via skin-breaking, painful blood gas assessments.

Airway obstruction and bronchodilator therapy

We have demonstrated that the vast majority of infants with sBPD who had infant pulmonary function testing have an obstructive physiology.[45] Nonetheless, there is essentially no evidence in sBPD that routine use of bronchodilator therapy improves outcomes.[65] In addition, it is possible that sBPD infants with tracheo- or bronchomalacia may be made worse with bronchodilator therapy. However, it is also clear that some patients with sBPD clearly respond to bronchodilators with improved respiratory function.[45] Therefore, it is imperative that bronchodilator therapy be evaluated clinically and limited to those sBPD patients who demonstrate significant positive responses. Such responses might include improvements in clinical stability 15-45 min after administration, decreased wheezing, increased gas exchange, and/or a reduction in FiO2 associated with bronchodilator administration.

Weaning and extubation in severe BPD

It is critical to understand that improvement in sBPD occurs very slowly and in parallel with the attainment of linear growth. Therefore, daily or even weekly weans may not be well tolerated. It is imperative to allow time for stabilization and to decrease respiratory support slowly (often weekly or even slower). If the infant responds to attempted weans by restlessness/air hunger and/or increased FiO_2/hypoxemic episodes, these changes should be reversed. In general, it is our experience that extubation can be considered when the patient is maintained on stable settings, tolerates cares, gains weight, and requires less than 40% oxygen. Extubation needs to be well planned, preferably to nCPAP, and followed closely. Extubation failure is not uncommon. Weaning from CPAP to nasal cannula is usually possible when oxygen requirement is less than 30% with nCPAP. Tracheostomy may be necessary in those infants that cannot be extubated, but should be relatively rare if appropriate growth occurs while intubated. There is no existing evidence or consensus to determine the optimal time for tracheostomy and there is high variability between centers; thus, further study is needed to determine the best approach to tracheostomy placement.[66–68]

Multidisciplinary approach to managing infants with severe BPD

Once it has been determined that an infant has evolving or established sBPD, the focus of the medical team must shift from prevention of BPD to providing the infant adequate respiratory support to allow good growth and the achievement of critical developmental milestones. In order to achieve these goals, it is imperative that medical decisions be based on comprehensive feedback from the multidisciplinary team.[7,69] Besides competence in neonatology and pulmonology, the multidisciplinary team should consist of representatives from pharmacy, nutrition, occupational therapy, physical therapy, respiratory therapy, nursing, gastroenterology, and the infant's family. Weans or changes in care that result in alterations in growth and/or poor tolerance of developmental activities should be immediately reversed while changes that improve stability should be reinforced. Based on multidisciplinary feedback, each infant's trajectory can be determined over time and reasonable expectations for progress can be set for the family.[70]

SUMMARY

Preterm infants, especially the most preterm, are at high risk of developing sBPD. Despite decades of work to identify strategies to prevent BPD, the incidence of BPD, as well as sBPD, continue to increase in extremely preterm infants. There have been very few well powered studies to provide the evidence needed for the care of patients with sBPD, thus the approach to these patients is highly variable, not only between centers but within centers.[7,71,72] There is a real and pressing need for large rationally designed randomized controlled trials to provide high-quality evidence related to clinically relevant questions that can guide the care of patients with sBPD. In our opinion, the areas with the most pressing needs for high-grade evidence include medication usage, respiratory support, optimal nutrition, and impacts of care on neurodevelopment in patients with sBPD. Until such high-grade evidence is available a multidisciplinary approach that is specific to the physiology and developmental needs of this unique population should be utilized to optimize outcomes for these patients and their families.[7,69,73]

Approaches to mechanical ventilation that are based on acute lung disease will not provide optimal patient support, but will lead to marked dyspnea, retractions, patient–ventilator asynchrony and high FiO_2 needs in patients with established sBPD. The approach to mechanical ventilation for established sBPD as described herein is based on the unique pathophysiology and lung structure of sBPD. Goals of the approach are to optimize oxygenation and provide chronic respiratory support to allow greater patient comfort, improved tolerance of physical and developmental therapies, and provide prolonged periods of quiet wakefulness and interaction without the need for sedatives, paralytics, or other neurotropic medications. The overall aims of CPV are to allow the patient to achieve important developmental milestones, improve growth, and avoid the development of pulmonary hypertension. With this support, the intention is to make sBPD patients thrive despite the presence of severe chronic lung disease. Thus based on our current understanding, to achieve optimal outcomes the clinician should reconsider changing treatment goals from a lung injury preventive ventilation strategy to a more CPV strategy in preterm infants with established sBPD, a strategy that still needs to be further evaluated in future studies.

ADDITIONAL INFORMATION

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BRONCHOPULMONARY DYSPLASIA COLLABORATIVE

Milenka Cuevas[5], William Truog[6], Michael Collaco[7], Martin Keszler[8], Paul Moore[9], Bruce Schulman[10], Beena Sood[11], Lystra Hayden[12], Ioana Cristea[13], Khana Lai[14], Lawrence Rhein[15], Sherry Courtney[16], David Cornfield[17], Robert DiGeronimo[18], Manvi Bansal[19], Susan Gage[20], Rajeev Bhatia[21], Roopa Siddaiah[22], Antonia Popova[23], Megan Lagoski[24] and Joanne Lagatta[25]

[5]Texas Children's Hospital, Houston, TX, USA. [6]Children's Mercy Hospital, Kansas City, KS, USA. [7]Johns Hopkins Medical Institutions, Baltimore, MD, USA. [8]Alpert Medical School of Brown University, Women and Infants Hospital, Providence, RI, USA. [9]Monroe Carell Jr Children's Hospital, Vanderbilt University School of Medicine, Nashville, TN, USA. [10]Joe DiMaggio Children's Hospital, Hollywood, FL, USA. [11]Wayne State University, Detroit, MI, USA. [12]Boston Children's Hospital, Boston, MA, USA. [13]Riley Hospital for Children, Indiana University Health, Indianapolis, IN, USA. [14]University of Utah Health, Salt Lake City, UT, USA. [15]UMass Memorial Medical Center, Worcester, MA, USA. [16]Arkansas Children's Hospital, Little Rock, AR, USA. [17]Lucile Packard Children's Hospital at Stanford, Pal Alto, CA, USA. [18]University of Washington/Seattle Children's, Seattle, WA, USA. [19]Children's Hospital of Los Angeles, Los Angeles, CA, USA. [20]Children's Hospital of Orange County, Orange, CA, USA. [21]Phoenix Children's Hospital, Phoenix, AZ, USA. [22]Penn State Health Children's Hospital, Hershey, PA, USA. [23]Children's Hospital of Michigan, Detroit, MI, USA. [24]Lurie Children's Hospital of Chicago, Chicago, IL, USA. [25]Children's Wisconsin, Medical College of Wisconsin, Milwaukee, WI, USA.