Ventilator-induced lung injury in children: a reality?

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Abstract: Mechanical ventilation (MV) is inextricably linked to the care of critically ill patients admitted to the paediatric intensive care unit (PICU). Even today, little evidence supports best MV practices for life-threatening acute respiratory failure in children. However, careful attention must be paid because this life-saving technique induces pulmonary inflammation that aggravates pre-existing lung injury, a concept that is known as ventilator-induced lung injury (VILI). The delivery of too large tidal volumes (Vt) (i.e., volutrauma) and repetitive opening and closure of alveoli (i.e., atelectrauma) are two key mechanisms underlying VILI. Despite the knowledge of these mechanisms, the clinical relevance of VILI in critically ill children is poorly understood as almost all of our knowledge has been obtained from studies in adults or experimental studies mimicking the adult critical care situation. This leaves the question if VILI is relevant in the paediatric context. In fact, limited paediatric experimental data showed that the use of large, supraphysiologic Vt resulted in less inflammation and injury in paediatric animal models compared to adult models. Furthermore, the association between large Vt and adverse outcome has not been confirmed and the issue of setting positive end-expiratory pressure (PEEP) to prevent atelectrauma has hardly been studied in paediatric clinical studies. Hence, even today, the question whether or not there VILI is relevant in pediatric critical remains to be answered. Consequently, how MV is used remains thus based on institutional preferences, personal beliefs and clinical data extrapolated from adults. This signifies the need for clinical and experimental studies in order to better understand the use and effects of MV in paediatric patients with or without lung injury.

Keywords: Mechanical ventilation (MV); ventilator-induced lung injury (VILI); children; clinical studies; experimental studies

Introduction

Paediatric acute respiratory distress syndrome (PARDS) is a manifestation of severe, life-threatening lung injury (1,2). The prevalence of PARDS in children admitted to the paediatric intensive care unit (PICU) may approximate 10%. Although PARDS related mortality seems to have decreased over time probably due to changes in ventilatory management of children with PARDS or institutional variation in management of PARDS, mortality rates may still be as high as 40–50% in severe PARDS (3). Mortality rates may be the lowest in children without co-morbidities (3).

Mechanical ventilation (MV) is inextricably linked with the daily care of children with PARDS. However, careful

attention must be paid when ventilating children with or without PARDS because this life-saving technique induces a pulmonary inflammation that can aggravate pre-existing lung injury, a concept that is known as ventilator-induced lung injury (VILI). The delivery of too large tidal volumes (Vt) (i.e., volutrauma) and repetitive opening and closure of alveoli (i.e., atelectrauma) are two key mechanisms underlying VILI (4). Understanding these mechanisms resulted in the concept of lung-protective ventilation (LPV), a strategy that focuses on the delivery of small Vt to avoid volutrauma and a certain level of positive end-expiratory pressure (PEEP) to prevent alveolar collapse. Translating to clinical practice, the importance of trying to minimize the likelihood of volutrauma became apparent when the National Heart, Lung and Blood Institute ARDS Network trial reported lower mortality rates in critically ill adults with ARDS randomized to low Vt ventilation [i.e., 6 mL/kg ideal bodyweight (IBW)] and plateau pressures (Pplat) less than 30 cmH_2O compared to 12 mL/kg IBW (5) and Pplat <50 cmH_2O (5). The clinical importance of atelectrauma remains not fully answered because adult studies have reported that setting higher PEEP levels to attenuate the risk of atelectrauma was only beneficial in patients with severe ARDS (6-8). Despite the knowledge of these mechanisms, the clinical relevance of VILI in critically ill children is poorly understood as almost all of our knowledge has been obtained from studies in adults or experimental studies mimicking the adult critical care situation.

VILI in children: data from animal studies

Experimental work in pediatric models showed interesting results although the number of studies are limited. One group of investigators observed that ventilation with Vt 25 or 40 mL/kg without PEEP resulted in a lower decrease in respiratory system compliance, alveolar injury and mRNA cytokine expression in healthy newborn (i.e., 5–8 days) rats compared to adult (i.e., 3–4 months) rats (9). A lower decrease in total lung capacity (TLC) and less histological evidence of lung injury was also observed in infant (~26 days old) compared with juvenile (5 weeks) or adult rats (12 weeks) after 1 hour of ventilation with Vt 30 mL/kg in an *ex vivo* non-perfused healthy lung model (10). Similar findings were made in mice in a double-hit model in juvenile (21 days) and adult (16 weeks old) C57BL/6 mice treated with aerosolised lipopolysaccharide and ventilated for 3 hours with Vt 15 mL/kg (11). Of note, all experimental studies used supraphysiologic Vt, which challenges

translating the results into clinical perspective although one study showed an exacerbation of acid-induced lung injury also occurring when physiological Vt was delivered (12). Furthermore, the findings of these studies may have been influenced by the fact that the injurious stimulus might be lower in the infant rat when Vt was dictated by bodyweight rather than by body size. It is known that the ratio of TLC over bodyweight (which represents the amount of inflatable lung volume) is smaller in the infant rat. Hence, it would make sense to normalize Vt to baseline TLC to deliver the same injurious stimulus. Nonetheless, this thinking is somewhat challenged by one group of authors who did normalize Vt to baseline TLC, but still observed lower injury in infant rats (10).

VILI in children: data from clinical studies

To date, there is little data on VILI in children. A pro-inflammatory response was observed in one small study of 12 infants without pre-existing lung injury elective ventilated for 2 hours with a Vt of 10 mL/kg, thereby suggesting that the paediatric lung may also be susceptible to MV induced stretch even in the absence of lung injury (13). Unfortunately, no control group was included so it cannot be ruled out that these observations were confounded by the procedure by other, unidentified factors. Others observed an increase in plasma tumour necrosis factor beta and interleukin 1 beta but not in broncho-alveolar lavage fluids of N=7 children with acute lung injury (ALI) after a single recruitment manoeuvre (14).

To date, there are no pediatric randomized controlled trials published that evaluated the effect of paediatric MV settings and outcomes. A paediatric equivalent of the ARDSNetwork trial has not been performed and is very unlikely (15). Thus, the issue of the "optimal" Vt remains subject of debate in. The PALIVE study showed reported the use of a median Vt of ~8 mL/kg actual bodyweight in children with ALI. Remarkably, paediatric retrospective and prospective observational studies have produced different results, with some showing a beneficial effect of larger Vt and others no effect of Vt on patient outcome (16-19). While some investigators did not confirm an independent association between Vt and mortality, others reported that higher Vt was independently associated with better outcome in pediatric ALI (16,20). Only one group of investigators observed lower mortality among children ventilated with Vt ~8 mL/kg actual bodyweight compared with ~10 mL/kg in a before-after retrospective study (21). However, in

a subsequent meta-analysis of seven studies including N=1,756 patients, not a single Vt threshold associated with increased mortality has been identified, whether or not ALI/ARDS was present or absent (22). No single threshold for Vt to be associated with adverse outcome could be identified in this systematic review, mirroring the three negative adult randomized trials in which Vt ~7 mL/kg was compared with ~10 mL/kg (23). Paediatric studies including one in 483 PARDS patients and one in 222 paediatric hematopoietic cell transplant recipients published after these meta-analyses showed similar findings (24,25). Lack of an association between Vt and outcome in children probably explains, at least partially, why adherence to LPV strategies in terms of Vt has been reported to be poor (26,27).

In contrast with the observations on Vt, a direct relationship between peak inspiratory pressure (PIP) and mortality has been observed in retrospective and observational studies of children with (severe) lung injury (16,17,20,28). Khemani and co-workers observed in non-survivors a median PIP of ~30 cmH$_2$O for the first three days of ventilation compared to ~25 cmH$_2$O in survivors (17). Likewise, the odds for mortality increased by 10% [odds ratio for death 1.1; 95% confidence interval (CI), 1.020–1.199] when the PIP >25 cmH$_2$O in a prospective observational multicentre study of the Australian and New-Zealand Pediatric Intensive Care Society (ANZPICS) study group (16). Imber *et al.* found in their cohort of 483 PARDS patients that those who survived had lower inspiratory pressures at 24 hrs compared to non-survivors (24). Higher inspiratory pressures were associated with adverse outcome in 222 paediatric hematopoietic cell transplant recipients (25). These observations on the potential importance of pressure is reflected in the recent meta-analysis by Amato *et al.*, who concluded from a reanalysis of data from N=3,562 patients with ARDS enrolled in nine previously reported randomised trials in adults that the driving pressure (i.e., the ratio of Vt over Crs) best stratified the risk for mortality (29). These findings were the most prominent in patient matched for Pplat as opposed to those matched for PEEP. Also, a systematic review of adult data concluded that achieving a Vt less than or equal to 6 mL/kg predicted body weight may not have been as attainable or important as targeting Pplat less than or equal to 30 cmH$_2$O (30). Given the fact that pressure controlled modes of ventilator are predominantly used in the paediatric context, whereas the meta-analysis by Amato *et al.* is based on volume-controlled mode of ventilation, the issue of pressure limitations warrants further study in children with

(severe) PARDS especially since from the available data the cause and effect relationship remains unclear.

There are also no paediatric studies on optimal PEEP in (severe) lung injury. In fact, paediatric critical care practitioners tend to use low levels of PEEP and inherently accept higher FiO$_2$ (31). The PALIVE study identified an average PEEP of 6.4±2.7 cmH$_2$O, which was only slightly higher in patients with ARDS 7.2±2.6 cmH$_2$O (32). Indeed, higher levels of FiO$_2$ were accepted in these patients (ALI 0.38±0.05; ARDS 0.57±0.19). However, PEEP levels higher than empirically chosen are required to restore end-expiratory lung volume (EELV) in paediatric acute respiratory failure (33). A possible explanation would be the feared detrimental effects on haemodynamics. This uncertainty surrounding PEEP is also reflected in adult data, from which it became clear that high levels of PEEP, as compared with low levels, did not reduce mortality before hospital discharge (34). However, this reluctance to PEEP may not be beneficial as recently Khemani *et al.* reported increased mortality among 1.134 PARDS patients when they were not managed according to the ARDSNetwork PEEP/FiO$_2$ grid (35). They also concluded that PEEP lower than recommended by the protocol remained independently associated with higher mortality after adjusting for amongst others hypoxemia and disease severity.

VILI in children: what about high-frequency oscillatory ventilation (HFOV)?

HFOV could be seen as an ideal lung-protective mode of ventilation. A continuous distending pressure (CDP) maintains recruited alveoli (thereby preventing atelectrauma) and delivers small superimposed pressure oscillations (thereby preventing volutrauma) (36). However, to date only one trial has been published studying the effects of HFOV on patient outcome in N=58 paediatric patients with acute hypoxaemic respiratory failure (37). Mortality rates were comparable between the two groups, although subjects randomised to HFOV had a lower need for supplemental oxygen at 30 days, suggestive for less lung injury. Another small study of 16 paediatric patients with ARDS showed less lung inflammation dictated by plasma soluble intercellular adhesion molecule-I (ICAM-I) (38). However, two large trials in adults including the Oscillation for Early ARDS (OSCILLATE) trial failed to show a beneficial effect of HFOV (39,40). Two retrospective paediatric observational studies seemed to confirm these adult data. Gupta

et al. found increased mortality and morbidity in patients managed with HFOV compared with conventional MV (CMV) when they analyzed the data from the virtual PICU (vPICU) database (41). Although propensity matching used in this study included severity of illness, important clinical variables that influence the decision to initiate HFOV, such as metrics of oxygenation and ventilator settings were not available, thus challenging the relevance of this publication (42-44). More recently, Bateman and co-workers performed a post-hoc analysis of data from the Randomized Evaluation of Sedation Titration for Respiratory Failure (RESTORE) study with propensity matching to match for severity of illness (45). They observed that early HFOV (i.e., initiated within 24–48 hours of intubation) was associated with a longer duration of MV but not with mortality compared with CMV/late HFOV after adjusting for risk category. The question is whether the outcomes of these recent studies confirm that HFOV is not beneficial or even harmful, or if it is a matter of how the oscillator was used that determined patient outcomes (46,47). Recently, a global multicentre 2×2 factorial adaptive randomised controlled trial examining the effects of prone positioning and HFOV on patient outcome has been launched and will provide much needed answers (www.prospect-network.org) (clinicaltrials.gov NCT03896763).

VILI in children: the verdict

In summary, neither the underlying mechanisms nor the clinical relevance of VILI in children is fully understood at this stage. This may be explained by numerous factors including amongst others patient-related factors such as heterogeneity of the study population calling for disease unpacking, or methodology-related factors such as errors in measuring Vt due to endotracheal leakage or in the ventilator rather than at the Y-piece, and lastly experimental design-related factors such as normalising Vt to bodyweight rather than to body size or residual inflatable lung volume (48-51). Furthermore, it makes be questioned if mortality is the best outcome parameter given the decrease in mortality and that most patients die with PARDS rather than from PARDS (3). Yehya and Thomas have recently argued that predictors of PARDS mortality were usually related to the underlying disease condition that led to the critical illness rather than being specific to PARDS.

When interpreting the experimental studies, the question comes up if it is really true that prematurely born infants and adults are more susceptible to VILI than (young) children. How does the experimental data relate to the daily clinical practice and supposedly confirm that VILI is less predominant in the paediatric context? Given the paucity of data, it is clear there is a strong need for well-designed clinical studies that will provide a direction towards more physiological and justified use of MV in PARDS patients. Despite the many hurdles including the need for large sample sizes, there seems to be an obvious need for clinical trials examining the effects of Vt and PEEP on outcome in PARDS (15). While awaiting these data, we must acknowledge that the current use of MV in PARDS cannot be supported by strong, rigorous evidence other than the expert opinion from the Paediatric Mechanical Ventilation Consensus Conference (PEMVECC) and the Paediatric Acute Lung Injury Consensus Collaborative (PALICC) (52,53).

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Footnote

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