Review paper

Neonatal ventilation techniques – which is best for prematurely born infants?

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Abstract

This review focuses particularly on recent evidence to determine which respiratory support techniques may be most advantageous to prematurely born infants. Meta-analyses of the results of randomised trials have demonstrated that, of invasive ventilation modes, only prophylactic high frequency oscillation is associated with a significant, but modest reduction in bronchopulmonary dysplasia, but both patient-triggered ventilation and volume-targeted ventilation (VTV) are associated with shorter durations of ventilation. Small numbers of infants, however, were included in the VTV trials and the level of volume targeting may be crucial to its success. Published randomised trials have failed to confirm the advantages of CPAP seen in non-randomised studies. Results of nasal non-invasive ventilation are encouraging, particularly with regard to reducing extubation failure, but larger trials are required to determine whether there are important side-effects.

Key words: patient-triggered ventilation, volume-targeted ventilation, high frequency oscillation, continuous positive airway pressure.

Introduction

Bronchopulmonary dysplasia (BPD) is a common adverse outcome of premature birth [1, 2]. Despite improvements in perinatal care, including the use of antenatal steroids and exogenous surfactant, the incidence of BPD has remained constant over the last ten years and may affect up to 50% of babies born with birth weights of 500 to 750 g [3]. Affected infants suffer chronic respiratory morbidity including prolonged home oxygen dependency [4] and frequent readmissions to hospital during the first two years after birth [5]. Recurrent respiratory symptoms remain common even at school age and in early adult life [6, 7]. The aetiology of BPD is multifactorial and includes baro/volutrauma. This has been an impetus to develop new ventilation techniques with the aim of reducing BPD. Several approaches have been used:

(i) synchronisation of the infant's respiratory efforts to ventilator inflations, patient-triggered ventilation modes,
(ii) minimisation of excessive volumes, volume-targeted ventilation (VTV) and high frequency oscillation (HFO), and
(iii) non-invasive modes with the avoidance of intubation, continuous positive airways pressure (CPAP) and nasal ventilatory modes.

This review focuses particularly on recent evidence to determine which techniques may be most advantageous to prematurely born infants.

Patient-triggered ventilation modes

Assist control ventilation and synchronised intermittent mandatory ventilation

Meta-analysis of the results of randomised trials of assist control ventilation (ACV) or synchronised intermittent mandatory ventilation (SIMV) compared to conventional ventilation demonstrated no significant difference in the incidence of BPD, but that use of ACV/SIMV was associated with a significantly shorter duration of ventilation [weighted mean difference 34.8 hours, 95% confidence interval (CI –62.1, –7.4)], but only if started in the recovery phase of the illness [8]. Comparison of SIMV (inflations triggered only by a predetermined number of breaths) to ACV (triggering by every breath that exceeds the critical trigger level) during weaning has been made in three randomised trials [9, 10]. This demonstrated that ACV was associated with faster weaning; the median duration of weaning was 24 vs. 50 hours when the SIMV rate was reduced below 20 inflations per minute [10]. Weaning is prolonged when the number of spontaneous breaths supported by ventilator inflations is reduced, as this effectively increases the work of breathing necessary to overcome the resistance of the endotracheal tube [11].

Pressure support ventilation

During pressure support ventilation (PSV), as with SIMV and ACV, the initiation of mechanical inflation is determined by the beginning of the infant's inspiratory effort but, in addition, termination of inflation is also determined by the infant's inspiratory effort. Exactly when inflation is terminated can be fixed as with the Draeger Babylog ventilator at 15% of peak inspiratory flow or as with the BIRD-VIP and SLE 5000 ventilators it can be manually adjusted (termination sensitivity). Increasing termination sensitivity has been shown to decrease the level of asynchrony, but this was associated with a shorter inflation time [12], which could adversely impinge on gas exchange. Reduction in asynchrony should theoretically decrease the incidence of pneumothorax, but this has not been adequately tested. PSV can be used alone (with or without volume targeting) or as an adjunct to SIMV. SIMV with PSV has been compared to SIMV alone in a randomised trial of 107 extremely low birth weight infants. A smaller proportion of infants were still ventilated at 28 days (69 vs. 47%, P=0.04) with SIMV and PS than by SIMV alone. Additionally, among infants with a birth weight of 700 to 1000 g those supported by SIMV with PSV required fewer days of supplementary oxygen (58 vs. 41 days, P=0.034) [13]. Those results further emphasise that it is disadvantageous to support only a proportion of a very prematurely born infant's breaths. In the trial [13] the peak pressures during PSV were lower (limited to half of the SIMV pressures) than those used during ACV. Further randomised studies are, therefore, required to examine the efficacy of PSV, in particular trials of PSV with SIMV vs. ACV and PSV vs. ACV.

Proportional assist ventilation

During proportional assist ventilation (PAV), the timing and frequency of ventilator inflations are controlled by the patient. The applied pressure is servo-controlled throughout each spontaneous breath, increasing in proportion to the flow and/or volume generated by the infant; this can be enhanced to reduce the work of breathing due to both compliance (elastic unloading) and resistance (resistive unloading) abnormalities [14]. It is important, however, to determine the most appropriate levels of elastic and resistive unloading in the various neonatal respiratory disorders. In an vitro study, using a lung model with compliance and resistance values similar to those of an infant with RDS, a resistance unloading equal to or greater than the resistance of the respiratory system resulted in oscillations in the delivered pressures. In addition, elastic unloading greater than the elastance of the model was associated with peak pressures in excess of 30 cm^3 H_2O and, although this could be avoided by applying a pressure limit of 20 cm^3 H_2O, it resulted in an abnormal airway pressure waveform with very short inflation times [15]. There have been very few clinical studies assessing PAV in prematurely born neonates, and those that have been performed have had short-term outcomes. In a crossover study involving infants with acute respiratory distress [16], gas exchange during PAV was maintained at lower mean and peak airway pressures than on ACV or SIMV. Similarly, in a crossover study involving infants with evolving BPD, gas exchange during PAV was maintained at lower mean airway pressures than on ACV (5.6 vs. 6.6 cm^3 H_2O, P<0.001). The infants on PAV, however, experienced significantly longer desaturations, emphasising the need for effective backup ventilation during this mode [17]. A new backup support with pulse oximetry guided operation has been developed which has resulted in a reduction in the incidence and duration of desaturations [18]. Available data, however, do not support routine use of this ventilation mode.

Minimisation of excessive volumes

Volume-targeted ventilation

During volume-targeted ventilation (VTV), a constant volume is delivered to the infant. There are different VTV modes, including volume control ventilation and volume guarantee. Ventilator manufacturers have used different methods of delivering VTV. As a consequence, for the same level of volume targeting different ventilator types deliver different inflation times, airway pressure waveforms and mean airway pressures [19]. Meta-analysis of the results of four randomised trials [20] demonstrated that VTV was associated with a significant reduction in the duration of ventilation and severe intraventricular haemorrhage and pneumothorax rates, but no difference in BPD or death. The numbers of infants included in each of the trials, however, were small (178 in total), and different ventilators were used which, as described above [19], may have influenced the results. Subsequent studies have shown only short-term advantages. In one trial [21], predetermined blood gas criteria related to ventilator settings were reached sooner on VCV compared to time cycled pressure limited ventilation, but the difference only reached statistical significance in the infants of birth weight less than 1000 g. In another study [22], arterial carbon dioxide tensions were more commonly within the desirable range in infants on SIMV with VG than SIMV alone, but only in infants of more than 25 weeks of gestational age. Target volumes of between 4 and 6 ml/kg have been used in the clinical studies; the limited evidence available suggests that tidal volumes at the higher range may be most beneficial. An increased level of pro-inflammatory cytokines and ventilation duration occurred in infants of gestational age between 25 and 32 weeks who were ventilated with a VG level of 3 ml/kg rather than 5 ml/kg [23], and a reduction in the duration of hypoxaemia was found when a VTV of 6 but not 4.5 ml/kg was used with SIMV [24]. Whether the most appropriate level of VTV differs according to neonatal respiratory disease requires testing.

High frequency oscillation

During high frequency oscillation (HFO), small tidal volumes are delivered at rates of 600-800 per minute. A high volume strategy is usually used, that is the mean airway pressure is increased to optimise alveolar recruitment. That strategy has been shown in preclinical models to reduce lung injury [25]. Meta-analysis of the results of eleven randomised trials of prophylactic HFO, that is commenced in the first 12 hours after birth [26], demonstrated that HFO was associated with a significant, but small reduction in BPD at 36 weeks postmenstrual age and at term, but importantly no significant differences in intraventricular haemorrhage or periventricular leucomalacia. The meta-analysis included the results of the United Kingdom Oscillation Study (UKOS). In that trial [1], a large number of the most high-risk infants were studied, 799 infants born prior to 29 weeks of gestation. The infants received their randomised mode of ventilation within the first hour of birth. Arguably the first few hours after birth may be the most important with regard to baro/volutrauma. No short-term benefits or disadvantages of HFO were demonstrated and lung function assessment at one year revealed no significant differences between the groups [27]. At one year, however, only a subset of infants was studied and small airway function was not assessed. Small airway function appears to decline over the first year after birth in prematurely born infants, and the results of a non-randomised trial suggest that this may be prevented by use of HFO rather than standard ventilation techniques [28]. It is, therefore, essential that infants entered into randomised trials are examined at school age to determine whether HFO may or may not confer long-term advantages to their lung function. HFO is frequently used as a rescue mode for infants with severe respiratory failure refractory to other ventilation techniques. In one randomised study involving prematurely born infants, use of rescue HFO was associated with a significant reduction in new air leaks but an increase in intracranial haemorrhage [29]. In addition, an observational study highlighted that the improvement in oxygenation in response to raising the mean airway pressure on initiating high volume strategy HFO does not guarantee a normal neuro-developmental outcome [30].

Nasal respiratory support

Continuous positive airway pressure

During continuous positive airway pressure (CPAP), there is a continuous distending pressure throughout the respiratory cycle. The effectiveness of CPAP is determined by the method of delivery. Variable flow CPAP via nasal prongs was demonstrated to result in better lung recruitment than nasal cannulae delivered CPAP or continuous flow CPAP [31], and bubble CPAP compared to continuous flow CPAP was associated with a lower lung clearance index, suggesting better gas mixing efficiency [32]. Nasal CPAP is considered by some as a gentler form of respiratory support, but adverse effects do occur, including nasal trauma. In some series, nasal trauma appeared to be more common when dual nasal prongs were used, but this has not been confirmed by the results of randomised trials

[33, 34]. Indeed, in one series [33] the only significant relationship to trauma was CPAP duration; hence it is important to wean CPAP efficiently. Two methods of CPAP weaning are frequently used: cycling on and off CPAP with increasing periods off CPAP, or gradual reduction of the pressure. A randomised trial showed that weaning by pressure was more successful than cycling and intriguingly was associated with less chronic oxygen dependency [35].

Meta-analysis of the results of trials of CPAP commenced soon after birth regardless of respiratory status (prophylactic CPAP) demonstrated no significant differences in outcomes, including BPD [36]. Others have investigated use of CPAP as soon as respiratory distress develops. In a recent randomised study of 300 infants of more than 30 weeks of gestational age and less than 24 hours of age, bubble CPAP compared to the standard treatment of headbox oxygen was associated with lower transfer rates to a tertiary centre or treatment failure (23 vs. 60%, P=0.002). This translated into an estimated cost saving of 10,000 Australian dollars for every six infants treated with CPAP, but a greater proportion of the CPAP group had pneumothoraces (9.3 vs. 3.4%, P=0.06) [37]. In a non-randomised trial, use of CPAP rather than surfactant and mechanical ventilation was associated with a significantly lower number of ventilator days, but there was no difference in the rate of BPD [38]. In other centres, infants are intubated to be given surfactant and then immediately extubated onto CPAP; this strategy can be successful in infants of less than 27 weeks of gestational age [39]. Meta-analysis of the results of six randomised controlled trials of early surfactant and rapid extubation onto CPAP versus selective surfactant with mechanical ventilation in infants with RDS demonstrated that there was less need for ventilation in the CPAP group [relative risk (RR) 0.67, 95% CI 0.57-0.79]. In addition, oxygen dependency at 28 days was lower in the CPAP group (RR 0.51, 95% CI 0.26-0.99) [40]. Recently, the results of the COIN trial, an international multicentre randomised comparison of nasal CPAP or intubation with mechanical ventilation, have been presented [41]. Infants of 25 to 29 weeks of gestational age were randomised in the delivery suite. The combined outcome of death or oxygen treatment at 28 days was lower in the CPAP group (RR 0.63, 95% CI 0.46-0.87, P=0.006), but there were no significant differences in days of respiratory support, the intraventricular haemorrhage rate or proportion of infants requiring home oxygen. There was, however, a significantly higher pneumothorax rate in the CPAP group (9 vs. 3%, P=0.003), which may be explained by the application of the high (8 cm^3 H_2O) distending pressure and/or the lower surfactant use in the CPAP arm. Post extubation, meta-analysis of the results of randomised trials has demonstrated that CPAP reduces the need for additional support, but not the need for intubation or supplemental oxygen at 28 days [42].

Nasal ventilation

A variety of ventilation modes, intermittent positive pressure ventilation (NIPPV), nasal intermittent mandatory ventilation (NIMV), synchronised nasal intermittent positive pressure ventilation (SNIPPV), NSIMV, NPSV and NHFO, can be delivered by nasal prongs. Nasal ventilation compared to CPAP can reduce chest wall distortion and the work of breathing [43] and an early meta-analysis of three trials demonstrated that NIPPV vs. CPAP was more effective in prevention of extubation failure (RR 0.21, 95% CI 0.10, 0.45) [44]. Subsequent randomised trials have demonstrated additional benefits, lower incidences of BPD with NIMV as compared to CPAP [45] and of BPD/death with SNIPPV compared to conventional ventilation [46]. Anecdotally, however, increased side-effects, such as pneumothorax, abdominal distension, gastro-intestinal perforation and delayed feeding, have been reported. All the randomised trials have been too small to adequately determine the true risks of those adverse outcomes. It is essential, then, that these forms of respiratory support be assessed in appropriately designed large trials with long-term outcomes.

In conclusion, unfortunately, despite advances in ventilator technology, BPD remains a common outcome of neonatal intensive care. This review highlights evidence in support of adopting certain practices, that is, weaning by ventilation modes which support every breath (ACV or ACV). Prophylactic HFO is associated with a significant but only modest reduction in BPD. Data are required from long-term follow-up of the randomised trials to assess the true risk benefits of this form of ventilation. The results of VTV are promising, but further studies are required to determine the optimum targeted volume and whether this differs according to respiratory disease.

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