Turkish Archives of Pediatrics

REVIEW
DOI: 10.5152/TurkArchPediatr.2022.22112

Pathophysiologically Based Ventilatory Management of Severe Bronchopulmonary Dysplasia

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ABSTRACT

Both "new" and "old" bronchopulmonary dysplasia features overlap in preterm infants with severe bronchopulmonary dysplasia. The optimal ventilation strategy for infants with severe bronchopulmonary dysplasia has not been clarified yet. Principally, the lung is a multi-compartmental heterogeneous tissue with regionally varying compliance and resistance.

Generally, 2 critical strategical errors are common while ventilating infants with established bronchopulmonary dysplasia: (i) ventilatory management as if they are still in the acute phase of respiratory distress syndrome and (ii) early extubation attempts with the aim of reducing ventilator-induced lung injury. Considering the heterogeneous character of bronchopulmonary dysplasia, although there is no unique formulation for optimal ventilation, the most physiologically appropriate ventilation mode may be the combined mode of volume-guaranteed synchronized intermittent mechanical ventilation and pressure support ventilation. With the volume-guaranteed synchronized intermittent mechanical ventilation mode, slow compartments of the lung with high resistance and low compliance can be adequately ventilated, while fast compartments having relatively normal resistance and compliance can be ventilated well with the pressure support ventilation mode. The following settings are advisable: frequency = 12–20 breaths per minute, tidal volume = 10–15 mL/min, positive end expiratory pressure = 7–12 cmH_2O, and inspiratory to expiratory time ratio = 1 : 5. Higher oxygen saturations such as 92%–95% should be targeted to avoid subsequent pulmonary hypertension.

In conclusion, there is no evidence-based ventilation recommendation for infants with severe bronchopulmonary dysplasia. However, given the changing pattern of the disease and the underlying pathophysiology, these infants should not be ventilated as if they were in the acute phase of respiratory distress syndrome.

Keywords: Bronchopulmonary dysplasia, chronic lung disease, premature infant, mechanical ventilation

INTRODUCTION

Bronchopulmonary dysplasia (BPD) incidence remains high between 10% and 50% despite the great advances in the last few decades. The lungs of preterm babies, corresponding with the end of the canalicular period and the beginning of the saccular period, are prone to damage by several antenatal and postnatal factors. Initially, alveolarization and microvascular maturation have been impaired, which are followed by a period of repair and regeneration lasting months or even years. Several genetic and epigenetic factors, nutrition, microbiota, and immune system modulation take part in this process.[1]

Transition from Acute Respiratory Illness to Bronchopulmonary Dysplasia

Generally, preterm babies exhibit 3 different respiratory patterns in the first 2 weeks of life in terms of the fraction of inspired oxygen (FiO_2) and respiratory support. The identification of 3 types of disease patterns is helpful for the prediction of early prognosis of BPD. In the

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Received: April 21, 2022
Accepted: May 14, 2022

Cite this article as: Özkan H, Duman N, Tüzün F. Pathophysiologically based ventilatory management of severe bronchopulmonary dysplasia. *Turk Arch Pediatr.* 2022;57(4):385–390.

first pattern, infants initially have mild lung disease and recover quickly. Infants in the second pattern develop early persistent pulmonary deterioration requiring prolonged mechanical ventilation (MV). In the third course, infants have minimal lung disease that resolves in the first postnatal week, followed by progressive respiratory decompensation requiring invasive MV and supplemental oxygen.[2]

The fully developed pathophysiology of BPD may not appear in the first month of life. A progressive increase in airway resistance starts almost in the first week. In the second to third week, heterogeneous manifestations of pulmonary ventilation, increased secretion, atelectasis, and hyperinflation areas are observed. The need for a progressive increase in tidal volumes beginning at the third week has been demonstrated in extremely low gestational-age neonates receiving MV.[3,4]

To date, a few definitions of BPD have been used. The efforts for the optimal definition of BPD, which was started by Northway et al[5], are still in progress with the survival of smaller preterm babies and the introduction of non-invasive ventilation methods. After the National Institutes of Health consensus definition in 2001,[6] the National Institute of Child Health and Human Development (NICHD) workshop took place in 2018,[7] and finally, NICHD Neonatal Research Network definition was developed.[8]

Pathophysiology of Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia covers 3 phenotypically overlapping components such as parenchymal, vascular, and major airway damage. The prominence of these structural changes in BPD varies among infants. As a result of parenchymal inflammatory damage and disruption of angiogenesis, there is a decrease in the number of alveoli and the respiratory active alveolar surface area. In the context of vascular development, decreased angiogenesis and vascular smooth muscle cell hyperplasia lead to abnormal vascular remodeling, increased vascular tone, and pulmonary hypertension (PH). With regard to airway damage, large airways develop tracheobronchomalacia due to increased compliance and prolonged cyclic stretching. Small airways exhibit an injury pattern dominated by epithelial damage, edema, smooth muscle hyperplasia, and hyperreactivity.[9]

The most prominent pathological finding in old BPD is airway damage. In new BPD, arrested lung development with dysregulation of pulmonary vascular development and an increase in elastic-collagen fibers is predominant. Though neonatal lung disease displays a homogeneous appearance in the acute phase of new BPD, it gradually progresses to a heterogeneous architectural appearance with areas of atelectasis and hyperinflation. Due to these changes, radiological and histological features such as emphysema and fibrosis appear in the later stages of new BPD as in the old BPD, suggesting a combination of new and old diseases.[10]

Physiological Principles-Guided Respiratory Support Strategies

Generally, 2 critical strategical errors are common while ventilating infants with established BPD: (i) ventilatory management as if they are still in the acute phase of RDS and (ii) early extubation attempts with the aim of reducing ventilator-induced lung injury.

Some issues should be reconsidered during the ventilation of these infants. On the basis of BPD pathophysiology, the multi-compartment lung model and the theoretical implications of mechanical ventilator strategies for severe BPD were proposed nearly a decade ago. Principally, the lung is a multicompartmental heterogeneous tissue with regionally varying compliance (C) and resistance (R). Relatively slow emptying compartments of the lung with longer respiratory time constants (Trs) require substantially higher tidal volumes (Vt) and longer inspiratory/expiratory times (Ti/Te) for optimal ventilation of these compartments (Figure 1), whereas fast compartments having relatively normal Trs require normal Vt and Ti to achieve adequate ventilation.[11,12] Unfortunately, it is not possible to evaluate the multi-compartmental lung structure in these patients neither with pressure–volume curves nor with pulmonary function tests.[4,13-18]

The most striking feature of the lung mechanics in BPD is increased total and expiratory airway resistance due to smooth muscle hypertrophy in the airways, peri-bronchial edema and inflammation, and decreased number of alveoli; secondly, "airway dysynapsis," the disproportion of the increase in airway diameter and lung volume, causes air restriction during expiration. Another aspect is the relative smallness of the

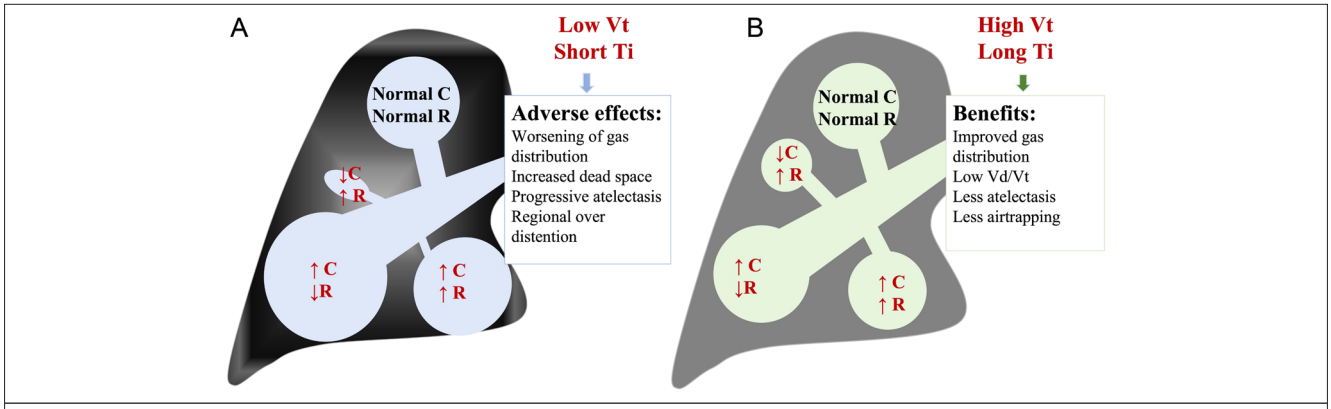

Figure 1. Illustration of the multi-compartment character of the lung parenchyma in severe BPD: (A) the effect of short inspiratory time (Ti) and low tidal volume (Vt), on aeration of the lung with areas of different compliance and resistance and (B) the effect of long Ti and high Vt, on aeration of the lung having areas of different compliance (C) and resistance (R). BPD, bronchopulmonary dysplasia.

surface area of the trachea and bronchi compared to terminal bronchioles. Especially, by the Venturi effect, the diameter of the proximal airways decreases and the resistance increases during the expiration.[10]

Lung compliance in BPD is partially reduced, usually due to narrowing of the small airways, interstitial fibrosis, edema, and atelectasis. Compliance and resistance are the determinants of respiratory time constant ($Trs = C \times R$). To complete 95% of inspiration and expiration, 5 Trs are required. In a preterm infant with BPD, Trs is 0.14 seconds in 3 weeks, 0.33 seconds in 6 months, and 0.48 seconds in 1 year. On the other hand, the time constants of the fast and slow lung compartments are also different from each other. With regard to the lung having 2 compartments, the slow compartment constitutes 2/3 of the tidal volume.[17,19]

A second important issue in babies with BPD is their substantially higher Vt requirement. Because of the increased alveolar and anatomical dead spaces due to air trapping and tracheomegaly, and lower respiratory rate need, higher tidal volumes are needed to provide minute ventilation. For example, in order to provide 250-300 mL/kg/min ventilation, a baby with BPD with a respiratory rate of 20/min should have a Vt of 12-15 mL/kg.[17]

Positive end expiratory pressure requirements are highly variable among infants with severe BPD. Airway closure due to tracheomalacia or bronchomalacia is common in infants with severe BPD, and the use of high PEEP values is beneficial in these infants as it will keep the airway open. Although it may seem contradictory, the use of higher PEEP values in the presence of air trapping facilitates complete emptying of the airways during expiration, especially in the slow compartment section. However, high PEEP levels increase the risk of air trapping and may not be well tolerated unless administered with low ventilator rates and adequate expiratory time.[12] If lower PEEP levels are used, flow–volume curves often exhibit expiratory flow limitation at low lung volumes because of the expiratory collapse of poorly supported small airways and air-trapping. In this situation, following flow–volume graphics, PEEP can usually be titrated upward until this expiratory flow limitation is resolved.[20] If appropriate PEEP values could not be selected, the lungs become overexpanded in the upper part of the pressure–volume curve resulting in decreased C, increased work of breathing, increased pulmonary vascular resistance, and increased oxygen demand and hypercapnia. When the diaphragm is depressed due to overexpansion, infants cannot produce enough Vt and their respiratory rate increases. Thus, in the presence of intrinsic PEEP, the infant cannot sufficiently trigger the ventilator, resulting in air hunger and agitation. For these reasons, careful monitoring and evaluation of pressure–volume, volume-flow, and time-flow graphs during ventilation of these infants are critical.[4,17,18]

To define ventilation strategy, it is critical to know whether atelectatic areas or areas of over-inflation predominate on chest radiographs. If atelectasis is predominant, the main problems are oxygenation and the higher PEEP value needs of the patient. If over-inflation is predominant, the main problems are ventilation and the requirement of higher tidal volumes (Vt) with longer inspiratory and expiratory times[17-19] (Figure 2).

Currently, no randomized controlled study exists in the literature suggesting the most appropriate ventilation strategy in severe BPD. Considering the heterogeneous character of BPD, although there is no unique formulation for optimal ventilation, the most physiologically appropriate ventilation mode may be the combined mode of SIMV+VG and pressure support ventilation (PSV). With the SIMV+VG mode, slow compartments of the lung with high R and low C can be adequately ventilated, while fast compartments having relatively normal R and C can be ventilated well with the PSV mode. Considering the pathophysiology, the following settings are advisable: frequency = 12-20 breaths per minute (bpm), Vt = 10-15 mL/min, PEEP = 7-12 cmH_2O, and inspiratory to expiratory time ratio (I : E) =1 : 5. The peak inspiratory pressure (PIP) support level

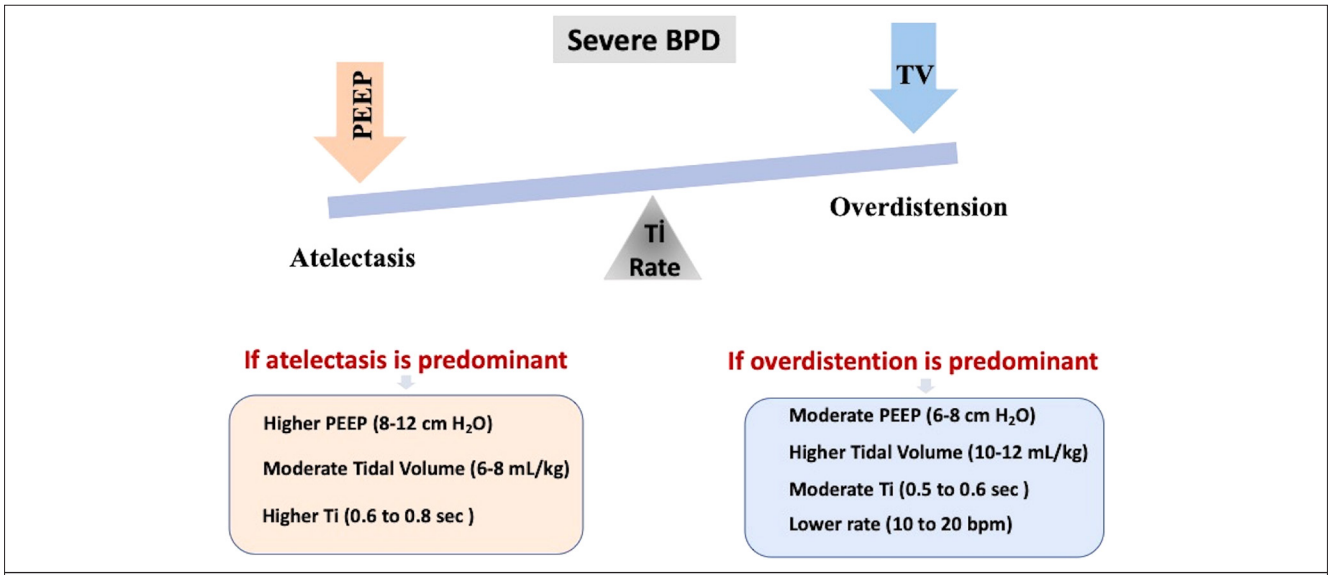

Figure 2. Critical impact of positive end expiratory pressure (PEEP) and tidal volume (Vt) levels on lung ventilation in severe BPD: Ventilatory strategies depending on lung aeration in severe BPD. BPD, bronchopulmonary dysplasia.

Table 1. Main Ventilatory Strategies in Severe BPD

Strategies for gas exchange	**Regional heterogeneity** • Larger Vt (10-15 mL/kg) • Longer Ti (0.5-1 seconds) **Airway collapse** • Higher PEEP levels (7-12 cmH_2O) **Over distention** • Slow rate (12-20/bpm), longer Ti and Te (Ti : Te = 1 : 5) **Mode preference** • SIMV-VG+PSV
Targets	• Target higher SaO_2 levels to prevent pulmonary hypertension (92%-95%) • Allow permissive hypercapnia (pCO_2 45-65) to facilitate weaning • Keep the infant calm without any need for sedatives • Wean with patience and caution • Monitor and facilitate somatic and neurodevelopmental growth

Vt, tidal volume; Ti, inspiratory time; Te, expiratory time; Ti, inspiratory time; SIMV+VG, volume-guaranteed synchronized intermittent mechanical ventilation; PSV, pressure support ventilation; PEEP, positive end expiratory pressure; BPD, bronchopulmonary dysplasia.

in PSV mode can vary from 6 to 18 cmH_2O as needed (Table 1). Recommended settings are based on expert recommendations considering pathophysiological changes.[4,7,13-,18]

In severe BPD, when the synchronized intermittent positive pressure ventilation or PSV modes are used alone, there is a risk of rapid breathing, insufficient expiration times, and consequent air trapping since each breath triggers the ventilator. Although volume-targeted ventilation modes provide a stable volume despite changing lung mechanics, these infants need substantially higher Vt, and neonatologists are not used to such high tidal volumes in daily practice. Also, the ventilator may not be able to provide adequate PIP support to maintain these high tidal volumes. High-frequency oscillatory ventilation (HFOV), on the other hand, is more effective in lung pathologies that require shorter time constants. It does not create high tidal volumes and one major concern with HFOV is the collapse of the poorly supported small airways and airways affected by malacia during the active exhalation phase.[4,13,21] Although neurally adjusted ventilatory assist seems like a promising model for this population, there is not sufficient evidence to comment on this yet.[22,23]

Higher oxygen saturation (SpO_2) such as 92%-95% should be targeted since chronic hypoxia may lead to vasoconstriction of pulmonary vessels and subsequent PH.[24-26] Pulmonary hypertension frequently accompanies and complicates the clinical course of preterm babies with BPD. In infants with BPD, PH develops in approximately 1 out of every 4 infants, and it adversely affects the clinical course and even increases the risk of mortality. Therefore, infants with proven or suspected PH should receive close follow-up, including preductal/postductal SpO_2 measurements, echocardiography, and laboratory work-up. The presence of PH should be investigated by echocardiography in these babies at the 36th week of post menstrual age (PMA) (it can also be evaluated from the 7th day), and repeated echocardiographic examinations are needed. Oxygen saturations ≥ 93% for suspected PH and ≥95% for proven PH have been recommended.[25]

Basic principles in the treatment of BPD include creating a family-centered chronic care model focusing on neurodevelopment, supporting ventilation, reducing agitation and desynchronization, drug treatments, optimal nutrition, screening and treatment of PH, gastroesophageal reflux treatment and gastric fundoplication if necessary, and bedside emergency approaches.[18-20]

The main goals of ventilator treatment in severe BPD should be to provide somatic and pulmonary growth and to improve neurodevelopment. As stated before, considering the pathophysiology, (i) longer Ti, (ii) higher Vt, (iii) substantially higher PEEP, and (iv) higher SaO_2 targets (92%-95%) are key elements.

Monitoring

In the follow-up, clinical findings and pulmonary graphs are practical and are non-invasive indicators for guiding the appropriate ventilation of these babies. Blood gases may not be very useful as they can show dramatic changes during painful procedures. Targeted blood gas values in severe BPD may be as follows: pH 7.25-7.35, PaO_2 50-70 mm Hg, and $PaCO_2$ 50-65 mm Hg. Oxygenation is monitored with SaO_2 and values of 92%-95% are targeted. Serial echocardiographic examinations should also be a part of monitoring as infants with BPD may be accompanied by PH.[25] Although there is insufficient evidence for the benefits of the closed-loop automated oxygen delivery system in these infants, a randomized controlled crossover study showed that there were fewer prolonged hypoxic episodes with the automated system and more time spent in the targeted oxygen range.[27]

In general, MV is needed if the baby shows respiratory distress, tachypnea, frequent episodes of desaturation, insufficient growth, and PH. It is observed that a baby receiving adequate ventilation support seems calm, relaxed, and in contact with the environment without sedation/analgesia.[4,13-18]

Weaning

In order to avoid ventilator-induced lung injury, quick weaning to non-invasive ventilation is targeted during the acute phase of RDS. However, in patients with severe BPD, it is important to achieve adequate gas exchange and to minimize the venti lation/perfusion (V/Q) mismatch. Minimizing the respiratory work, reducing the agitation and need for prolonged sedative requirement, preventing recurrent cyanosis attacks, and

avoiding the development or progression of PH are the main goals. Since alveolar growth is parallel to somatic growth, adequate nutrition and ensuring normal growth are critical during this process. Because of these goals, weaning should be done slowly with patience.[12,20,28] Weaning can be attempted cautiously in the absence of desaturation episodes, PH, and high oxygen requirement (FiO_2 > 0.40). Ventilator settings should be adjusted once or at most twice a week. Depending on the baby's condition, Vt or PEEP values should be decreased stepwise. After extubation, switching to non-invasive ventilation using high PEEP pressures (10-15 cmH_2O) followed by high-flow nasal cannulas seems logical.[4,29] The room air challenge test predicts readiness to separate from oxygen to room air in recovering infants.[26,30] Recently, monitoring of Transcutaneous carbon dioxide ($TcPCO_2$) has been proposed as a useful physiological test to predict success in weaning from non-invasive ventilation.[31]

When to Consider Tracheostomy?

Tracheostomy decisions and determining the optimal tracheostomy time in infants with severe BPD are challenging. According to a limited number of studies, tracheostomy requirement in severe BPD is associated with adverse respiratory and developmental outcomes.[32,33] Because of the complexity of the disease and the absence of a consensus, tracheostomy indications differ widely across different neonatal intensive care units.[34] Among infants with severe BPD, infants requiring tracheostomy before 36 weeks PMA have poorer long-term respiratory and neurodevelopmental prognosis compared to those who did not require it.[35] A retrospective cohort study from the NICHD Neonatal Research Network centers revealed that death or neurodevelopmental impairment (NDI) occurred in 83% of infants with tracheostomies and 40% of those without. This study also demonstrated that infants undergoing tracheostomy before 120 days of age had a reduced risk of mortality or neurodevelopmental impairment than those who underwent tracheostomy later.[33] In accordance with the previous studies and the results of recent survey analysis, the following ranges seem reasonable: existence of airway malacia, PCO_2 > 76-85 mmHg, FiO_2 > 0.60, PEEP > 9-11 cmH2O, respiratory rate > 61-70 bpm, PMA ≥ 44 weeks or postnatal day > 120 days (which is earlier), and weight < 10th percentile at 44 weeks PMA.[33,34]

CONCLUSION

Pulmonary vascular bed and alveolar development are interrupted in BPD. Both "new BPD" and "old BPD" features overlap in preterm infants with severe BPD. The optimal ventilation strategy for infants with severe BPD has not yet been clarified. However, given the changing pattern of the disease and the underlying pathophysiology, these infants should not be ventilated as if they were in the acute phase of RDS. Considering the pathophysiology, the most physiologically appropriate ventilation mode may be the combined mode of SIMV+VG and PSV. The following settings are advisable: frequency = 12-20 bpm, Vt = 10-15 mL/min, PEEP = 7-12 cmH_2O, and I : E = 1 : 5. The PIP support level in PSV mode can vary from 6 to 18 cmH_2O as needed. It should be kept in mind that even chronic lung disease improves over the years by providing optimal supportive ventilation. During this process, a multidisciplinary approach is essential in the care of infants receiving long-term respiratory support.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – H.Ö.; Design – F.T.; Supervision – H.Ö., N.D., Literature Review – H.Ö., F.T.; Writing – H.Ö, F.T.; Critical Review – H.Ö., N.D.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

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