

ORIGINAL ARTICLE

Lung protective ventilatory strategies in very low birth weight infants

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Respiratory distress syndrome (RDS) is the most common respiratory diagnosis in preterm infants. Surfactant therapy and mechanical ventilation using conventional or high-frequency ventilation have been the standard of care in the management of RDS. Bronchopulmonary dysplasia (BPD) continues to remain as a major morbidity in very low birth weight infants despite these treatments. There is no significant difference in pulmonary outcome when an optimal lung volume strategy is used with conventional or high-frequency ventilation. Lung injury is directly related to the duration of invasive ventilation via the endotracheal tube. Studies using noninvasive ventilation, such as nasal continuous positive airway pressure and noninvasive positive pressure ventilation, have shown to decrease postextubation failures as well as a trend toward reduced risk of BPD. Lung protective ventilatory strategy may involve noninvasive ventilation as a primary therapy or following surfactant administration in very preterm infants with RDS. Initial steps in the management of preterm infants may also include sustained inflation to establish functional residual capacity, followed by noninvasive ventilation to minimize lung injury and subsequent development of BPD.

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Introduction

Bronchopulmonary dysplasia (BPD) continues to be a major morbidity among preterm infants treated for respiratory distress syndrome (RDS). Application of positive pressure ventilation via the endotracheal tube (ET) and the duration of mechanical ventilation have a direct effect on the incidence of BPD. However, the incidence of BPD varies among different centers.

One reason for this variation is the lack of a standard definition for BPD. To standardize BPD incidence, Walsh *et al.*¹ proposed the term 'physiological BPD', based on a timed room-air challenge at 36 ± 1 weeks postmenstrual age in preterm infants. Preterm infants on mechanical ventilation or requiring $>30\%$ oxygen to maintain oxygen saturation between 90 and 96% were considered to have 'physiological BPD'. Infants receiving $\leq 30\%$ oxygen or effective oxygen $>30\%$ with saturations $>96\%$ were given room-air challenge for 30 min. Infants in whom saturations decreased to $<90\%$ were considered to have 'physiological BPD'. However, differences in BPD incidence remain, even with the use of this standardized definition of BPD.

BPD is a multifactorial disease. Mechanical ventilation via the ET is a major contributing factor for BPD. Significant improvements have been made in the use of ventilatory strategies in very low birth weight (VLBW) infants. Both tidal ventilation using conventional mechanical ventilators and nontidal ventilation using high-frequency ventilators have been extensively studied. High-frequency ventilators deliver smaller tidal volumes at supraphysiological rates. Nontidal ventilation using high-frequency oscillatory ventilation (HFOV), high-frequency flow interruption (HIFI) and high-frequency jet ventilation (HFJV) have all been studied in the management of RDS before and after surfactant therapy became available and in comparison with intermittent mandatory ventilation (IMV) as well as synchronized IMV (SIMV).² Among the six trials^{3–8} published during the presurfactant era, Clark *et al.*⁶ reported a decrease in BPD with HFOV when compared to IMV (Table 1). However, the incidence of severe intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL) was significantly higher in one of the HIFI trials published in 1989.³ Three trials^{9–11} were conducted after surfactants became available for treatment of RDS (Table 1). Two of these studies^{9,10} reported lower BPD incidence among infants randomized to high-frequency ventilation (HFV) when compared to IMV, while Wiswell *et al.*¹¹ had to stop their study because of increase in IVH or PVL among infants randomized to HFJV. Among the eight HFV trials^{12–19} published between 1998 and 2003, when

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Table 1 High-frequency ventilation vs conventional ventilation studies from 1989 to 2003 in preterm infants and bronchopulmonary dysplasia^a

<i>Presurfactant era trials (n = 6)</i>	<i>Number</i>	<i>Study population</i>	<i>Results</i>
HIFI ³ (1989)	673	750–200 g	HFOV: no change in BPD; increase in IVH/PVL
Carlo ⁴ (1990)	42	1000–2000 g	HFJV: no change in BPD
Keszler ⁵ (1991)	144	>750 g with PIE	HFJV: improved survival
Clark ⁶ (1992)	83	<1750 g	HFOV: decrease in BPD
HiFO ⁷ (1993)	176	>500 g	No change in BPD
Ogawa ⁸ (1993)	92	750–2000 g	HFOV: no change in BPD
<i>Surfactant era trials (n = 3)</i>			
Gerstmann ⁹ (1996)	125	<35 weeks	HFOV: decrease in BPD and surfactant use
Keszler ¹⁰ (1997)	130	700–1500 g; <35 weeks	HFJV: decrease in BPD
Wiswell ¹¹ (1996)	73	>500 g; <33 weeks	HFJV: no change in BPD; increase in severe IVH/PVL; trial stopped early
<i>Surfactant and SIMV era trials (n = 8)</i>			
Rettwitz-Volk ¹² (1998)	96	<32 weeks	HFOV: no change in BPD
Plavka ¹³ (1999)	43	500–1500 g	HFOV: decrease in BPD
Thome ¹⁴ (1999)	284	24–30 weeks	HIFI: no change in BPD; increase in air leaks
Moriette ¹⁵ (2001)	273	24–29 weeks	HFOV: no change in BPD
Courtney ¹⁶ (2002)	498	601–1200 g	HFOV: decrease in BPD
Johnson ¹⁷ (2002)	797	23–28 weeks	HFOV: no change in BPD
Craft ¹⁸ (2003)	46	<1000 g	HIFI: no change in BPD; increase in air leaks
Van Reempts ¹⁹ (2003)	300	<32 weeks	HFOV/HIFI: no change in BPD

Abbreviations: BPD, bronchopulmonary dysplasia; HFJV, high-frequency jet ventilation; HFOV, high-frequency oscillatory ventilation; HIFI, high-frequency flow interruption; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; SIMV, synchronized intermittent mandatory ventilation.

^aAdapted from Keszler.²

surfactant therapy and SIMV were commonly used, only two studies reported a decrease in BPD¹³ with HFOV use, and two studies^{14,18} reported an increase in air leaks with HIFI use. Finally, three trials compared elective use of HFV in RDS. One study¹⁶ reported a decrease in BPD, and a second study¹⁵ reported a nonsignificant increase in IVH among infants treated with HFOV. A third trial showed no difference in pulmonary or central nervous system outcomes. Differences in outcomes between HFV and IMV trials are primarily related to whether a lung protective ventilatory strategy was employed or not in both of these modes of ventilation. In studies where optimal lung volume strategy was used, there were no differences in pulmonary or nonpulmonary outcomes between HFV and IMV modes²⁰ (Figures 1 and 2).

Tidal ventilation using different patient triggered ventilation (PTV) modes is commonly used in RDS management. A number of modalities, such as SIMV, assist control, volume limit or volume guarantee and pressure support, are being used in VLBW infants. Randomized, controlled trials using different modes of PTV have been associated with short-term benefits, such as a decrease in the duration of mechanical ventilation or days on oxygen.^{21,22} PTV use was also associated with a decreased need for sedation in VLBW infants. None of these studies demonstrated a significant benefit in terms of reducing lung injury. However,

PTV is more 'physiological', and, therefore, should be used whenever feasible.

Noninvasive ventilation strategies

Since duration of mechanical ventilation via the ET has a direct correlation with BPD, clinicians are increasingly using noninvasive ventilation with nasal continuous positive airway pressure (NCPAP) or noninvasive positive pressure ventilation (NIPPV) to protect the preterm infant's lungs.²³ Noninvasive ventilation appears to be beneficial in the management of apnea of prematurity, for the prevention of extubation failures, and in the initial management of RDS.^{24–26} NCPAP has been used as a primary mode for RDS treatment, to prevent extubation failures, or extubation following surfactant administration. NCPAP can be delivered using conventional mechanical ventilators, bubble continuous positive airway pressure (CPAP), or infant flow driver systems. Bubble CPAP is accomplished by submerging the expiratory limb of respiratory circuit within a fluid column. The amount of pressure maintained within the system is determined by the depth of submersion and is generally independent of flow rate. Infant flow driver uses a fluidic flip system that has been shown to assist spontaneous breathing and reduce work of breathing by reducing expiratory resistance and

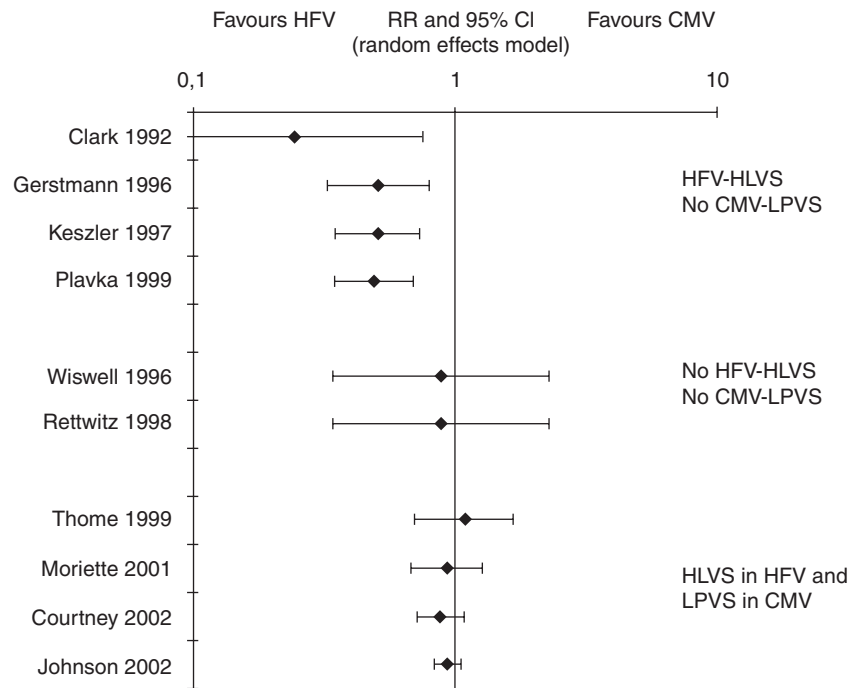


Figure 1 High-frequency ventilation vs conventional mechanical ventilation with and without lung protective ventilatory strategies and bronchopulmonary dysplasia.
*Reproduced with permission from Bollen *et al.*¹³

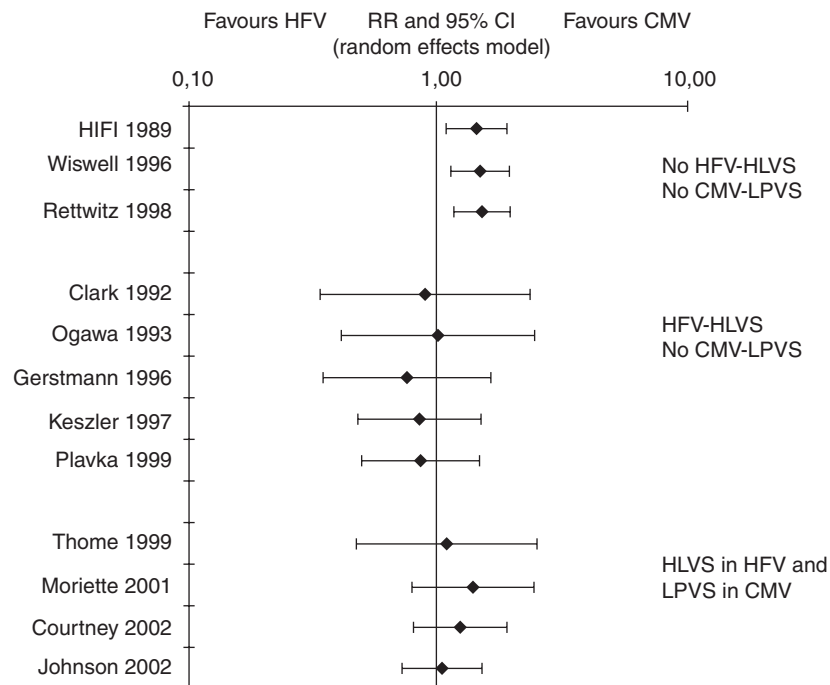


Figure 2 High-frequency ventilation vs conventional mechanical ventilation with and without lung protective ventilatory strategies and intraventricular hemorrhage.
*Reproduced with permission from Bollen *et al.*¹³

maintaining a stable airway pressure throughout the respiratory cycle.²⁷ NCPAP patient interfaces commonly used include single or binasal prongs as well as nasopharyngeal prongs. In some centers, nasal mask or high-flow (>2 liters per minute, l.p.m.) nasal

cannulae are used to deliver CPAP. Binasal prongs are more effective than single prongs in preventing extubation failures. Extubation failures were significantly lower even among extremely low birth weight infants (ELBW, <1000 g) when binasal prongs

were used (24 vs 88%).²⁸ It has been a routine practice in many centers to intubate ELBW infants at birth. Lindner *et al.*²⁹ in a retrospective, cohort study showed that adopting a policy of selective intubation in ELBW infants resulted in a significantly reduced need for intubation, lower incidence of BPD, IVH and reduced length of stay. Success rate with NCPAP use from the delivery room to avoid subsequent endotracheal intubation is still low in the United States. In a multicenter, randomized study, 80% of ELBW infants required intubation by 7 days of age.³⁰ Observational studies using bubble NCPAP have shown a decrease in BPD. In a prospective observational study, Meyer *et al.*³¹ demonstrated that use of bubble CPAP in ELBW infants was associated with significantly improved survival without BPD. Sahni *et al.*³² reported a very low incidence of BPD (7.4%) in infants <1250 g, who are at the highest risk for BPD, managed with bubble NCPAP. Bubble CPAP may also provide an inexpensive form of noninvasive HFV. Lee *et al.*³³ reported 2 to 4 cm H₂O amplitude at a frequency of 15 to 30 Hz when bubble CPAP was used. The frequencies recorded in their study are close to the resonant frequency of the lungs, where gas movement in and out of the lungs is independent of lung compliance. This may account for improved ventilation despite smaller tidal volumes in infants on bubble CPAP compared to conventional NCPAP. However, Morley *et al.*³⁴ showed that bubbling rates during bubble CPAP had no effect on ventilation or oxygenation. In preterm lambs, lung volumes were higher with bubble CPAP as compared to conventional CPAP.³⁵ Furthermore, bubble CPAP use in preterm lambs was associated with a significant decrease in neutrophil recruitment into the lungs, and the cells in alveolar wash had less H₂O₂.³⁵ Bubble CPAP system produces noisy pressure waveforms superimposed on pressure fluctuations, resulting in stochastic resonance. This results in improved lung recruitment in a poorly compliant lung and may also augment the efficiency of gas exchange.³⁶

A limited number of studies compared NCPAP delivered using conventional mechanical ventilators and infant flow drivers. Stefanescu *et al.*³⁷ found no difference in clinical outcomes when applying CPAP with the infant flow driver vs a conventional nasal CPAP device. Mechanical ventilation via the ET tube even for less than 48 h is associated with a longer length of stay.³⁸ Success with CPAP depended on the experience of the staff and gestational age of infants, especially infants <29 weeks.³⁸ Sandri *et al.*³⁹ in a multicenter trial demonstrated no difference in BPD in infants between 28 and 31 weeks gestational age treated with prophylactic or rescue NCPAP. A major limitation of NCPAP is the need for intubation due to frequent apnea, bradycardia or desaturations in preterm infants. Approximately, 30 to 40% of infants extubated from mechanical ventilation to NCPAP fail extubation, requiring reintubation. At present, there are no good tests to predict successful extubation in preterm infants. Kamlin *et al.*⁴⁰ used spontaneous breathing test (SBT) to predict successful extubation in preterm infants with a birth weight <1250 g. A failed SBT was

recorded if the infant had either bradycardia lasting for longer than 15 s and/or a drop in saturation below 85% despite a 15% increase in FiO₂ when infants were on CPAP via ET (ET CPAP) prior to a planned extubation. No pressure support for spontaneous breaths was given during ET CPAP in this study. Sensitivity and specificity for SBT in predicting successful extubation were 97 and 73%, respectively. Further studies are needed to evaluate if SBT may be used as a predictor of infant's readiness prior to extubation.

Nasal cannulae have been used to deliver oxygen at flow rates of 0.5 l.p.m. to as high as 6 l.p.m., usually with no intention of delivering CPAP. However, a significant amount of CPAP is generated, and is not measured continuously at the bedside. For example, use of flow rates of 2 l.p.m. via a nasal cannula with an outer diameter of 3 mm results in a mean CPAP of 9.8 cm H₂O.⁴¹ Complications reported with the use of high-flow nasal cannula included increased incidence of air leaks, gas trapping and volutrauma. One must exercise caution when delivering flow rates greater than 2 l.p.m. via nasal cannula without knowing the amount of pressure delivered. Technique to measure pressure delivered at the level of nasal interface is urgently needed, since, nasal cannula to deliver CPAP intentionally, or not, has become very common in the United States. Use of portable devices, such as Neopuff Infant Resuscitator (Fisher & Paykel Healthcare Corporation Limited, Irvine, CA, USA) to deliver consistent positive end-expiratory pressure in the delivery room and during transport from the delivery room, is gaining popularity.⁴²

Noninvasive positive pressure ventilation

NIPPV is an alternative option when infants are extubated from mechanical ventilation or for infants failing NCPAP. NIPPV is a form of noninvasive ventilation that combines NCPAP with IPPV breaths. NIPPV may augment NCPAP, prevent postextubation failures, minimize SIMV duration and potentially decrease BPD. NIPPV has been shown to decrease postextubation failures significantly compared to NCPAP. Two randomized studies using synchronized NIPPV at the time of extubation showed significant reduction in extubation failures with NIPPV as compared to NCPAP.^{25,43} In a retrospective study, Kulkarni *et al.*⁴⁴ demonstrated a significant reduction in BPD after introduction of NIPPV in their unit following a 2-week education of their staff. Studies comparing NIPPV vs SIMV have shown promising results. Kugelman *et al.*⁴⁵ compared NCPAP with NIPPV as a primary mode of respiratory support in preterm infants <35 weeks gestational age with RDS. NIPPV was more successful than NCPAP in decreasing the need for endotracheal intubation, and in the incidence of BPD. These authors did not report any adverse effects of NIPPV. This was the first study on using NIPPV as a primary mode for RDS treatment. However, study infants were larger and more mature. Only 40 of the 84 infants studied were VLBW (<1500 g). Studies whether rapid extubation to NIPPV would be an optimal approach as compared to

continued SIMV are currently underway in preterm infants treated with surfactant for RDS.

Sustained inflation followed by CPAP

Lung over distention—even with one or two large inflations during resuscitation of ELBW infants immediately after birth—initiates lung injury, eventually leading to BPD. Recently, te Pas *et al.*⁴⁶ reported results from a randomized, controlled trial of sustained inflation in the delivery room respiratory management of VLBW infants. These authors compared sustained inflation for 10 s at 20 cm H₂O applied via a nasopharyngeal tube followed by NCPAP vs manual inflations with a self-inflating bag and mask followed by NCPAP in 207 preterm infants. They showed that need for intubation, days on mechanical ventilation, days on NCPAP, air leaks and moderate to severe BPD were significantly lower when a sustained inflation was used to recruit the lung instead of bag and mask ventilation. More studies are needed to develop optimal lung protective ventilatory strategies in preterm infants.

Conclusions

Bronchopulmonary dysplasia remains as a major morbidity among very preterm infants. BPD is associated with short- and long-term adverse pulmonary and nonpulmonary outcomes. Significant advances have been made in the care of VLBW infants. High-frequency and conventional ventilatory techniques have been extensively evaluated in the management of RDS in preterm infants. When an optimal lung volume strategy is employed, there does not appear to be any significant difference between these two modalities. Noninvasive ventilation using NCPAP or NIPPV has been shown to significantly decrease BPD incidence. However, there are no guidelines for the use of noninvasive ventilation in preterm infants. More studies are needed before noninvasive ventilation becomes a routine lung protective strategy. Short binasal prongs are more effective than single nasal prongs to deliver NCPAP. Addition of backup rate via NIPPV decreases postextubation failure rates and may improve pulmonary outcomes. NIPPV is a useful method of augmenting the beneficial effects of NCPAP in preterm infants with respiratory distress. In summary, the use of noninvasive ventilation as a primary mode or following surfactant administration is associated with improved outcomes in preterm infants with respiratory distress.

Disclosure

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