·LECTURE·

Lung Development and Lung Injury - The New BPD

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The concept that there is a "New BPD" has developed because of the recent pathologic finding in ventilated preterm infants, the changing epidemiology of BPD, and recent results with experimental models[1]. The pathophysiology of BPD previously was characterized by severe airway epithelial dysplasia and injury, airway smooth muscle hyperplasia, parenchymal fibrosis and focal emphysema[2]. These lesions were caused by mechanical ventilation and prolonged exposures to high amounts of supplemental oxygen. More recent histopathology from infants who have died of BPD demonstrates minimal airway injury, less fibrosis but with incresed elastin, and a simplified lung architecture with fewed but larger alveoli[3,4]. These findings need to be interpreted within the context of the stage of lung development present after very preterm delivery (Figure 1).

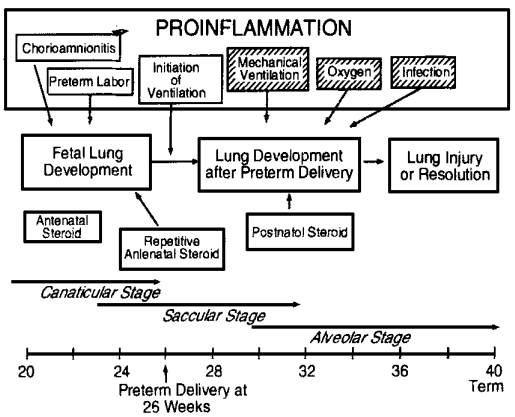

Figure 1

The lung at 26 weeks gestation is just completing the canalicular stage and is saccular structure without alveoli[5]. Alveoli will not begin to develop for another 4 to 6 weeks. Therefore the simplified lung probably represents an interruption of arrest in lung development from the saccular to the alveolar stages. Microvascular development also is abnormal and inadequate.

The epidemiology of BPD now includes primarily very preterm infants with birth weights < 1000 g. Previously BPD occurred primarily in infants who had received mechanical ventilation and supplemental oxygen. However, recently and more perplexing is the occurrence of BPD in the very tiny infant with minimal or no RDS who has received less mechanical ventilation and oxygen exposure[6] (Figure 2). As demonstrated in the figure, the oxygen requirements of infants without RDS can increase and result in these infants having the diagnosis of BPD.

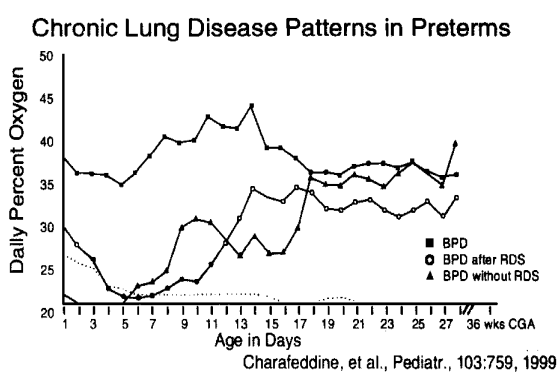

Figure 2

Factors Contributing to BPD (Figure. 1)

A scheme for thinking about BPD is given in

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Figure 1. I will present evidence to support the conclusion that ventilation is associated with an interference of lung development resulting in an arrest of alveolar and vascular development[3,4,7,8]. A likely mechanism for the ventilation mediated injury is the associated inflammation[9]. Based on the scheme in Figure. 1, ventilation is just one of the factors that can promote inflammation in the lung, and this inflammation may be a major contributor to the arrested lung development characteristics of the new BPD.

Ventilation Injury Resulting from the Initiation of Ventilation at Birth

The preterm lung is very susceptible to injury with the initiation of ventilation because it is fluid filled, it has a small potential gas volume/kg body weight relative to a term infant, it is often surfactant deficient, and the support matrix in the airways and parenchyma is deficient (less collagen and elastin)[10]. High pressures used to achieve reasonable tidal volumes cause volutrauma and inflammation. The lung is then less able to respond to surfactant treatment[11]. In figure 3, ventilation of ventilation with a tidal volume of 20 ml/kg resulted in poor compliance after surfactant treatment at 30 min of age (Figure 3). Surfactant treatment before ventilation decreased protein leak into the airspaces.

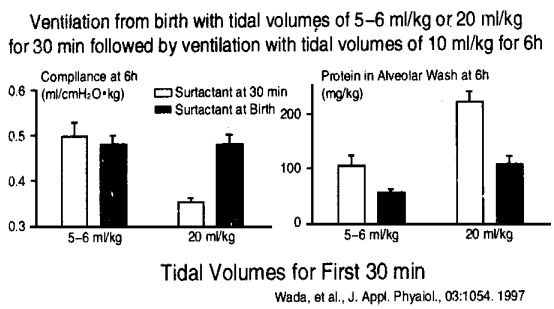

Figure 3

The new observation is that the initiation of ventilation even when performed as gently as possible is sufficient to initiate proinflammatory processes in preterm lambs[12]. The initiation of ventilation after preterm birth and surfactant treatment using regulated tidal volumes of 10 ml/kg, a PEEP of 4 cmH_2O, and a Pco_2 target >50 mmHg resulted in the recruitment of activated WBC and pro-inflammatory cytokine expression in the lungs. In the example in Figure 4, IL-1β and IL-6 expression was elevated even more when ventilation occurred without PEEP, the normal situation with delivery room resuscitation.

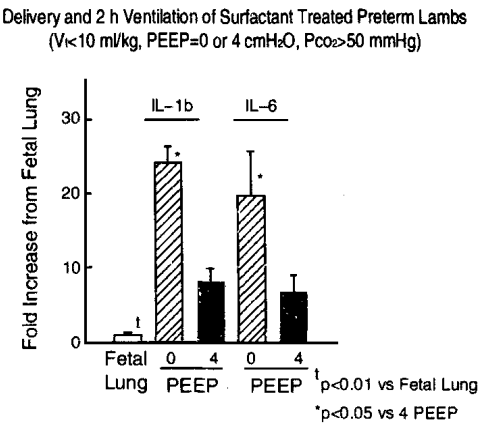

Figure 4

Routine Ventilation

Very elegant work by Dr. Coalson's group and Dr. Bland's group demonstrates that routine ventilatory management of very preterm baboons or sheep that were surfactant treated at birth resulted in the arrest of alveolar and vascular development that characterizes the new BPD[7,8] (Figure 5). This interference with development occurred similarly with high rate/low tidal volume ventilation in the lambs or with conventional ventilation or high frequency oscillation in the baboons[13]. The uniformity of inflation was better for the high rate/low tidal volume and HFOV strategies, but the developmental arrest was similar (Table 1).

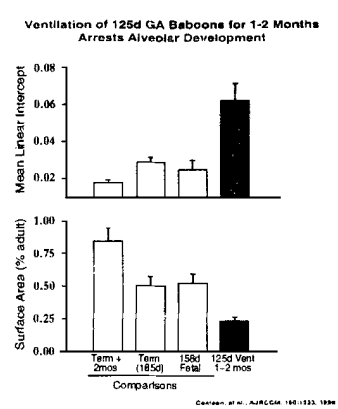

Figure 5

Table 1　Comparison of Lung Injury Following 30 d Ventilation of Preterm Baboons With CV or HIFOV

	CV	HFOV
FiO_2	Higher	Lower
Lung Mechanics	Worse	Better
In Tracheal Aspirates		
IL-6, IL-8, IL-1	No consistent differences	
IL-10	No consistent differences	
WBC	More	Less
Histopathology		
Uniformity of Inflation	Less	More
Alveolariation	Inhibited Similarly	

Yoder, et al., AJRCCM 162, 1867, 2000

Antenatal Infection and Ventilation

Clinical epidemiology indicates that a high percent of infants born before 30 weeks GA were exposed to a low grade, chronic and often clinically inapparent chorioamnionitis that has exposed the fetus to a pro-inflammatory environment[15]. Although this pro-inflammation can induce lung maturation, we have hypothesized that the lung already "primed" by a pro-inflammatory stimulus will amplify that stimulus resulting in more injury[9]. This concept is based on models of ventilation of mature lungs that become more injured after sensitization with pro-inflammatory stimuli[16]. Such "priming" rematins to be demonstrated in the preterm lung.

Slutsky and his colleagues have demonstrated that the injured lung can release toxic products (cytokines, endotoxin) from the lungs to the systemic circulation[17]. These products may then contribute to multisystem organ failure. In the adult lung, very injurious styles of ventilation are needed to cause release of lung derived inflammation to the systemic circulation. In contrast we found that the preterm lung leaks endotoxin from the lungs to the systemic circulation even when the lung is surfactant treated and gently ventilated[18] (Figure 6). The endotoxin induced a systemic inflammatory response-shock, WBC depletion and elevated cytokines in the blood. Therefore gentle ventilation of the inflamed/infected preterm lung may result in systemic injury.

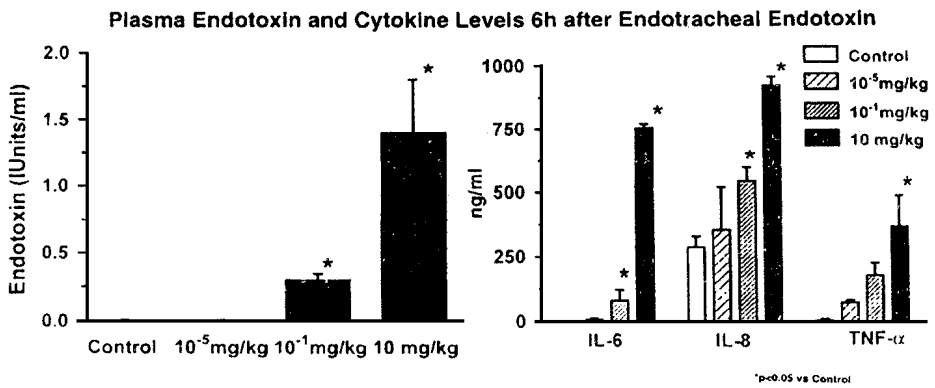

Figure 6

Setting Goals

The goals of management for ventilated infants have never been formally considered and validated. The general assumption that the appropriate goal is a normal pH and blood gas (pH = 7.4, Po_2 > 60 mmHg, Pco_2 = 40 mmHg) clearly has been changing in clinical practice.

Pco_2 is the variable most sensitive to the quantity (rate, tidal volume) of mechanical ventilatiomn. There are animal and human data demonstrating that low Pco_2 values are potentially harmful[19,20]. The answer to the question of what is a safe Pco_2 after birth and more chronically after hours, days, or weeks of adaptation is not known. However, many neonatologists target a Pco_2 around 50 mmHg in the first days of life for infants requiring mechanical ventilation. Clearly the amount of mechanical ventilation can be decreased if the Pco_2 target is increased. In a small pilot study Mariani, et al. [21]found that a Pco_2 of about 50 mmHg was safe and the lung outcomes suggested less BPD. A subsequent study by the NICHD neonatal network demonstrated that targeting a Pco_2 to > 52 mmHg verses < 48 mmHg decreased BPD in in-

fants < 750 g birth weight, although the study was underpowered. Any trials of ventilation techniques need to compare outcomes at comparable Pco_2 values. Information about safe levels of Pco_2 in the preterm is urgently needed. A provocative observation is that reperfusion injury to the lungs of adult rabbits can be prevented if the Pco_2 is maintained at 100 mmHg during and after the injury[22]. Furthermore, correction of the respiratory acidosis made the injury worse. A high Pco_2 may protected the preterm lung, but is it safe?

Po_2 targets also are improtant. In the ARDS Network trial of high vs low tidal volume ventilation, the low tidal volumes resulted in lower mortality[23]. However, over the first 72 h of randomization, the high tidal volume ventilation resulted in better oxygenation. Therefore, if the surrogate target had been oxygenation, high tidal ventilation would have been the preferred mode, The STOP-ROP trial targeted preterm infants with BPD to high saturation or low saturation ranges[24] (Table 2).

Table 2 Effect of Targeting Higher O_2 Sats on Indicators of BPD

	Sats of 89 - 94 %	Sats of 96 - 99 %
N	325	324
Birth Weight	721 ±160	731 ±161
Age at entry(wks)	35.3 ±2.6	35.4 ±2.5
Outcomes at 3 mos corrected age		
Remained		
Hospitalized	6.8 %	12.7 %
Remained on O_2	37.7 %	46.8 %
Remained on diuretics	24.4 %	35.8 %

STOP-ROP Multicenter Study Group-Pediatr 105; 295, 2000

The high saturation range resulted in the need for about 11 % higher oxygen concentrations and clinical indicators of more prolonged lung injury.

Tidal volume/ rate/ PEEP targets also are critical to minimizing ventilation. There are few studies in neonatology demonstrating benefit of one style of ventilation over another. Although HFov has been enthusiastically accepted as beneficial by some, others remain skeptical. The trials either show no compelling benefit to HFOV, indicate concerns about outcomes other than BPD, or are unconvincing.

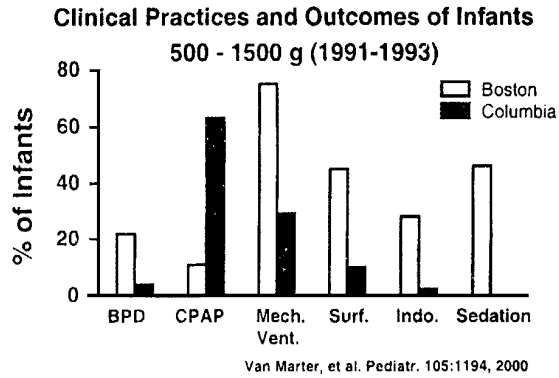

FIGURE 7

Avoidance of Ventilation

The association of ventilation with BPD is clear and compelling from both the clinical and animal model literature. The use of CPAP to avoid ventilation has been used by some clinicians for many years. Compelling information demonstrating a striking effect on the incidence of BPD is now appearing. Van Marter, et al. Compared the columbia experience with using bubble CPAP in the delivery room with the Boston experience of frequent cntubation in the delivery room[25] (Figure 7). The use of CPAP not only decreased BPD, but also decreased the use of surfactant, indomethacin and sedation, demonstrating overall differences in management practices. When adjusted for birth weight, race, and a number of other clinical variables, the major predictor of BPD was the initiation of ventilation in the 1st day of life. Clinical trials that address the best ways to administer CPAP, when to give surfactant, and what criteria should be used to identify CPAP failure need to be performed. The best amount of ventilation for a preterm infant is the least amount to achieve the clinical goals. We need to better define safe goals.

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