REVIEW

New modes of mechanical ventilation in the preterm newborn: evidence of benefit

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The introduction of modern mechanical ventilation in neonatal medicine in the 1960s was followed shortly thereafter by its use in premature infants with hyaline membrane disease. Most premature infants born before 30 weeks' gestation receive some form of respiratory support, particularly those with fewer weeks of gestation.[1] Although mechanical ventilation is frequently a life-saving therapy, its use increases the risk of lung injury, particularly in preterm infants in whom the incidence of bronchopulmonary dysplasia (BPD) remains high.[2]

Before the current generation of neonatal ventilators, conventional mechanical ventilation (CMV) was provided mainly with time-cycled pressure limited (TCPL) ventilators developed from adaptation of Ayre's T piece.[3] This method, also known as intermittent mandatory ventilation (IMV), was and probably still is in many centres, the most common mode of ventilation.

During IMV mechanical breaths of fixed duration are delivered at predetermined time intervals. This frequently leads to asynchrony depending on the phase of the spontaneous breath when these IMV breaths are delivered. Inspiratory asynchrony occurring when a mechanical breath is delivered at the end of and extends beyond spontaneous inspiration can produce an inspiratory hold that limits the spontaneous respiratory rate or results in excessive lung inflation. Expiratory asynchrony occurring when a mechanical breath is delivered during exhalation can delay lung deflation and elicit active expiratory efforts against positive pressure producing large fluctuations in intrathoracic pressure. Asynchrony can affect gas exchange, and has been linked to increased risk of air leaks[4 5] and intraventricular haemorrhage (IVH).[6] As volume monitoring was lacking in most IMV devices, it was difficult to detect excessive lung inflation, gas trapping or hypoventilation.

SYNCHRONISED MECHANICAL VENTILATION

Advances in ventilator technology allowed mechanical breaths to be synchronised with the onset of spontaneous inspiration. This was achieved by using signals derived from spontaneous respiratory activity. Synchronisation was also extended to termination of the positive pressure breath in synchrony with the end of spontaneous inspiration or when inflation is completed. Respiratory signals used for synchronisation have included abdominal wall motion, oesophageal pressure, thoracic impedance, airway pressure and gas flow. The latter is also used to terminate the mechanical breath in a modality known as flow cycling. Measuring gas flow also permits tidal volume (V_T) monitoring, which is available in most neonatal ventilators.

Patient triggered ventilation (PTV), also known as synchronised IPPV (SIPPV) or assist/control ventilation (A/C), is a mode of ventilation where every spontaneous inspiratory effort is assisted with a mechanical breath. IMV provides back-up ventilation in the absence of spontaneous breathing effort or when the inspiratory effort is insufficient to trigger a mechanical breath. Assistance of every spontaneous inspiration is believed to prevent fatigue and yield a better V_T to dead space ratio than unassisted spontaneous breaths.

Synchronised intermittent mandatory ventilation (SIMV) is an enhancement of IMV. In SIMV the number of mechanical breaths per minute is set by the operator, but the interval between mechanical breaths is variable to accommodate for synchronisation. The caregiver can adjust the SIMV rate and thus control the ventilator contribution to total ventilation, but each mechanical breath is still synchronised with an inspiratory effort.

Pressure support ventilation (PSV) is a mode where flow cycling is used to assist every spontaneous inspiratory effort and terminate the mechanical breath as the spontaneous inspiration ends or inflation is completed. Synchronous breath termination gives the infant greater control over the frequency and duration of inspiration, while the support pressure compensates for instrumental and disease induced loads. In the event of apnea, back-up IMV ensures ventilation. In some ventilators PSV can be combined with a low SIMV rate to provide a constant background ventilation level and preserve lung recruitment.

Abbreviations: A/C, assist/control ventilation; BPD, bronchopulmonary dysplasia; CMV, conventional mechanical ventilation; CTGI, continuous tracheal gas insufflation; ET, endotracheal tube; IMV, intermittent mandatory ventilation; IVH, intraventricular haemorrhage; MMV, mandatory minute ventilation; N-A/C, nasal A/C; NCPAP, nasal continuous positive airway pressure; N-SIMV, nasal SIMV; PAV, proportional assist ventilation; PIP, automated peak inspiratory pressure; PRVC, pressure-regulated volume-controlled; PSV, pressure support ventilation; PTV, patient triggered ventilation; RDS, respiratory distress syndrome; SIMV, synchronised intermittent mandatory ventilation; SIPPV, synchronised IPPV; TCPL, time-cycled pressure limited; VAPS, volume-assured pressure-support; VC, volume controlled ventilator; VG, volume guarantee ventilator; V_T, tidal volume

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Evidence of benefit of synchronised ventilation

Physiological studies

Physiological studies in preterm infants have reported improved gas exchange, ventilation and more consistent V_T with synchronised ventilation compared to conventional ventilation.[7–16] Synchronous ventilation was shown to reduce markers of stress and blood pressure variability.[12 15 17] Synchronised ventilation reduced breathing effort,[15 16] but it did not seem to influence the metabolic demands associated with breathing.[18] Avoidance of asynchrony between the infant and ventilator can play an important role in the shift from mandatory ventilation to gentle assistance of spontaneous inspiration and preservation of the preterm infant's breathing pattern. A recent report showed reduced hypoxaemia episodes with SIMV in comparison to IMV in ventilator-dependent infants.[19]

Inadequate synchronisation mechanisms can lead to trigger failure, delayed triggering or autocycling. Delayed triggering can lead to greater breathing effort[20] and result in an inspiratory pressure hold that can affect the breathing pattern similarly to a prolonged ventilator inspiratory time.[21 22] Autocycling can produce excessive ventilation, hypocapnia and gas trapping particularly in A/C or PSV. End inspiratory asynchrony occurs because of delayed triggering or excessively long ventilator breaths. Reports indicate that most mechanical breaths extend beyond the end of the preterm infant's spontaneous inspiration.[23] This can lead to inhibition of inspiratory activity or active exhalation against the positive pressure.

Clinical trials

Most reports based on short-term physiological measurements suggested synchronised ventilation had potential benefits. This evidence led to several prospective randomised comparisons of synchronised versus conventional ventilation.[24–29] Synchronisation facilitated weaning and led to a shorter duration of mechanical ventilation. However, these trials did not demonstrate consistent beneficial effects on survival, IVH, air leaks or BPD.

These trials differed from each other in many important aspects including range of gestational age (or birth weight), sample size (from 30 to >800 infants), age of entry into the study and device used. These differences limit the generalisability of the findings. It has been suggested that the largest study may have been affected by the use of an airway pressure trigger, a sub-optimal synchronisation method and a high rate of crossover out of the experimental arm.[28] It has also been suggested that experience in using ventilatory devices could influence randomised trials. Some of these studies assessed the effects of synchronised ventilation on weaning after a course of CMV. It is unlikely that a relatively brief exposure to the experimental modality would have a substantial beneficial effect on an already damaged lung.

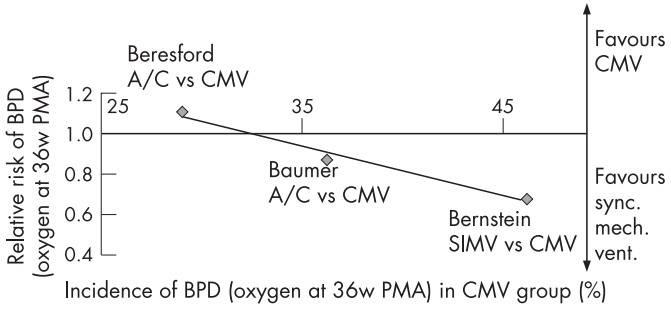

Figure 1 Relative risk of bronchopulmonary dysplasia (BPD) in relation to the incidence of BPD in the control group. Data are from three trials that enrolled at least 100 infants with birth weight ⩽2000 g (data from the study by Bernstein *et al*[24] are abstracted from the infants with birth weight 500–2000 g). A lower risk of BPD with synchronisation is observed in studies with higher rates of BPD in the control population. 36w PMA, 36 weeks' post-menstrual age.

The role of asynchrony on respiratory outcome may vary between different newborn populations. Moreover, large sample sizes are required in randomised trials to assess the effects of synchronised ventilation on multifactorial respiratory outcomes such as BPD. The incidence of BPD is largely influenced by prematurity and its incidence is particularly high among infants born before 28 weeks' gestation. Only one trial sought to assess the effect of synchronised ventilation in this population.[24] Stratified enrolment and analysis showed a reduction in severe BPD with synchronisation among infants with birth weight <1000 g.

The role played by asynchrony in BPD may also differ between centres with different incidences of BPD. In order to assess the relative effect of synchronised ventilation in populations with different risks of BPD, we analysed data from studies that enrolled at least 100 infants with birth weight ⩽2 kg (fig 1). This figure indicates there is a greater risk reduction with synchronisation in studies with a higher rate of BPD in the control population (CMV group). This suggests a baseline population dependent effect of synchronised ventilation with the benefits of synchrony being more evident among groups of infants where the rate of BPD is higher.

Autocycling is a potential drawback of synchronised ventilation that can lead to high ventilator rates. Most neonatal ventilators do not alert the operator when autocycling occurs, so it can continue undetected for significant periods of time during clinical use. Although not proven, this may have played a negative role in some of these trials.

The most commonly employed modes of synchronised ventilation in preterm infants are SIMV, A/C (PTV, SIPPV) and more recently PSV. Although SIMV and A/C are conceptually different, in practice they share similarities, particularly during acute respiratory failure when higher SIMV rates provide similar support to that given by A/C.[30] As weaning progresses, these modes of ventilation differ more because as the SIMV rate is decreased a greater number of breaths are unassisted and the infant is supported by end-distending pressure alone. Reports indicate that assistance of every spontaneous inspiration reduced breathing effort and the metabolic cost of breathing in A/C compared to SIMV.[15 18 31]

Randomised trials comparing weaning with A/C and SIMV in the recovery phase of respiratory distress syndrome (RDS)[32 33] suggested faster weaning with A/C. In those studies a large portion of the infants were ventilated for several days prior to study entry. Therefore, more data are needed to assess which of these modes is superior when used throughout the course of mechanical ventilation.

In PSV, similarly to A/C, assistance of every inspiration reduces breathing effort.[31] However, in preterm infants with an inconsistent respiratory drive and apneic episodes, PSV alone may not be sufficient. PSV can be used in combination with SIMV. In this manner, the constant SIMV rate provides a background ventilatory level when spontaneous drive is inconsistent, while PSV enhances spontaneous ventilation. This combination was shown to enhance V_T and minute ventilation during an acute reduction in SIMV rate.[34]

A randomised trial showed that the use of PSV in addition to SIMV during the first 4 weeks after birth facilitated weaning in infants of birth weight ⩽1000 g compared to SIMV alone. This was associated with a shorter oxygen dependency in infants of birth weight 700–1000 g.[35] These data indicate benefits resulting from assisting every spontaneous inspiratory effort with relatively low pressures and reducing exposure to high SIMV rates. These data also suggest that some maturity of the

respiratory centre is needed to benefit from a mode that depends on a stable respiratory drive such as PSV.

In summary, evidence of long-term benefits of synchronised ventilation is not conclusive. However, there is some indication of benefits based on physiological data, shorter duration of ventilation and decreased BPD particularly in lower birthweight infants. Therefore, providing that adequate set-up and proper monitoring are provided, the use of synchronised ventilation may be beneficial with relatively low risks involved.

NON-INVASIVE SYNCHRONISED MECHANICAL VENTILATION

Reduction in exposure to mechanical ventilation has been proposed as a strategy to prevent adverse pulmonary outcome. Synchronisation techniques enabled delivery of nasal A/C (N-A/C) or nasal SIMV (N-SIMV). In comparison to nasal continuous positive airway pressure (NCPAP), N-SIMV reduced chest wall distortion in preterm infants following extubation,[36] while N-A/C reduced breathing effort and improved ventilation.[37]

Three randomised trials have shown the consistent efficacy of N-SIMV in the post-extubation period as indicated by better respiratory evolution and lower extubation failure.[38–40] These reports suggest that reduced apnea is responsible in part for these effects and that infants with worse lung mechanics are likely to benefit more from N-SIMV. These data also showed a tendency towards reduced oxygen dependency among infants extubated to N-SIMV. The above-mentioned trials reported minimal gastrointestinal complications, which is reassuring in view of earlier concerns.[41]

Currently, there are limited data on non-invasive ventilation used early in the respiratory course. A recent study showed a reduced intubation rate and oxygen dependency with IMV delivered non-invasively compared to NCPAP in infants of less than 1500 g at birth.[42] Although the number of infants was relatively small, these results suggest the potential benefits of avoiding invasive mechanical ventilation altogether.

Although it is unknown if synchronisation during non-invasive ventilation is better than non-invasive IMV, synchronising the delivery and duration of the positive pressure breath with spontaneous inspiration may reduce the risk of gas accumulation in the stomach and lead to an effective unloading of the infant's respiratory pump. This underlines the need for an effective mode of synchronised non-invasive ventilation to not only assist spontaneous inspiration but also stimulate breathing during apnea.

In summary, data from physiological and clinical trials indicate that non-invasive synchronised ventilation has important benefits. Despite this evidence, the use of non-invasive synchronised ventilation is uncommon, perhaps because few such ventilators are available. More importantly, there are few data on the use of non-invasive synchronised ventilation to avoid earlier use of invasive ventilation.

VOLUME TARGETED VENTILATION

High inflation pressures or losses in alveolar volume due to insufficient ventilation can play a role in the development of lung injury in preterm infants. Changes in lung volume, lung mechanics and spontaneous respiratory drive are common in preterm infants and lead to changes in ventilation. Volume targeted ventilation is a modality aimed at reducing this variability by adjusting the peak pressure or duration of the mechanical breath to maintain tidal volume. Modalities of volume targeted ventilation vary as regards controlled volume parameters, whether this is volume delivered by the ventilator or actual tidal volume (inspired or exhaled), and timing of the adjustments (within the same breath or from breath to breath). These include volume controlled (VC), volume-assured pressure-support (VAPS), pressure-regulated volume-controlled (PRVC) and volume guarantee (VG). These modalities can be used in combination with A/C, SIMV or PSV modes.

Evidence of benefit of volume targeted ventilation

Physiological studies

The use of VG for automated peak inspiratory pressure (PIP) weaning showed dependency on the target V_T. Minimal weaning was achieved with a target V_T similar to the V_T produced by pressure limited SIMV. Pressure weaning was achieved with a lower target V_T, but this led to higher breathing effort and increased $PaCO_2$.[43 44] The use of VG to prevent excessive V_T also lowered the incidence of hypocapnia.[45] Compared to pressure limited ventilation, VG reduced V_T variability and attenuated spontaneous hypoxaemia episodes induced by hypoventilation.[43 45 46] Conversely, VG in PSV mode increased mean airway pressure and ventilation but did not improve gas exchange compared to SIMV.[47]

Clinical trials

In a randomised trial in infants of birth weight $\geqslant$1200 g, VC led to faster weaning and shorter duration of ventilation, but no effect on respiratory outcome compared to pressure limited ventilation was observed.[48] A recent randomised controlled trial in infants of birth weight 600–1500 g showed that weaning with VC tended to be faster, particularly in infants of birth weight $<$1000 g, but total duration of ventilation or other outcomes were not significantly improved.[49]

A randomised trial comparing PRVC to IMV in infants with RDS showed a lower incidence of IVH with a shorter ventilatory course in infants of birth weight $<$1000 g.[50] As PRVC assists every breath, it is unclear whether these effects were the result of volume targeting or the synchronous assistance of every inspiration. A subsequent randomised comparison of PRVC to SIMV in infants with RDS showed that PRVC lowered the incidence of acute respiratory deterioration but did not change the duration of ventilation or respiratory outcome.[51]

Excessive V_T can promote lung inflammation and contribute to lung injury. Analysis of tracheoalveolar fluid from preterm infants with RDS showed lower levels of proinflammatory cytokines with PSV+VG compared to PSV alone.[52] Conversely, a low V_T target in PSV+VG increased these markers.[53] A V_T target that is too low may lead to volume loss and more lung injury.

In summary, physiological data indicate improved ventilation and gas exchange stability with volume targeted ventilation, while data from clinical trials suggest faster weaning in comparison to pressure limited ventilation in preterm infants. The limited benefits for respiratory outcome observed in randomised trials of volume targeted ventilation may be in part due to a more conservative use of pressure limited ventilation. Currently, there is consensus that excessive or insufficient V_T should be avoided, but there is lack of data on optimal tidal volume or the most appropriate approach to volume targeting in preterm infants.

EXPERIMENTAL MODALITIES

Proportional assist ventilation

In proportional assist ventilation (PAV), airway pressure increases in proportion to the volume or flow produced by the patient, resulting in elastic or resistive unloading, respectively. PAV is used to compensate for obstructive or restrictive loads on the respiratory pump produced by the underlying lung disease and narrow endotracheal tubes (ETs).

Physiological and short-term clinical studies showed reduced breathing effort and chest wall asynchrony with PAV, and this was proportional to the degree of elastic unloading.[54] PAV improved ventilation and oxygenation and reduced peak airway and transpulmonary pressures and blood pressure variability

compared to A/C and IMV.[55 56] More research is needed to investigate the possible role of this novel ventilatory technique in improving long-term respiratory outcome.

Targeted minute ventilation

Many preterm infants need mechanical ventilation because of inconsistent respiratory effort and poor respiratory mechanics. A reduction in breathing effort or worsening of lung mechanics can impair ventilation. In targeted minute ventilation, the ventilator rate automatically adjusts to compensate for ventilatory deficit or excess with respect to a target level. This experimental modality reduced ventilator rate without impairing gas exchange compared to SIMV in preterm infants recovering from RDS.[57] Most of these infants were able to maintain their own ventilation and required only transient increases in ventilator rate during periods of apnea or reduced tidal volume.

Mandatory minute ventilation (MMV) is a modality where volume controlled breaths are delivered at a constant rate if minute ventilation falls below a preset level. Spontaneous breaths are non-assisted or assisted by PSV. MMV combined with PSV reduced ventilator rate and mean airway pressure compared to SIMV in near-term infants free of lung disease.[58]

Dead space reduction techniques

In addition to the relatively large anatomical dead space present in preterm infants, instrumental dead space can further reduce alveolar ventilation. This can lead to hypercapnia, higher ventilator settings and delayed weaning.

Continuous tracheal gas insufflation (CTGI) consists of gas insufflation to the distal end of the ET via built-in capillaries. This produces a washout of the ET tube and flow sensor. In preterm infants, CTGI reduced $Paco_2$ under constant ventilator settings or maintained a constant $Paco_2$ when settings were lowered.[59] Its use in a randomised trial resulted in more rapid weaning from the ventilator.[60]

Although flow sensors used for synchronisation and volume monitoring have relatively small dead space volumes, they can reduce alveolar ventilation and lead to higher $Paco_2$.[61] Continuous washout of the flow sensor with a proximal side stream gas leak is an experimental technique that clears exhaled CO_2 from the flow sensor. This technique was shown to be effective in reducing CO_2 rebreathing in small preterm infants while maintaining the ability to synchronise the ventilator.[62]

SUMMARY AND FUTURE DIRECTIONS

In spite of efforts to avoid mechanical ventilation, it is necessary for many preterm infants. Therefore, a better understanding of the benefits and limitations of the newer ventilatory modes and breath delivery modalities is required.

Based on existing evidence, newer modes of ventilation have not resulted in significant improvements in outcome as initially expected. Nonetheless, they have important benefits. The impact of these modes may have been diminished by a concomitant improvement in patient management.

The demographics of the target population have changed since the introduction of synchronised ventilation and the various modalities of mechanical breath delivery. Currently, most infants who require mechanical ventilation are smaller and more immature than was previously the case . It is uncertain if new studies comparing conventional with synchronised ventilation will be conducted in this population. More research is needed to assess the effects of newer ventilatory strategies in different respiratory diseases and across stages of these diseases. Improvements in invasive and non-invasive ventilatory support are needed to address these different requirements.

Because of the multifactorial nature of the morbidities affecting the preterm infant, it is unlikely that a given ventilatory strategy will have a significant effect. Although defining the effect of ventilatory strategies on outcomes such as BPD is essential, other outcomes such as duration of ventilation and oxygen therapy are worth exploring since they may indirectly reflect the effect of mechanical ventilation on the lung.

Future research efforts should target enrolment based on the characteristics and risk of specific groups of preterm infants. Otherwise, stratified analysis within populations of different risk should be reported for appropriate meta-analysis of the outcome data. The need to improve not only respiratory but also long-term neurological outcome in this population should be addressed in future studies. The short- and long-term effects of newly developed techniques should be carefully evaluated before such techniques are adopted for the care of preterm infants solely based on their availability.

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