

## MINI-SYMPOSIUM: NEONATAL LUNG DISEASE

## PEEP – a “cheap” and effective lung protection

Shelley Monkman and Haresh Kirpalani\*

*Neonatal Intensive Care Unit, Department of Paediatrics, McMaster University Medical Centre, Hamilton, Ontario, Canada*

## KEYWORDS

PEEP, mechanical ventilation, lung

**Summary** Mechanical ventilation is a complex therapy with several different parameters which can be altered. In preterm and term infants, more attention has been paid to the levels of peak inspiratory pressure than to the positive end-expiratory pressure (PEEP). An awareness that lung protection can be conferred by an appropriate level of PEEP has increasingly stimulated a renewed interest in achieving the “best PEEP” strategy. We review the history of the introduction of PEEP therapy, some of the early demonstrations of its potential for mischief, the evidence on what levels of PEEP are appropriate in infants, some data concerning the lung-protective value of PEEP and finally some recent efforts at defining measures to determine the so-called “best PEEP”. Some of this work has been performed in adults with the acute respiratory distress syndrome. In newborns, we are regrettably forced to conclude that there is, for the immediate present, no easy substitute for sensible clinical observations coupled with a judicious and cautious adjustment of PEEP. We anticipate that a more logical application of PEEP with individualisation of therapy, based on a pressure–volume relationship, will in future enable targeted tests of PEEP as a lung-protection strategy.

© 2003 Elsevier Science Ltd. All rights reserved.

## INTRODUCTION

Much discussion has emphasised the concept that whereas mechanical ventilation achieves gas exchange, it may simultaneously damage the lung. From early in the modern history of mechanical ventilation of newborns, many workers attempted to dissect out which of the various components of the complex interactions in mechanical ventilation had the most beneficial impact on the baby’s respiratory gas status. Most attention focused on the potential for damage resulting from the peak inspiratory pressure but the importance of other parameters was accorded by the prominent place held by the mean airway pressure. This value arithmetically summed all the components of the ventilation into one number.<sup>1</sup> In retrospect, the simplifying but reductionist elegance that focused upon a single unitary number may have misled the field. We argue that comparatively little attention has been paid to determining the appropriate level of positive end-expiratory pressure (PEEP) to be applied,

more attention having been paid to its possible dangers than to its potential for benefit. The lack of clear evidence has, unsurprisingly, led to varying opinions. When we recently conducted a survey of neonatologists across Canada, we put a specific case scenario to tertiary care neonatologists and asked them whether they would increase the PEEP, decrease the PEEP or leave it the same. The answers fell almost exactly into a third for each camp.<sup>2</sup> This review tries to assess how PEEP should be viewed today. It takes an explicitly historical view, which allows the relative merits of prior work to be acknowledged while suggesting how this may have led to an undervaluation of the potential for PEEP.

## EARLY CONCEPTS OF THE APPLICATION OF POSITIVE END-EXPIRATORY PRESSURE

The concepts of continuous positive airways pressure (CPAP) and PEEP are similar, both originating in clinical observations that newborns with hyaline membrane disease “grunt”.<sup>3</sup> It was argued that, in trying to keep the lung

\*Correspondence to: Haresh Kirpalani. Tel.: +1-905-521-2100;  
E-mail: [kirpalan@mcmaster.ca](mailto:kirpalan@mcmaster.ca)

expanded, the infant kept the glottis shut for as long as possible, producing a very short expiration with a very rapid and forceful expulsion of gas resulting in the characteristic sound of a baby in trouble. This notion of an end-expiratory pressure led to the clinical treatment strategy of CPAP. Following these observations on the role of the glottis, it was noted that intubated infants would, of necessity, have their glottis bypassed, and the “bypass” phenomenon could be prevented by using CPAP.

The beneficial effects of CPAP were linked with observations that the chest wall of newborns was almost infinitely compliant, leading to the collapse and in-drawing characteristically seen in sick newborns.<sup>4</sup> This was quickly mimicked in ventilated infants by the use of PEEP. It was first achieved by adopting a strategy of using a high inspiration:expiration ratio (i.e. a longer inspiratory time than normal) such that when higher rates were used, the expiratory time was too short to enable complete expiration. This resulted in a higher end-expiratory pressure by a process of “air trapping”. An extension of this was quickly applied using a “reversed inspiration:expiration (I:E) ratio”, where the inspiratory time was even further increased above that of the expiratory time in order to maintain lung volumes. The same result was, however, more purposely achieved when Llewellyn started to use a positive expiratory pressure in newborn ventilation in 1970.<sup>5</sup> In applying CPAP, Gregory *et al.* had used a simple rule of thumb to determine the best pressure, i.e. increasing the pressure in 2 cmH<sub>2</sub>O increments until a PaO<sub>2</sub> of over 50 mmHg was achieved.<sup>4</sup> This process was one of attempted individualisation.

Others tried to refine the process. Bonta and co-workers used oesophageal pressure measurements to find the point at which there was a maximal transmission of CPAP applied pressure through the lung to the pleura.<sup>6</sup>

## EARLY INVESTIGATION INTO THE EFFECTS IN NEWBORNS OF POSITIVE END-EXPIRATORY PRESSURE

The systematic investigation of the effects of changing each ventilator parameter (respiratory rate, peak inspiratory pressure, I:E ratio, and PEEP) began with manipulation of the I:E ratio by inspiratory gas flow changes.<sup>7</sup> This focus on the I:E ratio was retained in much of the early work,<sup>8,9</sup> largely for technical reasons as it was easily adjusted on the ventilators. In 1973, however, Herman and Reynolds showed that an increase in the I:E ratio, coupled with an increase in PEEP, reduced barotraumas,<sup>10</sup> and Boros showed in 1977 that PEEP increased the PaO<sub>2</sub>/FiO<sub>2</sub> ratio.<sup>11</sup> It was these experiments that led Boros to urge the numeric amalgamation of these individual parameters – peak inspiratory pressure, respiratory rate, I:E and PEEP – into the “mean airway pressure”.<sup>1,11</sup>

Some attempts to unravel the mean airway pressure into its constituent parts continued, however, and perhaps the most systematic demonstration of the effects of PEEP on oxygenation was provided by Stewart *et al.*<sup>12</sup> These researchers established that the major impact on oxygenation in newborns with respiratory failure was the level of PEEP. They showed that whereas PEEP (raising or lowering it 4 cmH<sub>2</sub>O) increased oxygenation, it also increased the mean carbon dioxide by 7 mmHg. In the whole group of infants, there was no relationship between PEEP and raised intra-cranial pressure (ICP), although changes in mean airway pressure associated with peak inspiratory pressure alterations were related to ICP elevations.

## CAUTIONS RAISED ABOUT POSITIVE END-EXPIRATORY PRESSURE THERAPY

Early concerns were raised about the potential side-effects of PEEP, especially with regard to cardiac function.<sup>9</sup> A problem was then highlighted that increased the overall concerns; this was unrecognised, or “inadvertent”, PEEP. Simbruner showed that this could be detected by clamping the expiratory limb of the ventilator at end-expiration.<sup>13</sup> If this was followed by an increase in expiratory time, the level of “inadvertent PEEP” fell and the measured compliance (a measure of unit lung volume per unit pressure used to obtain that volume) would rise. This led to a heightened awareness of the deleterious effects of PEEP.<sup>14</sup> More evidence of the potential for mischief during routine applications of PEEP continued to accumulate, as demonstrated by a fall in minute ventilation and carbon dioxide accumulation,<sup>15</sup> an increase in effective left ventricular afterload,<sup>16</sup> an increase in carbon dioxide and a consequent increased cerebral blood flow velocity.<sup>17</sup>

Although many authors cautioning about the side-effects of PEEP were aware of the important caveats demonstrated by Holzman and Scarpelli,<sup>18</sup> the net cumulative message was that PEEP was harmful and that its level should be kept low. Holzman and Scarpelli had, however, shown in animal experiments that although cardiac output fell in compliant (i.e. healthy) lungs, this fall was much less explained in unhealthy lungs. The mechanism they invoked was that the sickest lungs did not transmit the intrathoracic pressure to the pleural space and therefore did not much affect the venous return; as preload was preserved, cardiac output was not affected. The clinical implication was that we should be most concerned about the effects of PEEP on cardiac output in the most healthy lungs rather than in the sickest lungs; in fact in the very patients we were most anxious to wean off the ventilator!

Other clues to a larger role for PEEP lay in the debate on respiratory frequency vs. I:E ratio, in which the potential role of PEEP appeared to be ignored. Although the interaction between inadvertent PEEP and I:E ratio had been long understood, the results of the key trial – OCTAVE<sup>19</sup> – were

interpreted only in terms of the beneficial effect being related to low I:E ratios and fast ventilator rates. In retrospect, at least some of the benefit observed in the OCTAVE trial in the lower barovolutrauma group might have been related to an unappreciated value of PEEP, “inadvertent PEEP” perhaps.

## DOES THE LEVEL OF POSITIVE END-EXPIRATORY PRESSURE AFFECT LUNG INJURY?

This question is not trivial as alveolar epithelial disruption and capillary leak leads to an infiltration of acute inflammatory cells in newborns even following the first breath.<sup>20</sup> It is now generally agreed that zero end-expiratory pressure (ZEEP), or near-ZEEP, is deleterious.<sup>21,22</sup> The beneficial effects of PEEP upon various airway and histological markers of inflammation were found in an isolated, non-perfused rat lung model in which low end-expiratory lung volume and ZEEP significantly augmented lung injury.<sup>23</sup> If, however, PEEP was set at greater than the opening pressure, or the “lower inflection point”, histopathological lung injury was reduced.<sup>23</sup> This *in vitro* work has been paralleled in adults with acute respiratory distress syndrome: if they were ventilated with a PEEP greater than the lower inflection point, the bronchoalveolar concentrations of inflammatory mediators were significantly reduced at 36 h compared with controls.<sup>24</sup>

Whether these anti-inflammatory effects of an appropriate PEEP are mediated by the surfactant system is unclear but PEEP has long been known to preserve surfactant function, one school of thought having advocated to “keep the lung open” partly because of this.<sup>25–27</sup> Animals sustain lung injury within 3 h of high-volume ventilation and ZEEP, whereas PEEP prevents a compression-induced inactivation of the surfactant.<sup>27</sup> When lambs are ventilated using a tidal volume of 10 ml/kg and PEEP, higher levels of PEEP (7 cmH<sub>2</sub>O rather than 3 cmH<sub>2</sub>O) ensure that surfactant is still maintained in its active form.<sup>28</sup> Although this data is convincing, does information in the human newborn allow us to derive a safe or a standard level of PEEP to use?

## SHOULD – AND CAN – THERE BE A STANDARD SETTING FOR POSITIVE END-EXPIRATORY PRESSURE?

Simbruner<sup>13</sup> showed that actual measurements could be made on infants being ventilated to determine the true PEEP a baby was receiving. Simbruner’s recommendation was in fact that a so-called “patient-tailored” ventilation incorporating measures of the inadvertent PEEP would enable the clinician to achieve “optimal PEEP”. This was a term used by Suter and co-workers where the level of PEEP was such as to give optimal compliance and ventilation at the lowest mean airway pressures.<sup>29</sup> This did not,

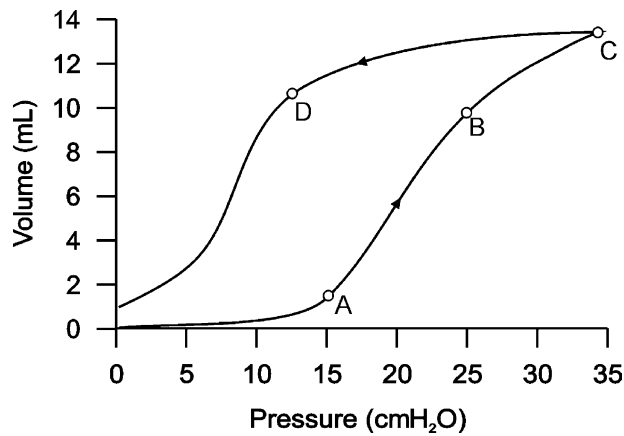
however, become standard clinical practice. The approach was usually to adopt a “normative range” – the difficulty being to know what that was. It was clear that functional residual capacity in infants increased in a stepwise fashion as PEEP values were increased<sup>30,31</sup> but what levels were appropriate? In 1992, Greenough *et al.* assessed which level of PEEP achieved the best oxygenation – just as Gregory had for CPAP – in 16 infants at a median gestational age of 29 weeks.<sup>32</sup> It appeared that in acute hyaline membrane disease and the chronic stages of bronchopulmonary dysplasia, PEEP of 3–6 cmH<sub>2</sub>O promoted better oxygenation than PEEP of 0–3 cmH<sub>2</sub>O. It became obvious that results from the pre-surfactant era would need to be modified following the introduction of surfactant therapy since the ensuing rapid recruitment of previously closed lung segments led to an increase in functional residual capacity.<sup>33</sup>

Accordingly, when Dimitriou repeated earlier studies on PEEP levels, the results suggested that, within 18 h of giving surfactant, an appropriate level of PEEP was 3 cmH<sub>2</sub>O, as judged by the higher carbon dioxide level at 6 cmH<sub>2</sub>O.<sup>34</sup> Caution was expressed, however, since the sample of eight infants was small and there was a trend to higher oxygenation with higher PEEP values that did not achieve statistical significance. In attempts to derive easy rules from such results, the varying time of study from surfactant administration is also a limiting factor. In Dimitriou’s study, this ranged from 12 to 68 h after the use of surfactant. We are now far more aware of the rapidity with which acute lung injury can occur and ensuing changes in the pressure–volume relationships of the lung over such a period of time make simple clinical rules difficult to apply. If simple standard guidelines allowing a clinician to set a PEEP level cannot be stated unequivocally, what other approaches can be adopted? Can we individualise PEEP levels, in the same way that authors have tried to individualise CPAP levels.<sup>6</sup>

## EARLY ATTEMPTS TO INDIVIDUALISE POSITIVE END-EXPIRATORY PRESSURE FOR NEWBORNS

Although clinicians have tried to individualise ventilator settings to particular infants, it was of necessity left vague.<sup>35</sup> Several attempts have been made to utilise the physiological principles that underlie the pressure–volume curve (or alternatively the flow–volume curve).

Mathe *et al.* used the characteristics of the inflationary limb of the pressure–volume curve (Fig. 1) to determine what they called the “appropriate PEEP”, or APEEP.<sup>36</sup> They instilled gas at a flow rate of 10 ml/kg over 20–30 seconds while monitoring airway pressures, trying to find the point at which the lower portion of the volume–pressure loop abruptly became straight. Mathe *et al.* argued that this was the point of “APEEP”. If APEEP was set within the first 24 h, it



**Figure 1** Idealised pressure–volume curve of a single breath to demonstrate the principles underlying the location of the points referred to in the text. The up-going arrow represents the inflationary limb and the down-going arrow the deflationary limb. A, the lower inflection point or appropriate positive end-expiratory pressure, as described by Mathe *et al.*<sup>36</sup> or the P flex mentioned by Gattinoni *et al.*<sup>45</sup> B, the end of the linear portion of the curve that represents the most desirable portion of the curve avoiding underdistension and collapse and overdistension and the potential for barovolutrauma. This corresponds to the so-called upper inflection point, described by Mergoni *et al.*<sup>46</sup> and used by Rimensberger *et al.*<sup>38</sup> C, the point of ‘maximum’ inflation, at which inflation ends and deflation begins. D, the so-called closing pressure, as used by Rimensberger *et al.*<sup>38</sup> Rimensberger *et al.* found that the pressure at point D was less than that at B.

appeared that infants had a shorter duration of exposure to oxygen. The drawback was that these infants were curarised and there was a potential risk of developing a pneumothorax, although none of the 40 babies studied did so. Sinha *et al.* describe a variant of this approach, using one of the commercially available pulmonary graphics packages.<sup>37</sup>

A recent summary describing the lung’s elastic properties has, however, rightly concluded that it is too early to apply in a routine manner to the ventilated infant.<sup>31</sup> The potential for this approach has nevertheless been illustrated by Schibler *et al.*, who described how an improvement in the use of PEEP can be followed by visual displays of an increasing dynamic compliance and decreasing dynamic resistance.<sup>31</sup>

## FINDING THE RIGHT POINT

If it was easy to set the PEEP, ventilation strategies could be optimised to the individual subject. Apart from Mathe *et al.*’s pioneering study,<sup>36</sup> most work has been done in animals or adult humans. The point that was labelled by Mathe *et al.* as the point of APEEP<sup>36</sup> is now more frequently known as the lower inflection point or opening pressure. Both the location of this point and its corollary at the top end of the pressure–volume curve on the deflation hysteresis limb – found following a ‘sigh manoeuvre’ (often known as the upper inflection point or closing pressure; see below) – are

now the focus of attention. Rimensberger *et al.* found that the closing pressure was lower than the upper inflection point on the inspiratory limb,<sup>38</sup> but finding the closing pressure has so far been described only in animals.

Evidence from the adult literature indicates the potential benefits of ‘individualisation’ since, as in newborns, there is a great variability in the clinical spectrum of respiratory failure with acute respiratory distress syndrome.<sup>39</sup> Such variability may explain the differing results in when workers have utilised these concepts. Pepe *et al.* could not demonstrate any benefit from a simple raised PEEP strategy<sup>40</sup> but two randomised trials showed benefits of PEEP set above the lower inflection point on a static pressure–volume curve, in terms of improved lung function,<sup>41</sup> mortality at 28 days, increased weaning rate and decreased barotrauma.<sup>42</sup>

There is, however, a lack of agreement on which point on the pressure–volume curve to use to keep the lung open,<sup>25</sup> or even on the terminology. Some authors describe the lower inflection point on the inflation limb and set the PEEP just above this,<sup>43,44</sup> the same point is called ‘P flex’ by others.<sup>45</sup> Others use the upper inflection point, or deflection point on the inflation limb.<sup>46</sup> Others describe a ‘closing pressure’ point on the deflation limb of the pressure–volume curve, found by a superimposed sigh, as the optimal point for lung recruitment, arguing that this strategy avoids the potential for overinflation.<sup>38</sup>

Further difficulty lies in disagreement over whether the various points can be found in all subjects. Although some report that neither the upper nor the lower inflection point is a consistently observed phenomenon,<sup>47,48</sup> we have recently been able to observe a lower inflection point in all newborn piglets studied,<sup>49</sup> and Mathe *et al.*<sup>36</sup> did not report any infants whose APEEP point could not be found. The safety and reproducibility of finding these points needs, however, further detailed confirmation in newborns. In addition, the exact method for how these points can in practice be safely determined at the cot-side and which point is the ‘best’ point to use for tailoring ventilation, needs to be determined. This is by far the most difficult one to address and has not yet yielded any agreement. In adult populations, a technique employing the ‘super-syringe’ has been extensively used.<sup>50</sup> This allows detection of the lower inflection point after building the inspiratory limb of the pressure–volume curve by injecting a known volume of gas at a fixed rate and recording the equilibrium pressures thereby obtained. This is similar to Mathe *et al.*’s technique.<sup>36</sup> It is, however, tricky to perform, especially in sick patients.

## CONCLUSION: WHAT DOES THIS MEAN IN CLINICAL PRACTICE?

No convincing benefits have yet been demonstrated by randomised data in infants, leaving it impossible to make firm recommendations. Some general and uncontroversial principles can, however, be suggested (see Practice points).

These can be subsumed into the old adage of the clinician to “look at your patient” – perhaps to be modified as “look at your patient and her/his monitors”.

### PRACTICE POINTS

- ZEEP is deleterious even in diseases such as meconium aspiration with apparent areas of overinflation. This is often accompanied by areas of collapse or underdistension, for which the presence of even a small degree of PEEP could be useful. In hyaline membrane disease, the nature of the lack of homogeneity is even more obvious making ZEEP a contraindication.
- When changing ventilator settings ensure that each step is accompanied by an adequate time interval to enable the effects of the changes to be detectable at steady state. Attention should be paid to oxygen saturation, and the evidence of adequate peripheral perfusion and central blood pressure. A blood gas level should be obtained to verify the observed non-invasive trends of oxygen saturation and/or transcutaneous carbon dioxide monitoring.
- A chest X-ray may be helpful. There may be areas of regional collapse or underdistension that might benefit from a higher level of PEEP.

Note whether the heart is “squeezed” or compressed, suggesting a need to volume-prime to increase the preload or to make a slight reduction in the degree of PEEP applied. The future is likely to reveal some more logical means by which to titrate levels of PEEP.

### REFERENCES

1. Boros SJ. Variations in inspiratory:expiratory ratio and airway pressures wave form during mechanical ventilation: the significance of mean airway pressure. *J Pediatr* 1979; **94**: 114–117.
2. Abubhakar K, Zurbrigg H, Kirpalani H, Schmidt B. Management of neonatal pulmonary interstitial emphysema: results of a Canadian survey. *Pediatr Res* 1996; **39**: 322A.
3. Reynolds EOR, Robertson NRC, Wigglesworth JS. HMD, RDS, and surfactant deficiency. *Pediatrics* 1968; **42**: 758–768.
4. Gregory GA, Kitterman JA, Phibbs RH, Tooley WH, Hamilton WK. Treatment of the idiopathic respiratory distress syndrome with continuous positive airways pressure. *New Engl J Med* 1971; **284**: 1333–1340.
5. Llwellyn MA, Swyer PR. Positive expiratory pressure during mechanical ventilation in the newborn. *Program of the Society for Pediatric Research, Atlantic City, 1970*; 224.
6. Bonta BW, Uauy R, Warshaw JB, Motoyama EK. Determination of optimal CPAP for the treatment of IRDS by measurement of esophageal pressure. *J Pediatr* 1977; **91**: 449–454.
7. Owen-Thomas JB, Ulan OA, Swyer PR. The effect of varying inspiratory gas flow rate on arterial oxygenation during IPPV in the RDS. *Br J Anesth* 1968; **40**: 493–502.
8. Smith PC, Daily WJR, Fletcher G, Meyer HPP, Taylor G. Mechanical ventilation of newborn infants. I. The effect of rate and pressure on arterial oxygenation of infants with RDS. *Pediatr Res* 1969; **3**: 244–254.
9. Reynolds EOR. Effect of alterations in mechanical ventilator settings on pulmonary gas exchange in hyaline membrane disease. *Arch Dis Child* 1971; **46**: 152–159.
10. Herman S, Reynolds EOR. Methods for improving oxygenation in infants mechanically ventilated for severe hyaline membrane disease. *Arch Dis Child* 1973; **43**: 612.
11. Boros SJ, Matalon SV, Ewald R, Leonard AS, Hunt CE. The effect of independent variations in inspiratory–expiratory ratio and end expiratory pressure during mechanical ventilation in hyaline membrane disease: the significance of mean airway pressure. *J Pediatr* 1977; **91**: 794–798.
12. Stewart AR, Finer NN, Peters KL. Effects of alterations of inspiratory and expiratory pressures and inspiratory/expiratory ratios on mean airway pressure, blood gases, and intracranial pressure. *Pediatrics* 1981; **67**: 474–481.
13. Simbruner G. Inadvertent possible end-expiratory pressure in mechanically ventilated newborn infants: detection and effect on lung mechanics and gas exchange. *J Pediatr* 1986; **108**: 589–595.
14. Bancalari E. Inadvertent positive end-expiratory pressure during mechanical ventilation. *J Pediatr* 1986; **108**: 567–569.
15. Field D, Milner AD, Hopkin IE. Effect of positive end expiratory pressure during ventilation of the preterm infant. *Arch Dis Child* 1985; **60**: 843–847.
16. Hausdorf G, Hellwege HH. Influence of positive end-expiratory pressure on cardiac performance in premature infants: a doppler-echocardiographic study. *Crit Care Med* 1987; **15**: 661–664.
17. Shortland DB, Field D, Archer LNJ *et al*. Cerebral haemodynamic effects of changes in positive end expiratory pressure in preterm infants. *Arch Dis Child* 1989; **64**: 465–469.
18. Holzman BH, Scarpelli EM. Cardiopulmonary consequences of positive end-expiratory pressure. *Pediatr Res* 1979; **13**: 1112–1113.
19. OCTAVE Study Group. Multicentre randomized controlled trial of high against low frequency positive pressure ventilation. *Arch Dis Child* 1991; **66**: 770–775.
20. Nilsson R, Grossmann G, Robertson B. Lung surfactant and the pathogenesis of neonatal bronchiolar lesions induced by artificial ventilation. *Pediatr Res* 1978; **12**: 249–255.
21. Froese AB, McMulloch PR, Sugiura M, Vaclavik S, Possmayer F, Moller F. Optimizing alveolar expansion prolongs the effectiveness of exogenous surfactant therapy in the adult rabbit. *Am Rev Respir Dis* 1993; **148**: 569–577.
22. Corbridge TC, Wood LDH, Crawford GP, Chudoba MJ, Yanos J, Sznajder JL. Adverse effects of large tidal volume and low PEEP in canine acid aspiration. *Am Rev Respir Dis* 1990; **142**: 311–315.
23. Muscedere JG, Mullen JBM, Gan K, Slutsky AS. Tidal ventilation at low airway pressures can augment lung injury. *Am J Respir Crit Care Med* 1994; **149**: 1327–1334.
24. Raniieri VM, Suter P, Tortorella C *et al*. Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. *J Am Med Assoc* 1999; **282**: 54–61.
25. Lachmann B. Open up the lung and keep it open. *Intens Care Med* 1992; **18**: 319–321.
26. Rider ED, Jobe AH, Ikegami M, Sun B. Different ventilation strategies alter surfactant responses in preterm rabbits. *J Appl Physiol* 1992; **73**: 2089–2096.
27. Wyszogrodski I, Kyei-Aboagye K, Taeusch HW Jr, Avery ME. Surfactant inactivation by hyperventilation: conservation by end-expiratory pressure. *J Appl Physiol* 1975; **38**: 461–466.
28. Michna J, Jobe AH, Ikegami M. Positive end-expiratory pressure preserves surfactant function in preterm lambs. *Am J Respir Crit Care Med* 1999; **160**: 634–639.

29. Suter PM, Fairley HB, Isenberg MD. Optimum end-expiratory pressure in patients with acute pulmonary failure. *New Engl J Med* 1975; **292**: 284.
30. Thome U, Topfer AS, Scahler P, Pohlandt F. The effect of positive end-expiratory pressure, peak inspiratory pressure and inspiratory time on functional residual capacity in mechanically ventilated preterm infants. *Eur J Pediatr* 1998; **157**: 831–837.
31. Schibler A, Frey U. Role of lung function testing in the management of mechanically ventilated infants. *Arch Dis Child Fetal Neonatal Ed* 2002; **87**: F7–F10.
32. Greenough A, Chan V, Hird MF. Positive end expiratory pressure in acute and chronic respiratory distress. *Arch Dis Child* 1992; **67**: 320–323.
33. Goldsmith LS, Greenspan JS, Rubenstein SD, Wolfson MR, Shaffer TH. Immediate improvement in lung volume after exogenous surfactant: alveolar recruitment versus increased distension. *J Pediatr* 1991; **119**: 424–428.
34. Dimitrou G, Greenough A, Laubscher B. Appropriate positive end expiratory pressure level in surfactant-treated preterm infants. *Eur J Pediatr* 1999; **158**: 888–891.
35. Field D, Milner AD, Hopkin IE. Inspiratory-to-expiratory ratio during ventilation for idiopathic respiratory distress syndrome. *Pediatr Pulmonol* 1989; **7**: 2–7.
36. Mathe JC, Clement A, Chevalier JY, Gaultier C, Costil J. Use of total inspiratory pressure–volume curves for determination of appropriate positive end-expiratory pressure in newborns with hyaline membrane disease. *Intens Care Med* 1987; **13**: 332–336.
37. Sinha SK, Nicks JJ, Donn SM. Graphic analysis of pulmonary mechanics in neonates receiving assisted ventilation. *Arch Dis Child* 1996; **75**: F213–F218.
38. Rimensberger PC, Cox PN, Fendova H et al. The open lung during small tidal volume ventilation: concepts of recruitment and “optimal” positive end-expiratory pressure. *Crit Care Med* 1999; **27**: 1946–1952.
39. Gattinoni L, Pelosi P, Suter PM et al. Acute respiratory distress syndrome caused by pulmonary and extra-pulmonary disease: different syndromes? *Am J Respir Crit Care Med* 1998; **158**: 3–11.
40. Pepe PE, Hudson LD, Carrico CJ. Early application of positive end-expiratory pressure in patients at risk for the adult respiratory-distress syndrome. *New Engl J Med* 1984; **311**: 281–286.
41. Amato MBP, Barbas CSV, Medeiros DM et al. Beneficial effects of the “open lung approach” with low distending pressures in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1995; **152**: 1835–1846.
42. Amato MBP, Barbas CSV, Medeiros DM et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *New Engl J Med* 1998; **338**: 347–354.
43. Roupie E, Dambrosio M, Servillo G et al. Titration of tidal volume and induced hypercapnia in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1995; **152**: 121–128.
44. Marini JJ. Inverse ratio ventilation – simply an alternative, or something more? *Crit Care Med* 1995; **23**: 224–228.
45. Gattinoni L, Presenti A, Avalli L, Rossi F, Bombino M. Pressure–volume curve of total respiratory system in acute respiratory failure. *Am Rev Respir Dis* 1987; **136**: 730–736.
46. Mergoni M, Martelli A, Volpi A et al. Impact of positive end-expiratory pressure on chest wall and lung pressure–volume curve in acute respiratory failure. *Am J Respir Crit Care Med* 1997; **156**: 846–854.
47. Lichtwarck-Aschoff M, Mols G, Hedlund AJ et al. Compliance is nonlinear over tidal volume irrespective of positive end expiratory pressure level in surfactant depleted piglets. *Am J Respir Crit Care Med* 2000; **162**: 2125–2133.
48. Scott-Harris R, Hess DR, Veengas JG. An objective analysis of the pressure–volume curve in the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2000; **161**: 432–439.
49. Monkman S, Andersen C, Nahmias C, Ghaffer H, Schmidt B, Kirpalani H. Setting PEEP above the lower inflection point reduces neutrophil influx during experimental acute lung injury. *Pediatr Res* 2001; **49**: 275A.
50. Lee WL, Stewart TE, MacDonald R et al. Safety of pressure–volume measurement in acute lung injury and ARDS using a syringe technique. *Chest* 2002; **121**: 1595–1601.