

## Postnatal Changes in Pulmonary Mechanics and Energetics of Infants with Respiratory Distress Syndrome following Surfactant Treatment

Vinod K. Bhutani<sup>a</sup> Frank W. Bowen<sup>b</sup> Emidio M. Sivieri<sup>b</sup>

<sup>a</sup>Department of Pediatrics, Division of Neonatal and Developmental Medicine, Stanford University School of Medicine, Stanford, Calif., and <sup>b</sup>Department of Pediatrics, Division of Neonatology, University of Pennsylvania, Philadelphia, Pa., USA

### Key Words

Surfactant treatment · Respiratory distress syndrome · Bronchopulmonary dysplasia · Pulmonary mechanics · Pulmonary energetics · Functional residual capacity · Postnatal maturation

### Abstract

**Background:** Postnatal alterations in pulmonary mechanics, energetics and functional residual capacity (FRC) describe the structural maturation of the preterm respiratory system. **Objective:** To evaluate longitudinal changes in pulmonary function in infants with respiratory distress syndrome (RDS) treated with oxygen, positive pressure ventilation and synthetic surfactant (Exosurf<sup>®</sup>). **Methods:** Serial pulmonary function tests were performed in surfactant-treated infants [mean  $\pm$  SD birth weight (BW) = 1,112  $\pm$  276 g, gestational age (GA) = 29  $\pm$  3 weeks] at postnatal ages: <3 days, 1, 2, 3, 4 and 6–8 weeks until term postmenstrual age (PMA). Tidal volume, pulmonary compliance ( $C_L$ ), pulmonary resistance ( $R_T$ ) and flow-resistive work were analyzed following simultaneous measurements of airflow and transpulmonary pressure signals. Serial FRC measurements were made in a randomly selected group. **Results:** Prior to 28 weeks' PMA,  $C_L$  was unchanged irrespective of GA. At age 1 week the likelihood ratio (LR) for bron-

chopulmonary dysplasia (BPD) based on  $C_L$ ,  $R_T$  and GA was predicted to be >90% for those with BW <750 g (LR >100) as compared to <10% probability (LR = 0.3) for infants >1,500 g. Significant linear increase in  $C_L$  to PMA was evident >28 weeks' PMA ( $r = 0.86$ ,  $p < 0.01$ ) at 0.17 ml/cm H<sub>2</sub>O/kg/week. By term PMA, mean  $C_L$  was 2.60  $\pm$  0.07 ml/cm H<sub>2</sub>O. Improvements in FRC of preterm infants with RDS who recovered occur at a more rapid rate (~25 ml/kg) compared to those who developed BPD (~20 ml/kg). **Conclusions:** Slow but incremental postnatal pulmonary improvement, minimal <28 weeks' PMA, were comparable for all infants. Along with diminished FRC, these changes reflect persistent deleterious effects of positive pressure ventilation, alveolar hyperoxia and unrecognized pulmonary overdistension.

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### Introduction

Decreased pulmonary compliance ( $C_L$ ), the hallmark of neonatal respiratory distress syndrome (RDS), abnormalities in gas exchange and decreased functional residual capacity (FRC) were anticipated to be corrected with surfactant-replacement therapy in preterm infants with respiratory failure due to surfactant deficiency [1, 2]. Though improvement in oxygenation and gas exchange

were readily apparent, improvement in  $C_L$  was only evident after the tidal volume ( $V_T$ ) overdistension was controlled [3, 4]. The apparent increase in FRC following surfactant replacement was also confounded by lung overdistention during ventilation [5, 6]. In fact, the role of volume, pressure and flow-induced overdistension became more readily discernible with the advent of bedside use of pulmonary graphics [7–11] and clinical practices have evolved to seek optimal and less traumatic ventilation strategies. The recognition of the confounding increase in the resistive components of pulmonary function of infants on continued mechanical ventilation (>48 h duration) [12, 13], even though the elastic dysfunction had been corrected, corroborate with the clinical onset of bronchopulmonary dysplasia (BPD) and observations of airway barotrauma as well as end-expiratory airflow limitation [14, 15].

The structural cost of positive pressure ventilation to the airways and lung parenchyma is now being recognized as one of the multifactorial reasons for chronic lung disease of infancy [16–18]. The structural consequences are likely to be modulated by postnatal aging and growth. As suggested by Agostoni and Hyatt [19], ‘the main static change of the respiratory system during growth is the increasing outward recoil of the chest wall. It is not clear how much of this is due to changes in the mechanical properties of the chest wall and how much to the disproportionate growth of the chest wall relative to that of the lungs’. In growing preterm neonates with RDS who receive surfactant replacement with concurrent positive pressure ventilation, it remains unclear whether there are sequelae of mechanical ventilation that perpetuate or deter the infant’s respiratory function and the infant’s ability to promote lung maturation.

To better understand how postnatal aging and growth of preterm infants and the evolving changes in both elastic and resistive loads affect the core clinical measure of respiratory structure, we compared the serial data on pulmonary mechanics and energetics determined from birth to term postmenstrual age (PMA) in preterm infants with RDS who received synthetic surfactant and positive pressure ventilation with oxygen supplementation.

## Methods

We reviewed data from our pulmonary function database to identify preterm infants with RDS in whom serial pulmonary function measurements had been made from soon after birth until hospital discharge. The preliminary dataset was reported as an abstract to the Pediatric Academic Society meeting in 1992.

### *Patient and Study Protocol*

This study was performed at Pennsylvania Hospital which was participating in multicenter trials of a synthetic surfactant preparation, Exosurf Neonatal<sup>®</sup> (Burroughs Wellcome Co, Research Triangle, N.C., USA) [20]. The evaluation of pulmonary mechanics and energetics was performed concurrent to the clinical trials under a separate protocol. All protocols were approved by the Research Review Committee of the Pennsylvania Hospital and written parental consent was obtained for participation.

### *Inclusion Criteria*

All infants were born at Pennsylvania Hospital between July 1988 and July 1991. Inclusion criteria were: (a) clinical diagnosis of RDS based on clinical signs, blood gases and radiographical findings; (b) administration of 2 or more doses of surfactant; (c) birth weight (BW) range from 500 to 2,000 g and (d) PMA of 34 weeks or less (corroborated by a Dubowitz examination).

### *Surfactant Administration*

The surfactant, Exosurf<sup>®</sup>, was administered through a side-port as per the manufacturer’s guidelines, while the infant was receiving mechanical ventilation. Each dose was 5 ml/kg equivalent to 67.5 mg/kg of dipalmitoylphosphatidylcholine. The timing of administration was within 30 min of birth for infants less than 1,000 g BW and within about 2 h of birth for infants who met the clinical and gas exchange criteria for RDS (see above).

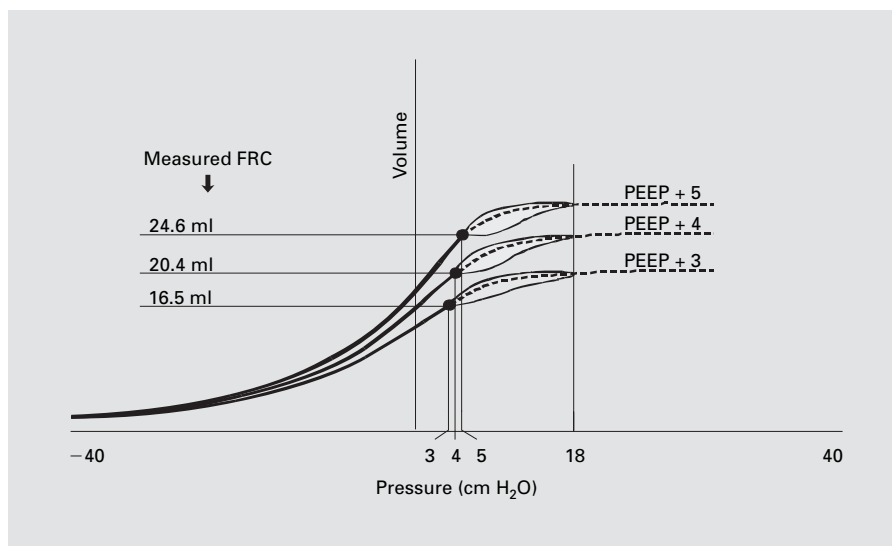
### *Measurement of Pulmonary Function*

Pulmonary mechanics were measured during both spontaneous and mechanical ventilation. Data collection during spontaneous breathing was performed at a positive end-expiratory pressure (PEEP) of 3 cm H<sub>2</sub>O while the ventilator rate was decreased to zero for the 45- to 60-second sampling period. Pulmonary function data of extubated infants were measured by a facemask pneumotachometer device. For infants in whom data collection was difficult during spontaneous ventilation, such as infants with apnea or chest wall distortion, data were collected during mechanical ventilation. The ventilator settings used for data collection were uniform: ventilator flow of 8 l/min, PEEP of 2 cm H<sub>2</sub>O, an inspiration time of 0.5 s, a respirator rate of 60 cycles/min while the peak inflating pressure was maintained at settings that were being used clinically. Infants were studied in supine, head-neutral posture [21] and prior to any enteral feed [22]. Sedation was not used. Simultaneous measurements of gas flow and transpulmonary pressure signals were measured and computed for analysis and graphic display. Detailed description of this methodology has been reported previously in several papers [11, 23–25]. The devices for pulmonary function measurements had a minimal resistance (13.2 cm H<sub>2</sub>O/l/s) and dead space (1.2 ml).  $V_T$  was measured by digital integration of the flow signals. The pneumotachometers were individually calibrated by use of regulated flow meters with traceable accuracy such that the output was linear from 0 to 0.15 l/s. Calibration sensitivity and operating techniques of the apparatus were similar to those previously reported in detail. FRC was measured by a custom-designed helium dilution technique in a selected number of infants [26, 27].

### *Pulmonary Function Schedule*

Pulmonary function was measured at the following postnatal ages for each infant: 48 and 72 h, 1 week  $\pm$  1 day, 2 weeks  $\pm$  2

**Fig. 1.** FRC measurements with concurrent transpulmonary P-V relationship at PEEP of 3, 4 and 5 cm H<sub>2</sub>O in an infant at 27 weeks' GA following surfactant replacement at age 3 days and obtained during positive pressure ventilation with a peak inflating pressure of 18 cm H<sub>2</sub>O. The data are presented as an 'integrated P-V relationship' with theoretical extensions beyond the measured tidal volume-transpulmonary pressures. The P + V loops show evidence of terminal flattening that is a characteristic of overdistension.



days, 3 weeks  $\pm$  3 days, 4 weeks  $\pm$  4 days, 6–8 weeks and term PMA (38–40 weeks). When there were multiple pulmonary function measurements for each infant, the following criteria were used to select the representative test to provide a serial profile: (a) data obtained with spontaneous breathing, (b) mechanical breaths with a mean  $V_T$  that ranged from 3.5 to 8.0 ml/kg and (c) closest to the study postnatal age. FRC was measured in some infants provided they weighed at least 1,000 g. When measured at age <1 week and in infants on mechanical ventilation, FRC values were dependent on the level of PEEP (fig. 1). Thus FRC data were excluded when measurements were made on infants receiving positive pressure ventilation. Data were included if a study infant had two or more serial measurements. At each evaluation, two to three consecutive FRC measurements were made to confirm accuracy and to allow use of an average value. During pulmonary function testing, all infants were monitored for their hemodynamic and gas exchange status with a continuous cardiorespiratory monitor and pulse oximetry.

#### Data Analysis

Simultaneous records of airflow, volume and transpulmonary pressure were sampled at a rate of 75 Hz/channel by a custom-designed software program. The values for dynamic  $C_L$ , pulmonary resistance ( $R_T$ ) and flow-resistive work were calculated for inspiration, expiration and total breath [11]. In addition, values for  $V_T$ , minute ventilation, respiratory frequency and time constant were obtained. Sampled breaths were considered for analysis if they met previously described criteria as well as demonstrating absence of overdistension ( $V_T < 8.5$  ml/kg). Pulmonary mechanics and energetics were calculated by the two-factor least mean squares technique [11]. A minimum of 15 breaths (usually 25–45) were evaluated after sampling over a 2-min period, with a correlation coefficient of at least 0.98 for the least mean squares analysis. Mean values from the analyzed breaths were used to represent lung mechanics [10, 11]. In addition, demographic criteria on each infant were collected including BW, gestational age (GA), exposure to antenatal steroids, patent ductus arteriosus, use

of postnatal steroids, intraventricular hemorrhage, necrotizing enterocolitis, pneumothoraces, BPD based on oxygen requirement at age 4 weeks, chronic lung disease (based on oxygen requirement at 36 weeks' PMA) and duration of both ventilatory and oxygen support.

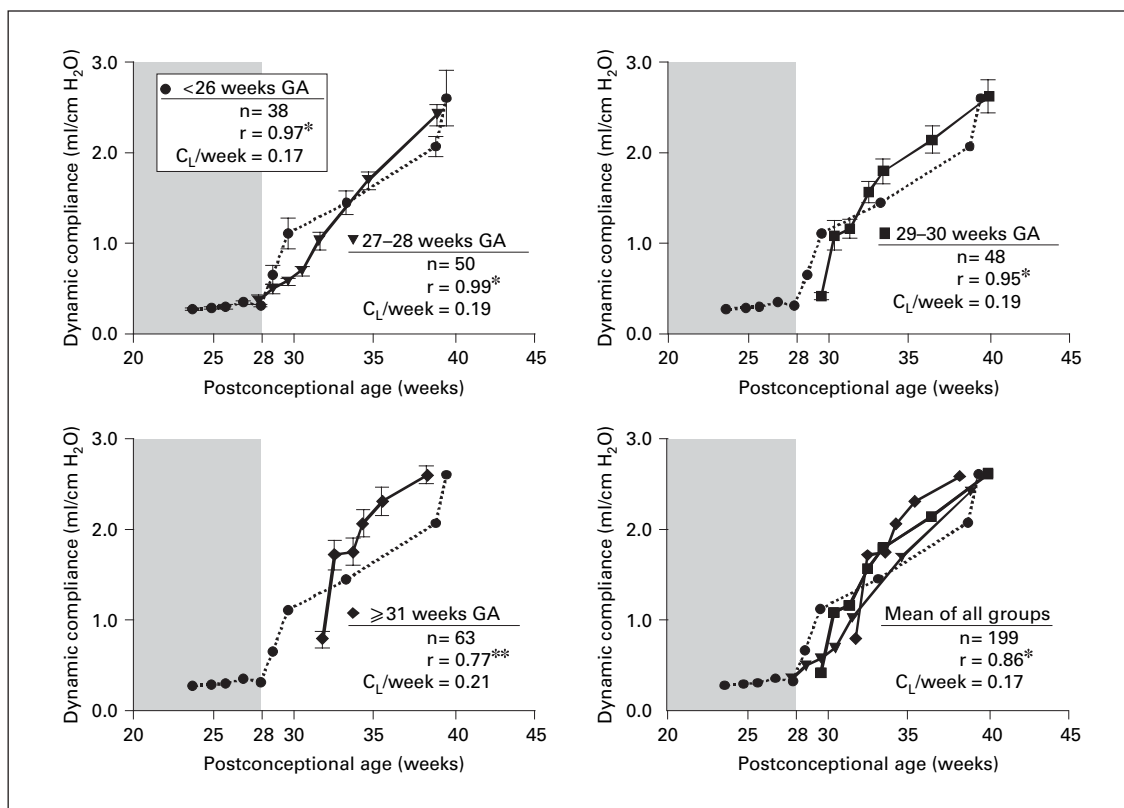
#### Statistical Analysis

Infants were categorized into four groups based on their GA, completed weeks at birth ( $\leq 26$  weeks, 27–28 weeks, 29–30 weeks and  $\geq 31$  weeks) or by BW for statistical analysis.  $C_L$  and the rates of change in  $C_L$  were used as indices for structural pulmonary maturation. Linear regression analysis was performed to examine the data as a function of the infant's postnatal age. Likelihood ratios (LR) for prediction of BPD were calculated using a previously described predictive model based on  $C_L$ , RT and GA [13].

## Results

A total of 199 infants (BW 500–2,000 g) meeting the inclusion criteria were identified. Their mean  $\pm$  SD values were: for BW  $1,112 \pm 276$  g and for GA  $29 \pm 3$  weeks (range: 23–34 weeks). Clinical characteristics were: exposure to antenatal steroids 65.3%, patent ductus arteriosus 16.1%, use of postnatal steroids 15.1%, grades III and IV intraventricular hemorrhage 3%, BPD 24.1%, chronic lung disease 6% with a mean duration of ventilation  $9.0 \pm 1.7$  days and mean duration of supplemental oxygen  $19.0 \pm 4.5$  days.

Pulmonary mechanics and energetics data at age <3 days measured at a time of clinical and hemodynamic stability and over 48 h beyond surfactant replacement are listed in table 1. The postnatal changes in  $C_L$  are illus-



**Fig. 2.** Postnatal changes in dynamic pulmonary compliance in preterm infants with RDS treated with surfactant-replacement therapy as a function of both gestational age (GA) and postmenstrual age. \*  $p < 0.01$ ; \*\*  $p < 0.05$ .

**Table 1.** Pulmonary mechanics and energetics at age <3 days for infants with RDS who received surfactant replacement immediately after birth

Infants grouped by GA at birth	≤26 weeks (n = 38)	27–28 weeks (n = 50)	29–30 weeks (n = 48)	≥31 weeks (n = 63)
Tidal volume, ml/kg	6.1 ± 1.7	5.7 ± 1.5	5.1 ± 1.2	5.2 ± 0.8
Pulmonary compliance, ml/cm H <sub>2</sub> O/kg	0.27 ± 0.18	0.35 ± 0.22	0.40 ± 0.23	0.77 ± 0.75
Pulmonary resistance, cm H <sub>2</sub> O/l/s	194 ± 161	139 ± 117	101 ± 64	87 ± 76
Flow-resistive work, g·cm/kg	38 ± 29	28 ± 17	21 ± 14	15 ± 1.2

trated in figure 2 for study infants stratified by GA at birth. No significant improvements in  $C_L$  were noted prior to 28 weeks' PMA, irrespective of GA at birth. Significant linear regression relationships of  $C_L$  to PMA were determined beyond 28 weeks' PMA ( $r = 0.86$ ,  $p < 0.01$ ) with an improvement in compliance at a mean rate of 0.17 ml/cm H<sub>2</sub>O/kg/week (table 2).

At age 1 week, the pulmonary mechanics data predicted >90% probability of BPD (LR = 537) for infants with BW <750 g as compared to <10% probability (LR = 0.3) for infants with BW >1,500 g (table 3). The predicted probability of BPD was consistent with the actual occurrence of BPD among survivors. At term PMA, pulmonary mechanics and energetics, listed in table 4, showed the magnitude of pulmonary dysfunction as a function of GA

**Table 2.** Rate of increase\* in pulmonary compliance after 28 weeks' PMA for infants with RDS who received surfactant replacement immediately after birth

Infants grouped by GA at birth	≤ 26 weeks	27–28 weeks	29–30 weeks	≥ 31 weeks
Slope of linear regression analysis	0.17	0.19	0.19	0.21
Correlation of linear regression analysis	r = 0.97	r = 0.99	r = 0.95	r = 0.77
Change in compliance per week (after 28 weeks' PMA)	0.16 ml/cm H <sub>2</sub> O/week	0.19 ml/cm H <sub>2</sub> O/week	0.19 ml/cm H <sub>2</sub> O/week	0.24 ml/cm H <sub>2</sub> O/week

\* Linear regression analysis for pulmonary compliance and postnatal age (from birth to hospital discharge).

**Table 3.** Predicted probability of BPD based on pulmonary mechanics and gestational age based on a predictive model for the study infants with RDS categorized by birth weight

Birth weight, g	Gestational age, week	Pulmonary compliance ml/cm H <sub>2</sub> O/kg	Pulmonary resistance cm H <sub>2</sub> O/l/s	Likelihood ratio for BPD	Percent predicted probability
500–750	26 ± 0.4	0.3 ± 0.03	102 ± 16	537 ± 171	93 ± 3%
751–1,000	28 ± 0.3	0.5 ± 0.05	176 ± 24	76 ± 35	73 ± 5%
1,001–1,250	29 ± 0.3	1.0 ± 0.2	96 ± 11	5.5 ± 1.8	42 ± 7%
1,251–1,500	31 ± 0.3	1.5 ± 0.2	69 ± 8	0.8 ± 0.3	15 ± 5%
1,501–2,000	32 ± 0.3	1.8 ± 0.3	69 ± 11	0.3 ± 0.1	8 ± 3%

Predicted probability and likelihood ratio (LR) of BPD evaluated on the previously reported predictive model based on GA and pulmonary mechanics:  $LR = \exp \{33.6 - 1.13GA - 0.93C_L/kg - 0.001R_{\downarrow}\}$ .

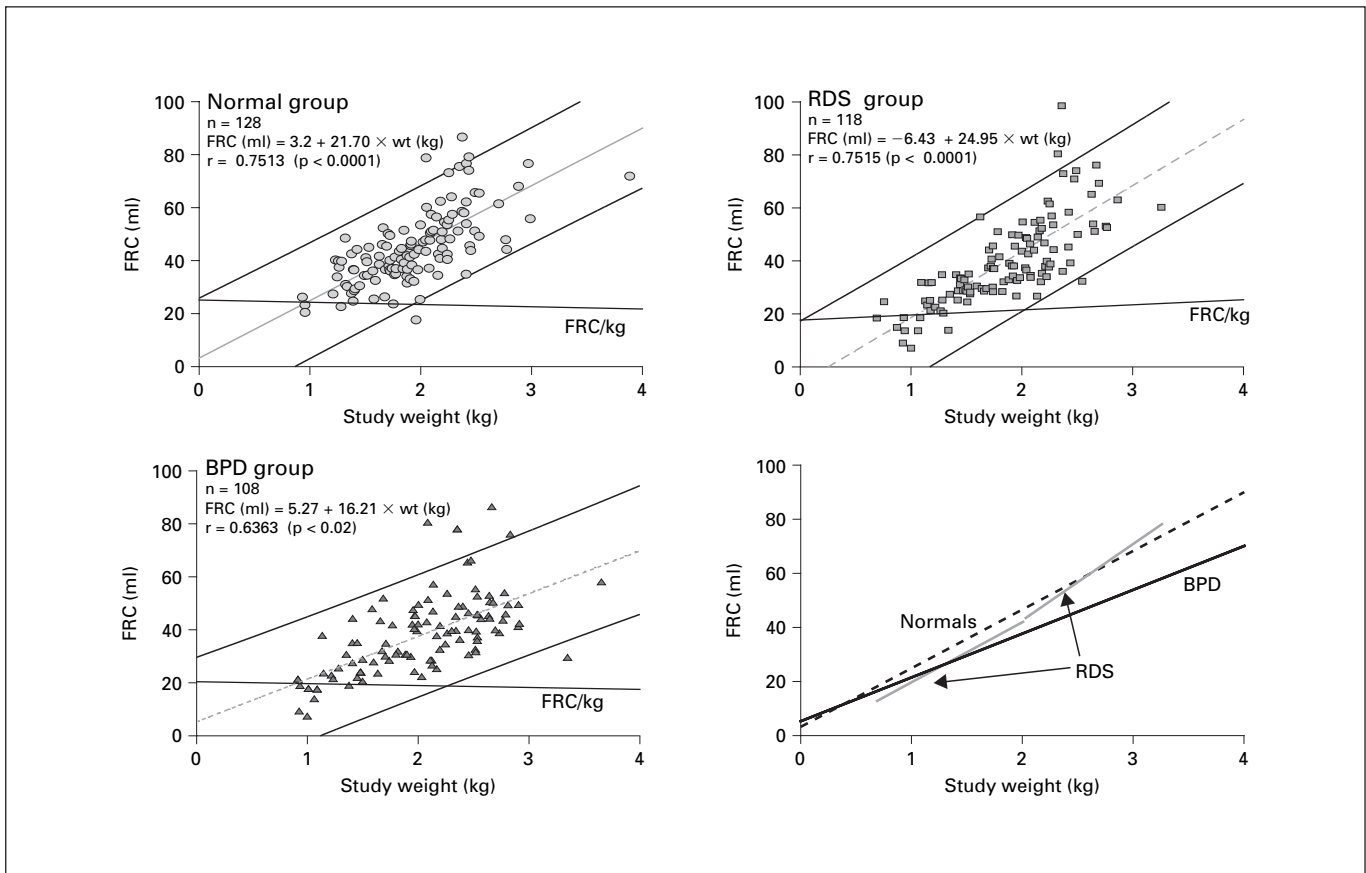
**Table 4.** Pulmonary mechanics and energetics at term PMA of surviving infants with RDS who received surfactant replacement immediately after birth

Surviving infants grouped by GA at birth	≤ 26 weeks (n = 25)	27–28 weeks (n = 35)	29–30 weeks (n = 38)	≥ 31 weeks (n = 59)
Term PMA (mean values), weeks	38.7	38.8	39.9	38.0
Tidal volume, ml	13.3 ± 4.1	14.3 ± 4.2	15.2 ± 4.4	14.4 ± 4.7
Pulmonary compliance, ml/cm H <sub>2</sub> O	2.6 ± 0.9	2.4 ± 0.8	2.6 ± 1.3	2.1 ± 0.6
Pulmonary resistance, cm H <sub>2</sub> O/l/s	61 ± 41	59 ± 31	57 ± 31	40 ± 20
Flow-resistive work, g · cm/kg	29 ± 19	29 ± 20	30 ± 19	25 ± 18

at birth; the mean ± SD  $C_L$  was  $2.60 \pm 0.07$  ml/cm H<sub>2</sub>O for all study infants.

Data for a total of 211 serial FRC measurements performed at random in the study infants are shown in figure 3 as a function of the clinical diagnosis of RDS and no BPD (n = 118) and RDS with BPD (n = 103). The rate of change in FRC values with increased bodyweight are compared to a total of 128 FRC measurements in a

matched group of preterm infants who had no clinical signs of RDS and did not require surfactant replacement. Average FRC in preterm infants with RDS who recovered was ~25 ml/kg as compared to ~20 ml/kg in those who developed BPD while values for preterm infants without BPD were ~25 ml/kg.



**Fig. 3.** Postnatal changes in functional residual capacity (FRC) in preterm infants with RDS treated with surfactant. FRC values for infants with RDS and no BPD are shown by lightly shaded bars, those with BPD are shown by clear bars. Comparative data for a matched group of infants with no RDS and indicated as normal are shown by darkly shaded bars (Student's t test comparison between groups at specific gestational age shows significance as illustrated with \*  $p < 0.01$ , \*\*  $p < 0.05$ ).

## Discussion

Neonatologists' care for infants with very low BW whose surfactant deficiency is successfully ameliorated with surfactant replacement but confounded by postnatal structural immaturity of airways, chest wall and lung parenchyma that continues to undergo extrauterine developmental maturation. Our observations of the pulmonary mechanics data describe a slow but incremental postnatal pulmonary improvement that is minimal prior to 28 weeks' PMA but is subsequently comparable for all infants irrespective of their GA. We observed a steady increase in  $C_L$  and a variable decrease in  $R_T$  while both  $V_T$  and minute ventilation were maintained. The lack of improvement in pulmonary mechanics prior to 28 weeks' PMA (fig. 2) was likely to have been confounded by unrecognized or inad-

vertent barotrauma that results from overventilation, airtrapping and ventilation at nonoptimal FRC.

Optimal FRC, defined by the surface area of the lung during expiration can be influenced by time determinants for inspiration or expiration. Of these, adequate exhalation is important but is significantly affected by flow-resistive and elastic properties of the lung. Resistive loads would slow the equilibration time while elastic loads hasten the equilibration time. The key to successful ventilation is the delivery of the minimum level of ventilatory support to allow breathing at the baby's FRC. The lung volume at which respiratory cycling occurs during spontaneous breathing, i.e., the FRC, is about 40% of total lung capacity. Thus, for healthy term infants a value of about 30–35 ml/kg represents the most linear component of the static pressure-volume (P-V) relationship of the

lung. Our data suggest that FRC values in preterm infants with RDS who recover were about 25 ml/kg and this was comparable to preterm infants without RDS. On the other hand, infants with RDS who develop BPD demonstrated lowered values of FRC (about 20 ml/kg). These data are influenced by the technological and physiological limitations of accurately measuring FRC in 'healthy' preterm neonates, for those who had RDS and those who develop BPD. This has been largely due to paucity of user-friendly and accurate technologies. One of the major limitations of the available technologies includes the inability for reasonable accuracy of  $\pm 1$  ml (which is about  $\pm 10\%$  of FRC values observed in babies with RDS). However, our observations do provide an insight into the slower increase in FRC values in infants with RDS who go on to develop BPD as compared to those who recover. Ventilating at low FRC requires higher inflating pressures as compared to ventilation at the most linear component of the respiratory P-V loop. The challenge in caring for a sick newborn is that the FRC of a baby alters unpredictably with varying respiratory elastic and resistive loads. These phenomena are evident in infants with evolving BPD who manifest varying combinations of both elastic and resistive lung diseases. Resistive loads caused by mechanical ventilation-induced barotrauma further augment the fluctuations in FRC [14]. Thus, indirect estimates of FRC (other than chest radiographs) rely on interpretation of pulmonary graphics (identification of tidal P-V overdistension, as shown in fig. 1) and measures of  $V_T$  with incremental changes of driving pressure [18]. From the perspective of postnatal maturation, FRC values of an infant are best described as a function of body length and body weight, an observation that underscores the need to focus on enhancement of optimal somatic growth.

Even though there is an immediate significant improvement in pulmonary mechanics from surfactant-replacement therapy for RDS, these mechanical changes are apparent only during spontaneous respiration and can be masked if measurements are made during mechanical ventilation [4, 10, 11, 27]. Bedside evidence of respiratory barotrauma can be due to driving pressure-induced overdistension, volume-induced overdistension (high FRC due to excessive airflow or inadvertent PEEP), measurements of large  $V_T$  ( $>8.5$  ml/kg) or actual evidence of high or low FRC. Pulmonary mechanics data at age  $<3$  days illustrate the magnitude and severity of pulmonary compromise, regardless of the timing of the surfactant replacement. These values may also mask the confounding effect of positive pressure ventilation and ventilation

at nonoptimal FRC. We have reported that the beneficial effects of surfactant on pulmonary mechanics were not apparent 2 h after dosing but were found 24 h after dosing, and only persisted for the first 7–14 days of life [23]. At age 1 week, application of a previously reported predictive model for BPD (developed for infants not treated with surfactant) based on pulmonary mechanics, BW and GA provides the LR and predicted probability for subsequent BPD diagnosis and categorizes the magnitude of acute lung injury [13]. Corroboration with the actual outcome of BPD in survivors of this study also helps to define the potential clinical usefulness of this predictive model in surfactant-treated infants. Regardless of the diagnosis of BPD, preterm neonates who have been mechanically ventilated often do not meet all of the usual clinical definitions but have residual pulmonary dysfunction during infancy. As an increasing number of very low birth weight infants survive in the surfactant era, some of the pulmonary dysfunction is due to barotrauma sustained by extremely compliant airways [23, 24].

The rates of postsurfactant improvement in pulmonary mechanics are comparable in infants  $<31$  weeks' GA, irrespective of GA at birth but after 28 weeks' PMA the incremental rate, though slower than that for infants  $>31$  weeks' GA, compares favorably such that the  $C_L$  increases at a mean rate of 0.17 ml/cm  $H_2O$ /week). These rates are likely to have been confounded by intercurrent pulmonary infections and other complications such as suboptimal nutrition, use of postnatal steroids and intractable apnea requiring ventilatory support. Limitations of this study include the concurrent issues listed above as well as the inability to measure FRC data in all study infants. Furthermore, these data represent clinical and ventilation practices prevalent in the 1990s and the use of the first clinically available exogenous synthetic surfactant in the USA. In addition, clinical practices represented the preponderant use of postnatal steroids over use of antenatal steroids. Though we were aware and had reported the original observations of  $V_T$  overdistension [10, 27], the role of excessive airflow, long inspiration time ( $>0.3$  s) and ventilation at nonoptimal FRC were not thoroughly appreciated and had not influenced ventilation strategies.

Does mechanical ventilation-induced lung injury (with overdistension and excessive mechanical stretching) release cytokines and other proinflammatory mediators? Previous animal studies have identified a role for activation of innate immunity in the pathogenesis of ventilator-associated lung injury. Jobe and Ikegami [28] hypothesized that proinflammatory cytokines could pro-

mote or interfere with lung development as well as promote lung injury and that such an injury could result in surfactant protein A or SP-A depletion, macrophage activation and migration of activated granulocytes into the lungs to release inflammatory cytokines, oxidants and proteases and possibly interfere with surfactant function [29, 30]. Studies in adult animal models have used large  $V_T$  ventilation to study the effect of alveolar overdistension on induction of inflammatory pathways [31]. Furthermore, moderate hyperoxia exacerbates lung injury in a large  $V_T$  model of ventilator-induced lung injury. The mechanism by which this occurs is not mediated by increased lipid peroxidation [32]. Ventilation strategy possibly modifies lung cytokine responses to lipopolysaccharide, likely through an effect on the alveolar macrophage population [33]. More recently, Wilson et al. [34] have shown that high  $V_T$  ventilation in the absence of underlying injury induces intrapulmonary tumor necrosis factor  $\alpha$  and macrophage-inflammatory protein-2 expression in mice [34]. The apparently transient nature of tumor necrosis factor  $\alpha$  upregulation may help to explain previous controversy regarding the involvement of cytokines in ventilator-induced lung injury. In newborn animal studies, the inflammatory response is most likely dependent on  $V_T$ , duration and supplemental oxygen [35]; however, it still remains controversial whether injurious ventilation per se, without preceding lung injury, can initiate

cytokine-mediated pulmonary inflammation. Future studies of postnatal changes in pulmonary mechanics with concurrent assessment of proinflammatory mediators may lead to a better understanding of mechanisms for acute lung injury, healing, maturation and resolution.

In conclusion, our data, despite their vintage of nearly a dozen years are relevant to current practice as we seek to optimize ventilation practices and strategies with an intent to minimize respiratory barotrauma prior to 28 weeks' PMA. In addition, the favorable and potential for postnatal incremental improvement beyond 28 weeks' PMA serves as a basis to focus on somatic growth with specific attention to body length in an effort to enhance an infant's FRC.

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### References

- 1 Avery ME, Mead J: Surface properties in relation to atelectasis and hyaline membrane disease. *Am J Dis Child* 1959;97:517–523.
- 2 Fujiwara T, Maeta H, Chida S, Morita T, Watabe Y, Abe T: Artificial surfactant therapy in hyaline membrane disease. *Lancet* 1980;1:55–59.
- 3 Davis JM, Veness-Meehan K, Notter RH, Bhutani VK, Kendig JW, Shapiro DL: Changes in pulmonary mechanics after the administration of surfactant to infants with respiratory distress syndrome. *N Engl J Med* 1988;319:476–479.
- 4 Fisher JB, Mammel MC, Coleman JM, Bing DR, Boros SJ: Identifying lung overdistention during mechanical ventilation by using volume-pressure loops. *Pediatr Pulmonol* 1988;5:10–14.
- 5 Goldsmith LS, Greenspan JS, Rubenstein SD, Wolfson MR, Shaffer TH: Immediate improvement in lung volume after exogenous surfactant: Alveolar recruitment versus increased distention. *Pediatrics* 1991;119:424–428.
- 6 Cotton RB, Olsson T, Law AB, Parker RA, Lindstrom DP, Silberberg AR, Sundell HW, Sandberg K: The physiologic effects of surfactant treatment on gas exchange in newborn premature infants with hyaline membrane disease. *Pediatr Res* 1993;34:495–501.
- 7 Polgar G, Lacourt G: A method for measuring respiratory mechanics in small newborn (pre-mature) infants. *J Appl Physiol* 1972;32:555–559.
- 8 Bancalari E: Pulmonary function testing and other diagnostic laboratory procedures in neonatal pulmonary care; in Thibeault DW, Gary GA (eds): *Neonatal Pulmonary Care*, ed 2. East Norwalk, Appleton-Century Crofts, 1986, pp 195–234.
- 9 McCann EM, Goldman SL, Brady JP: Pulmonary function in the sick newborn infant. *Pediatr Res* 1987;21:313–325.
- 10 Bhutani VK, et al: Pulmonary mechanics: Lung compliance and pulmonary resistance; in Bhutani VK, Shaffer TH, Vidyasagar D (eds): *Neonatal Pulmonary Function Testing: Physiological, Technical and Clinical Considerations*. Ithaca, Perinatology Press, 1988, pp 13–78.
- 11 Bhutani VK, Sivieri EM, Abassi S, Shaffer TH: Evaluation of neonatal pulmonary mechanics and energetics: A two factor least mean square analysis. *Pediatr Pulmonol* 1988;4:150–158.
- 12 Bhutani VK, Abassi S: Long-term pulmonary consequences in survivors with bronchopulmonary dysplasia. *Clin Perinatol* 1992;19:649–671.
- 13 Bhutani VK, Abbasi S: Relative likelihood of bronchopulmonary dysplasia based on pulmonary mechanics measured in preterm neonates during the first week of life. *Pediatrics* 1992;120:605–613.
- 14 Bhutani VK: Tracheobronchial abnormalities complicating bronchopulmonary dysplasia. *J Pediatr* 1988;112:843–844.
- 15 Tepper RS, Morgan WJ, Cota K, Taussig LM: Expiratory flow-limitation in infants with bronchopulmonary dysplasia. *J Pediatr* 1986;109:1040–1046.
- 16 Gerhardt T, Hehre D, Feller R, Reifenberg L, Bancalari E: Serial determination of pulmonary function in infants with chronic lung disease. *J Pediatr* 1987;110:448–456.

- 17 Clark RH, Gerstmann DR, Jobe AH, Moffitt ST, Slutsky AS, Yoder BA: Lung injury in neonates: Causes, strategies for prevention, and long-term consequences. *J Pediatr* 2001;139:478–486.
- 18 Bhutani VK: Clinical applications of pulmonary function and graphics. *Semin Neonatol* 2002;7:391–399.
- 19 Agostoni E, Hyatt RE: Static behavior of the respiratory system; in Geiger SR (ed): *Handbook of Physiology, Section 3: The Respiratory System*, Macklem PT, Mead J (volume eds), Volume III, Mechanics of Breathing, Part I, Fishman AP (section ed). Bethesda, American Physiological Society, 1986, pp 113–130.
- 20 Long W, Corbet A, Cotton R, Courtney S, McGuinness G, Walter D, Watts J, Smyth J, Bard H, Chernick V: A controlled trial of synthetic surfactant in infants weighing 1,250 g or more with respiratory distress syndrome. *N Engl J Med* 1991;325:1696–1703.
- 21 Reiterer F, Abassi S, Bhutani VK: Influence of head-neck posture on airflow and pulmonary mechanics in preterm neonates. *Pediatr Pulmonol* 1994;17:149–154.
- 22 Blondheim O, Abassi S, Fox WW, Bhutani VK: Effect of enteral gavage feeding rate on pulmonary functions of very low birth weight infants. *J Pediatr* 1993;122:751–755.
- 23 Bhutani VK, Abassi S, Long WA, Gerdes JS: Pulmonary mechanics and energetics in preterm infants who had respiratory distress syndrome treated with synthetic surfactant. *J Pediatr* 1992;120:S18–S24.
- 24 Greenspan JS, Abassi S, Bhutani VK: Sequential changes in pulmonary mechanics in the very low birth weight (less than or equal to 1,000 grams) infant. *J Pediatr* 1988;113:732–737.
- 25 Abassi S, Bhutani VK: Pulmonary mechanics and energetics of normal, non-ventilated low birthweight infants. *Pediatr Pulmonol* 1990;8:89–95.
- 26 Gerhardt T, Reifenberg L, Hehre D, Feller R, Bancalari E: Functional residual capacity in normal neonates and children up to 5 years of age determined by an N<sub>2</sub> washout method. *Pediatr Res* 1986;20:668–671.
- 27 Bhutani VK, Sivieri EM, Abassi S: Evaluation of pulmonary function in the neonate; in Polin RA, Fox WW (eds): *Fetal and Neonatal Physiology*, ed 1. Philadelphia, WB Saunders, 1994.
- 28 Jobe AH, Ikegami M: Prevention of bronchopulmonary dysplasia. *Curr Opin Pediatr* 2001;13:124–129.
- 29 Jobe AH, Ikegami M: Lung development and function in preterm infants in the surfactant treatment era. *Annu Rev Physiol* 2000;62:825–846.
- 30 Jobe AH, Ikegami M: Surfactant and acute lung injury. *Proc Assoc Am Physicians* 1998;110:489–495.
- 31 Dreyfuss D, Rouby JJ: Mechanical ventilation-induced lung release of cytokines: A key for the future or Pandora's box? *Anesthesiology* 2004;101:1–3.
- 32 Sinclair SE, Altemeier WA, Matute-Bello G, Chi EY: Augmented lung injury due to interaction between hyperoxia and mechanical ventilation. *Crit Care Med* 2004;32:2496–2501.
- 33 Whitehead TC, Zhang H, Mullen B, Slutsky AS: Effect of mechanical ventilation on cytokine response to intratracheal lipopolysaccharide. *Anesthesiology* 2004;101:52–58.
- 34 Wilson MR, Choudhury S, Goddard ME, O'Dea KP, Nicholson AG, Takata M: High tidal volume upregulates intrapulmonary cytokines in an in vivo mouse model of ventilator-induced lung injury. *J Appl Physiol* 2003;95:1385–1393.
- 35 Copland IB, Martinez F, Kavanagh BP, Engelberts D, McKerlie C, Belik J, Post M: High tidal volume ventilation causes different inflammatory responses in newborn versus adult lung. *Am J Respir Crit Care Med* 2004;169:739–748.