REVIEW

Current aspects of paediatric mechanical ventilation for acute respiratory failure

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Abstract · The need for mechanical ventilation (MV) for acute respiratory failure is one the most common indications for children to be admitted to a paediatric intensive care unit (PICU). Despite worldwide daily use of MV in children, numerous issues remain unsolved and much of the current clinical practice is based upon anecdotal experience in combination with data originating from studies in critically ill adults. Current practice of paediatric mechanical ventilation for acute respiratory failure includes low tidal volume strategy (6 – 8 ml/kg ideal body weight), permissive hypercapnia (i.e. accepting respiratory acidosis with pH as low as 7.20 – 7.25), application of a sufficient level of PEEP, and early switch to high-frequency oscillatory ventilation (HFOV). Whereas prone positioning and nitric oxide does not seem to have any benefit on patient outcome, the effects of exogenous surfactant and corticosteroids remains unclear. Liberation of mechanical ventilation is another important issue in paediatric critical care that is not yet positively influenced by the application of available weaning protocols. Importantly, the lack of available evidence should encourage those dealing with critically ill children to embark on multicentre randomized controlled trials.

Keywords · children, mechanical ventilation, tidal volume, PEEP, adjunctive therapy

Introduction

The need for mechanical ventilation (MV) for acute respiratory failure is one the most common indications for children to be admitted to a paediatric intensive care unit (PICU). Recent data from the United States and Europe demonstrate that up to 64% of children admitted to a PICU are mechanically ventilated for at least 24 hrs [1,2]. Despite worldwide daily use of MV in children, numerous issues remain unsolved and much of the current clinical practice is based upon anecdotal experience in combination with data originating from studies in critically ill adults [3].

Ventilator-induced lung injury (VILI) is an important potential drawback of MV. This may be of even more importance in young children with developing lungs. The process of alveolization continues until the age of 5 years [4]. This suggests that physiological differences in the respiratory system between small babies, children and adults means that all data obtained from adults cannot be easily extrapolated to children [5]. In general, ventilator settings should be carefully selected to minimize VILI in previously healthy or injured lungs. Not only paediatric intensivists, but also anaesthesiologists or intensivists who ventilate children should be familiar with the current understanding of paediatric MV for acute respiratory failure. The main focus of this review, therefore, is to summarize the current concepts of paediatric mechanical ventilation.

When to initiate paediatric MV

MV is initiated (a) to support or maintain gas exchange (i.e. sufficient oxygenation and clearance of CO₂), (b) to restore or maintain adequate functional residual capacity (FRC) and (c) to reduce the work of breathing in the presence of high airway resistance and/or reduced compliance. The decision to initiate MV when primary respiratory failure is present is never debated. In general this decision is based upon clinical characteristics of the patient (progression of presence of tachypnoea and tachycardia, intercostal retractions, nasal flaring, grunting, progressive cyanosis or increased need for oxygen supplementation) preferably in combination with arterial blood gas interpretation.

However, the decision to initiate MV in the presence of secondary respiratory failure is frequently debated. This includes children with decreased consciousness in which patency of the airway is at risk. In these patients endotracheal intubation is advised if the Glasgow Coma Scale is less than 8 [6,7]. Because of their low FRC, young children with septic shock also require pre-emptive endotracheal intubation and MV to prevent hypoxaemia [8]. In septic shock there is increased oxygen consumption that becomes dependent on oxygen delivery at an early stage.

The use of non-invasive ventilation (NIV) to delay or prevent endotracheal intubation has attracted increased interest in paediatric critical care. Although no randomized-controlled trial has been performed, both retrospective and prospectively collected data from case studies demonstrate that NIV has a feasible and beneficial effect [3,9]. However, there are numerous hurdles associated with the use of NIV in paediatric critical care, including the availability of appropriate face masks and
the expected tendency of younger children in particular to fight these masks which, at present, hampers routine application [10].

Setting the ventilator
Initial ventilator settings in children are influenced by age-related physiological parameters including respiratory rate and inspiratory time as well as disease resulting in the indication for MV [11]. Ventilator settings should be carefully selected to minimize VILI. Importantly, when setting the ventilator one should keep in mind that maintaining spontaneous breathing is an important aspect. In other words, even in the presence of severe pulmonary dysfunction if no contra-indications are present the ventilator should assist rather than take over the child’s respiration as this is associated with improved gas exchange, blood flow and oxygen supply to tissues [12].

Modes of ventilation
Conventional modes
Both volume-controlled and pressure-controlled ventilation are used in critically ill children. It is no surprise that there is no randomized clinical trial (RCT) investigating which ventilator mode is superior, so choice of mode depends on numerous factors including age, presence of pulmonary pathology and familiarity with a specific ventilator mode. Nowadays, most modern adult ICU ventilators are capable of ventilating small infants and children [13]. In volume-controlled ventilation (VCV) a preset volume is delivered by the ventilator either time-cycled or volume-cycled. The benefit of this mode is that the tidal volume (Vt) and minute ventilation are guaranteed, but a major drawback of this mode is variation in Vt due to air leaks or inaccurate volume measurement. Therefore, this mode is not advised in infants as the set Vt based upon the patient’s weight might be too low to adequately ventilate the patient. In pressure controlled ventilation (PCV), inspiratory pressures are limited. However, an important drawback is delivery of a too low tidal volume in the event of a decrease in respiratory system compliance. Hybrid modes such as pressure-regulated volume control ventilation (PRVC) combine specific characteristics of both VCV and PCV. However, the clinical benefit of this mode compared with traditional modes needs to be established.

Alternative modes
High-frequency oscillatory ventilation (HFOV) is an alternative mode of ventilation that employs continuous distending pressure (CDP) which is usually higher than the mean airway pressure during conventional ventilation. Superimposed on this CDP are oscillations which are highly attenuated at alveolar level [14]. HFOV delivers Vt that are smaller than dead space, pointing out the theoretical advantages of HFOV over conventional ventilation in light of lung-protective ventilation. Gas exchange mechanisms are complex, but include bulk convection, turbulence, pendelluft and molecular diffusion [15].

It is beyond the scope of this review to discuss HFOV extensively. Nevertheless, despite the fact that HFOV is mainly used as rescue therapy (i.e. patients fail conventional mechanical ventilation), its early use is advocated [16]. This is supported by data from the only randomized paediatric trial comparing HFOV with conventional ventilation [17]. Various authors have reported their experiences with paediatric HFOV and conclude that it is feasible, safe, and significantly improves gas exchange and oxygenation especially in patients with reversible lung disease [18-20]. Therefore, HFOV remains an important alternative to conventional ventilation in acute respiratory failure.

Inspiratory time and I:E ratio
In general, the respiratory rate is set in accordance with the child’s age but in small airway disease a lower frequency is usually set. The inspiratory time varies between 0.5 seconds for infants, 0.6 – 0.8 seconds for older children and 1 second for teenagers [21]. However, these inspiratory times may be reduced in the presence of small airway disease, or increased if hypoxia originates from acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). The benefits of inversed-ratio ventilation (i.e. I:E ratio > 1) to increase mean airway pressure in adult patients with ALI/ARDS have not been demonstrated in randomized trials [22,23].

Tidal volume
It has been learned from experimental work that alveolar overdistension (“volutrauma”) is an important feature of VILI although this effect seems to be age-dependent [24]. Young rats are less susceptible to VILI when ventilated with high Vt compared with older rats [25,26]. Animal data were confirmed in RCTs performed in critically ill adults comparing low Vt with high Vt [27-29], resulting in low Vt being applied in daily paediatric critical care. However for several reasons, it can be questioned if this adult practice should be directly translated into paediatric practice. First, there are methodological controversies relating to the RCTs performed in critically ill adults, including high mortality rates in the control group which are not representative of daily care, overventilation in the control group, and differences in individual ventilatory strategy before and after randomization [28,29]. Second, observational retrospective and prospective studies on Vt produce conflicting results. In a prospective study of 328 children with ALI/ARDS, the mean exhaled Vt was 10.0 ± 4.9 ml/kg but this was not associated with a lower number of ventilator-free days or increased mortality [30]. This finding is in agreement with data from a retrospective study of 398 children with acute hypoxaemic respiratory failure ventilated with a Vt between 6 – 10 ml/kg showing no association between Vt and mortality or prolonged ventilatory support [31]. In contrast, Albuali and colleagues retrospectively observed a significant reduction in mortality (35% to 21%, p = 0.04) when studying the mean Vt between two time periods (1988 – 1992 mean Vt 10.2 ± 1.7, 2000 – 2004 mean Vt 8.1 ± 1.4 ml/kg (actual body weight) [32]. Recently, Randolph recommended that plateau pressures (Pplat) of ≤ 30 cmH2O should be maintained in mechanically-ventilated children in order to minimize Vt [33]. However, doing this without assessing the role of the chest wall is to ignore the increasing awareness that it is actually the transmural pressure (Ptm) (i.e. the difference between airway pressure (Paw) and pleural pressure (Ppl)) that is
of more importance to alveolar stress [34]. In daily practice, the oesophageal pressure (Pes) can be used as a substitute for Ppl. Preliminary data from critically ill adults shows that a ventilatory strategy guided by Pes measurement is feasible, and significantly improves oxygenation and lung compliance [35]. This approach warrants further investigation.

**PEEP and lung recruitment**

The issue of positive end-expiratory pressure (PEEP) is complicated. PEEP is used to maintain recruited alveoli and prevent atelectasis (i.e. preventing atelectrauma which is also an important feature of VILI), but may also negatively affect outcome through overdistention of the lungs and subsequent circulatory compromise. However, the adult ALVEOLI trial has clearly shown that routine application of PEEP does not positively influence outcome [36].

In general, in children with a healthy respiratory system a PEEP of 3 – 5 cmH\(_2\)O should be applied when on the ventilator. The appropriate level of PEEP in acute respiratory failure is unknown and should most likely be tailored to the individual patient, although it is difficult to determine the optimal response to PEEP. Whereas impaired oxygenation is significantly associated with worsened outcome in paediatric ALI, it may not be a suitable target when setting the level of PEEP [30,37]. Improved oxygenation resulting from prone positioning of critically ill children did not positively influence patient outcome, and in adults improved oxygenation was associated with worse outcome in the ARDSNetwork trial [28,38].

It is suggested that determining the level of PEEP without a prior recruitment manoeuvre seems futile [39]. Yet, not all lung diseases are recruitable, and the potential for lung recruitability is highly variable [40]. Halbertsma et al recently summarized the existing paediatric literature on the efficacy of recruitment procedures and in line with data from critically ill adults concluded that the effect of these manoeuvres remains unclear and should therefore not be routinely applied [41,42]. However, there are various recruitment manoeuvre techniques which vary in inspiratory pressures, maximum duration and end-expiratory pressures. Importantly, the same authors observed a significant increase in the plasma concentration of the pro-inflammatory mediators TNF-a and IL-1b in seven critically ill children, 15 minutes after a single recruitment manoeuvre [43]. Its clinical relevance needs to be determined.

One approach would be to set the level of PEEP at the point of optimal compliance of the respiratory system (Crs) on the expiratory limb of the pressure-volume curve that is associated with adequate oxygenation, providing that fluid status is adequate [44,45]. Preliminary animal work suggests it may be a better approach than setting PEEP just above the lower inflection point of the P-V curve [46].

**Targets of ventilation**

Targets of ventilation, i.e. the definition of acceptable gas exchange, are complex and there are no validated values for PaCO\(_2\), PaO\(_2\) and SpO\(_2\) to aim at. We suggest that adequate oxygenation may be arbitrarily defined by SpO\(_2\) 88-92% and FiO\(_2\) < 0.6 in patients with lung injury, but this warrants clinical validation. On the other hand, there are strong arguments to allow a degree of hypercapnia in paediatric patients even if lung injury is not present. Traditionally, CO\(_2\) is considered to be a waste gas that should be eliminated. In fact, in specific disease conditions such as traumatic brain injury or in infants born prematurely, hypercapnia worsens outcome [47,48]. On the other hand, permissive hypercapnia is considered to be an element of lung-protective ventilation by limiting plateau pressures and thereby accepting respiratory acidosis [49]. Both experimental and human studies show that hypercapnic acidosis has beneficial effects and in combination with lung-protective ventilatory strategy, improvements in patient outcome that warrant application in paediatric critical care [50,51]. Most paediatric clinicians allow a pH as low as 7.20 – 7.25 as there is little evidence that pH levels as low as 7.20 exert detrimental effects on myocardial performance or tissue oxygen delivery [52]. On the other hand, there are also some concerns associated with permissive hypercapnia including the effects on haemodynamics and to which extend hypercapnic acidosis can be accepted before it becomes deleterious. Although pCO\(_2\) levels as high as 39 kPa have very rarely been described as occurring without serious neurological sequelae, others have demonstrated otherwise including diffuse cerebral swelling and severe motor handicaps, hence caution is warranted [53].

**Failure of conventional ventilation**

If conventional mechanical ventilation fails (i.e. persistent hypoxaemia with FiO\(_2\) > 0.6 or refractory severe respiratory acidosis), there are two alternatives. These are HFOV (discussed earlier) and extra-corporeal membrane oxygenation (ECMO) [54]. The choice of which modality is applied depends on availability and experience.

**Adjuncts to mechanical ventilation**

Adjuncts of paediatric mechanical ventilation used to some degree in daily paediatric critical care include prone positioning, exogenous surfactant, nitric oxide, fluid management and corticosteroids. Prone positioning improved lung mechanics and gas exchange in critically ill children, but failed to significantly improve patient outcome in a randomized controlled trial investigating the efficacy of 20 h prone positioning for 7 days versus standard supine positioning [38,55-57].

The efficacy of exogenous surfactant has been evaluated in one large RCT comparing calfactant with placebo [58]. Although the number of ventilator-free days was not significantly different between the treatment and control groups, administration of exogenous surfactant led to a significant improvement in oxygenation and in-hospital mortality (36% to 19%). Unfortunately, these differences became insignificant when the results were adjusted for the immune status of the patient. However, these findings warrant further study into the use of exogenous and the identification of which patient might benefit from such a therapy [59].
Inhaled nitric oxide (iNO) is frequently used in paediatric critical care in refractory hypoxaemia. In iNO the pulmonary vascular resistance is selectively reduced and pulmonary blood flow towards ventilated alveolar units is increased [60]. However, despite the short-term improvement in oxygenation, at present there is no significant effect of iNO on patient outcome defined by mortality or ventilator-free days [81]. Alternatively, prostaglandin I$_2$ (PGI$_2$) may be considered. Dahlem and co-workers evaluated the efficacy of aerosolized PGI$_2$ in fourteen children with ALI who were mechanically ventilated, and observed a significant improvement in oxygenation [62].

Alveolar oedema is a key component of ALI/ARDS, hence it seems rational to attempt to reduce extravascular lung water by fluid restriction and administration of diuretics with or without concomitant use of albumin [63-65]. Such an approach has been proven to significantly reduce the length of ventilatory support but not mortality in a large randomized trial of 1000 patients with ALI [66]. Comparable paediatric data is lacking, although Randolph and co-workers have shown that cumulative fluid intake minus output was not associated with the duration of ventilator weaning or extubation outcomes in 301 critically ill children enrolled in a trial studying the efficacy of weaning protocols [67].

ALI/ARDS is characterized by an overwhelming host inflammatory reaction, hence corticosteroids have been studied in critically ill adults as a possible treatment for ALI/ARDS. A recent meta-analysis of adult data showed that the use of low-dose corticosteroids is associated with decreased mortality and morbidity without an concomitant increase in adverse reactions (infection or neuro-myopathy) [68]. At present paediatric data are lacking.

**Weaning off mechanical ventilation**

Weaning off MV starts at the moment of intubation, and there are numerous approaches to weaning a child off the ventilator. One such approach could be the use of weaning protocols although the results from one randomized trial by the PALISI investigators studying the effect of physician directed pressure support weaning, automated ventilator-adjusted volume support protocol, or no protocol were negative [69]. Others have also failed to demonstrate any beneficial effect on length of ventilation when weaning protocols were used [70,71]. Accurate extubation criteria in critically ill children remain a subject of debate [72].

Extubation failure is an important issue in paediatric critical care; it occurs in 4% to 19% of all PICU patients [3]. Post-extubation stridor is an important cause of extubation failure. The air-leak test is often used in an attempt to predict which patient is at risk for post-extubation stridor [73]. However, its validity has been questioned by a recent prospective cohort study in 59 critically ill children in whom an air leak > 30 cmH$_2$O failed to predict post-extubation stridor [74].

Corticosteroids are frequently used to prevent or treat post-extubation stridor in critically ill children. Yet 15 years ago in a prospective randomized trial that included 59 critically ill children, Tellez and co-workers were unable to find any significant effect on the occurrence of post-extubation stridor of the administration of 0.5 mg/kg dexamethasone (first dose 6 to 12 hrs before extubation, then every six hours for six doses in total) [75]. However, all studies examining the effect of corticosteroids have recently been summarized in a Cochrane review [76]. The outcome of this review suggests a tendency towards a beneficial effect of corticosteroids on post-extubation stridor, indicating a well-designed RCT is needed.

**Approach to the child with acute respiratory failure**

We would like to propose a part evidence-based, part expert-opinion based approach to the management of paediatric mechanical ventilation that is individually targeted at each patient with or without lung injury.

In patients with no pulmonary pathology (e.g. patients with severe traumatic brain injury or patients admitted post-operatively), or in patients who need prolonged ventilation (e.g. patients with neuromuscular disorders with decreased mucous clearance), volume-controlled ventilation could be the preferred mode. In patients with pulmonary pathology or with endotracheal tube leakage, pressure-controlled MV is the preferred mode of ventilation.

The following basic principles apply to all paediatric patients with or without primary or secondary lung injury, and include (i) optimizing haemodynamic status by ensuring intravascular volume and inotropic support to tolerate high levels of PEEP, (ii) minimizing the degree of non-aerated lung by recruitment if the lung is recruitable, and (iii) avoiding excessive Ptm and Vt. In practice, this means (a) application of Vt 6 – 8 ml/kg ideal body weight, (b) measurement of oesophageal pressure as representative for Ppl to evaluate Ptm, to determine what the maximum Pplat, (c) application of permissive hypercapnia might be (i.e. pH ≥ 7.20 – 7.25), and (d) if the lung is recruitable, application of a sufficient level of PEEP at the point of optimal compliance of the respiratory system (Crs) on the expiratory limb of the pressure-volume curve that is associated with adequate oxygenation, arbitrarily defined by SpO$_2$ 88-92% and FIO$_2$ < 0.6. If the lung is not recruitable, then high levels of PEEP should be avoided because of the associated haemodynamic compromise.

Our approach can be applied in daily practice, but may also be used as an approach for eagerly awaited, well-designed RCTs similar to those performed in critically ill adults comparing, for instance, low Vt (6 ml/kg bodyweight) versus “normal” Vt (8 – 10 ml/kg bodyweight) or different approaches in setting PEEP.

**Conclusions**

Although mechanical ventilation is a cornerstone in the management of critically ill children, it has little support from evidence-based literature. Current practice of paediatric mechanical ventilation is aimed at minimizing VILI. Yet, the lack of available evidence should encourage paediatric intensivists worldwide to embark on multicentre randomized controlled trials to obtain firm evidence that would serve as a basis for the daily care of critically ill children.

**Conflict of interests statement**

All authors declare that have no conflicts of interest to disclose.
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