

Respiratory support and outcomes in preterm infants

Ulrich H. Thome

Division of Neonatology and Paediatric Critical Care, University Children's Hospital, Ulm, Germany

Bronchopulmonary dysplasia is common

BPD has been defined as chronic pulmonary dysfunction, occurring primarily in preterm infants. Formerly characterised by epithelial metaplasia and fibrosis, the appearance of BPD has changed. Currently, the main features are arrested lung development, with reduced alveolar formation, gas-exchange area and microvascular development.^[1] The most widely accepted definition is that infants of ≥ 36 weeks PMA, and who continue to require oxygen or ventilatory support, have BPD.

Conventional ventilation — avoid volutrauma

Clearly, MV can aggravate pulmonary injury in preterm infants, and volutrauma is more important than barotrauma as a potential exacerbating factor.^[2]

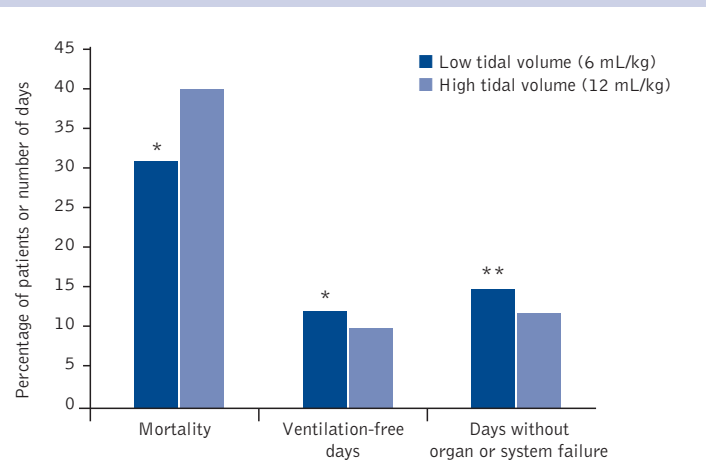
Volutrauma-induced lung injury can result from overdistension, when tidal volume or functional residual capacity are too high, as demonstrated in animal studies. For instance, in immature, 'bagged' lambs given six large breaths (35–40 mL/kg) at birth, the effects of subsequent rescue surfactant therapy were reduced relative to control animals: 4 hours after delivery, inspiratory capacity and maximal deflation compliance were almost 3-fold less in bagged than control lambs ($p < 0.01$).^[3] In adults with ARDS, a low tidal volume (6 instead of 12 mL/kg of predicted bodyweight) was associated with a significantly lower mortality rate (31.0% vs 39.8%, $p = 0.007$) [Figure 1].^[4]

Furthermore, lung injury can result from shear forces exerted in atelectasis, and animal studies suggest that such injury may manifest when PEEP levels are too low. However, in adults with ARDS, no significant difference in clinical outcome was noted between two different PEEP levels (8.3 vs 13.2 cm H₂O) during MV.^[5] Randomised studies of the optimal PEEP level in preterm infants have not been published, although empirically, an appropriate level may be 3–6 mbar.

Use low tidal volumes

Thus, when MV is used in preterm infants, low tidal volumes should be used to reduce lung injury; an increased respiratory rate is then required to maintain respiratory minute ventilation (roughly the product of tidal volume and respiratory rate).

Figure 1. Significantly improved primary and secondary clinical outcomes with a low rather than high tidal-volume strategy in adults with ARDS.^[4] Primary outcomes were mortality rate before hospital discharge in patients with unassisted breathing, and mean number of ventilator-free days (days 1–28); a secondary outcome was mean number of days (days 1–28) without nonpulmonary organ or system failure. * $p = 0.007$; ** $p = 0.006$.



Increase respiratory rate

Pooled data from studies in preterm infants show that a high versus low respiratory rate (60 vs ≤ 40 breaths/min) was associated with a significantly lower incidence of pneumothorax (14–18% vs 33–35%; $p \leq 0.013$)^[6,7] and PIE.^[8] Numbers needed to treat (NNTs) were low: 11 infants would need treatment with HFPPV versus CMV to prevent one case of pneumothorax; whereas five infants would need treatment with HFPPV to prevent one case of PIE. In addition, a nonsignificant trend towards reduced mortality was evident with high- versus low-rate ventilation, although there was no decrease in the incidence of BPD.

These studies were conducted before the introduction of surfactant; therefore, the relevance of results to current clinical practice is uncertain.

Synchronised ventilation does not definitively improve outcomes

Potential advantages of SV in preterm infants comprise improved patient comfort and gas exchange, whereas a potential disadvantage is increased volutrauma. Synchronised ventilators require triggering, and main stream flow sensors used for this purpose in most ventilators generally introduce an additional dead space of 1 mL; in a 500 g neonate being ventilated with a tidal volume of 6 mL/kg, i.e. 3 mL, this dead space represents approximately one-third of the infant's tidal volume. To compensate for dead space, increased tidal volumes are needed to maintain alveolar ventilation; therefore, the use of flow sensors may lead to increased volutrauma and lung injury and may thus be regarded as contraindicated in ELBW infants (<1000 g). Additional volutrauma may originate from a more frequent occurrence of Head's reflex (a paradoxical increase in inspiratory effort), which is associated with synchronised ventilation.^[9]

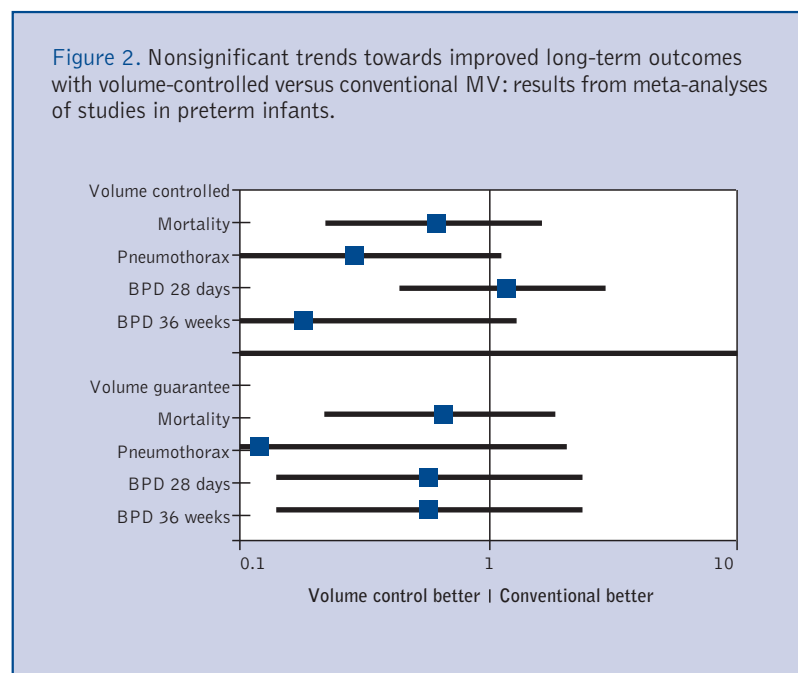
Meta-analyses of studies in infants undergoing SIMV or PTV versus CMV^[10–14] showed weak, nonsignificant trends towards reduced relative risks of BPD, at both 28 days postnatal age and 36 weeks PMA. However, a slight trend towards increased mortality negates any possible benefit with SV versus CMV. The risk of air leaks was not different between the two ventilation strategies.^[10–14] Overall, therefore, SV does not appear to improve long-term outcomes in preterm infants.

Volume-controlled ventilation not clearly superior

In VCV, either inspiratory or expiratory tidal volume is controlled by the ventilator. The ventilator automatically adjusts peak pressure to ensure that the correct tidal volume is delivered, and the device immediately responds to changes in pulmonary mechanics.

However, such systems require a flow sensor, and the increased dead space may lead to greater volutrauma in ELBW infants (<1000 g), similar to synchronised ventilation.

Only very small studies are available. Meta-analyses of data from studies of VCV in preterm infants generally revealed nonsignificant trends towards better long-term outcomes than with CMV: that is, reduced relative risks of BPD, pneumothorax and mortality (Figure 2).



However, it cannot be definitively documented that VCV is superior to its conventional counterpart, because results in the control groups receiving CMV may have been better if flow sensors had been omitted.

No major clinical benefit with high-frequency ventilation

HFV (5–20 Hz) involves very small tidal volumes, with incomplete inspiration and expiration, and dampening of oscillations in the airways, thus leading to very small intra-alveolar pressure amplitudes.

Meta-analyses of data from 17 randomised studies indicate a nonsignificant trend towards a reduced relative risk of BPD with HFV versus CMV, but a significant increase in the relative risk of air leaks ($p < 0.05$). For every 28 infants treated with HFV versus CMV, one additional major air leak occurs (number needed to harm [NNH] = 28).^[15]

In studies using high pressure-volume strategies or the SM3100[®] ventilator (SensorMedics, Yorba Linda, CA), HFV was significantly superior to the CMV strategies used in these trials regarding a lower incidence of BPD at 36 weeks PMA. The NNT to prevent one such case of BPD in HFV-treated patients was 16–26.^[15] However, CMV strategies used in the latter studies were not optimal.

Limiting meta-analyses to include only studies in which low pressure-volume strategies in CMV (i.e. reduced tidal volume, or high respiratory rate) were used, negated the above-mentioned advantage for HFV over CMV.^[15]

Overall, therefore, there appears to be no major clinical benefit for HFV over an optimised CMV in preterm infants.

Whether HFV may be beneficial in preterm infants with the most severe respiratory failure remains an open question.

Permissive hypercapnia does not improve long-term outcomes

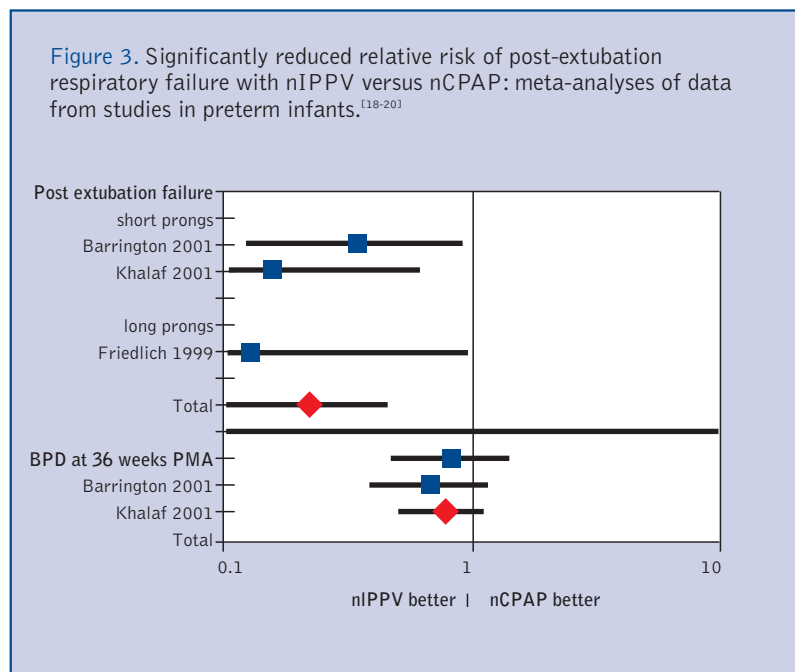
Pooled data from three randomised trials^[15–17] do not demonstrate a clear advantage of permissive hypercapnia over normocapnia in preterm infants regarding relative risks of BPD at 36 weeks PMA, mortality, and severe (grade 3–4) intraventricular haemorrhage. However, differences between the carbon dioxide levels of the treatment groups were small.

Therefore, moderately high PaCO₂ goals may be safe, but have not yet been shown to improve long-term outcomes.

Noninvasive ventilation is beneficial

In preterm infants with RDS, noninvasive ventilation has been associated with reduced relative risks of respiratory failure and mortality, but an increased risk of pneumothorax, in comparison with no mechanical ventilatory support. Indeed, a meta-analysis of nCPAP versus CNP identified NNTs of 4.0 for respiratory failure and 4.5 for mortality, and an NNH of 8 for pneumothorax. In another analysis, nCPAP immediately after extubation, compared with a headbox, also demonstrated a lower relative risk of respiratory failure (NNT=6).

Furthermore, pooled data^[18–20] show that nIPPV was associated with a significantly lower incidence of post-extubation respiratory failure than nCPAP (Figure 3).



A nonsignificant trend towards a reduced risk of BPD at 36 weeks PMA was also noted for nIPPV versus nCPAP, although the number of infants included in the latter analysis was small (≈ 30).^[18-20]

Conclusion: use ventilation cautiously

Ventilation should be used in preterm infants only when absolutely necessary. Optimisation of the selected ventilation strategy is more important than selection of any one strategy over another. Thus, tidal volumes as low as possible, and high respiratory rates (>60 breaths/min), should be used; an optimal value for PEEP appears to be 3–6 mbar. SV or VCV may be beneficial in special circumstances, although the use of flow sensors is contraindicated in ELBW neonates. HFV is unnecessary for most preterm infants, but may be beneficial in those with the most severe respiratory failure. Permissive hypercapnia with a moderately high PaCO₂ goal may also be helpful, but benefits and safety of higher PaCO₂ goals remain uncertain. Noninvasive ventilation appears to be beneficial because it reduces the need for invasive ventilation, although risks of air leaks are still higher than with the application of supplemental oxygen alone.

References

1. Jobe AJ. *Pediatr Res* 1999;46:641–3.
2. Dreyfuss D and Saumon G. *Am J Respir Crit Care Med* 1998;157:294–323.
3. Bjorklund LJ et al. *Pediatr Res* 1997;42:348–55.
4. Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000;342:1301–8.
5. Brower RG et al. *N Engl J Med* 2004;351:327–36.
6. Heicher DA et al. *J Pediatr* 1981;98:957–61.
7. OCTAVE Study Group. *Arch Dis Child* 1991;66(7 Spec No):770–5.
8. Pohlandt F et al. *Eur J Pediatr* 1992;151:904–9.
9. Hummler H et al. *Pediatr Pulmonol* 1997;24:195–203.
10. Beresford MW et al. *Arch Dis Child Fetal Neonatal Ed* 2000;82:F14–8.
11. Bernstein G et al. *J Pediatr* 1996;128:453–63.
12. Donn SM et al. *J Perinatol* 1994;14:90–4.
13. Baumer JH. *Arch Dis Child Fetal Neonatal Ed* 2000;82:F5–10.
14. Chan V and Greenhough A. *Eur J Pediatr* 1993;152:51–4.
15. Thome U et al. *Arch Dis Child Fetal Neonatal Ed* 2005;90:F466–73.
16. Mariani G et al. *Pediatrics* 1999;104:1082–8.
17. Carlo WA et al. *J Pediatr* 2002;141:370–4.
18. Barrington KJ et al. *Pediatrics* 2001;107(4):638–41.
19. Friedlich P et al. *J Perinatol* 1999;19:413–8.
20. Khalaf MN et al. *Pediatrics* 2001;108:13–7.