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WHAT'S NEW IN INTENSIVE CARE

The top ten unknowns in paediatric mechanical ventilation

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Introduction

There is inconsistent mechanical ventilation (MV) practice in children [1] given the fact that even today it is largely based on expert opinion and data extrapolation from adults despite the paediatric catchphrase "a child is not just a small adult". Unique maturational differences related to lung growth and maturation (to the age of about 8 years), respiratory system development (e.g. small airways, compliant chest wall), immune response and surfactant homeostasis prevent data generated in adults being directly applicable to children. Moreover, a possible age-related susceptibility to ventilator-induced lung injury has been suggested [2]. Furthermore, there is a much larger spectrum of pathologies associated with hypoxemic and/or hypercapnic respiratory failure in infants and children than in adults.

Given this context, we identified 10 major unknowns regarding paediatric MV in the following categories: (1) lung "protective" ventilation strategies, (2) concepts to assist spontaneous breathing, (3) use of non-invasive support and (4) weaning from MV.

Lung "protective" strategies

1. Small tidal volume ventilation and/or pressure limitation strategies

The lung protective effect of low Vt ventilation has never been documented in children [3]. However, observational studies suggest a direct relationship between observed end-inspiratory pressures and mortality [4, 5].

Disease severity at onset of MV, expressed by oxygenation metrics, respiratory system compliance, lung injury scores and mortality prediction scores, seems to be more sensitive in predicting outcome (i.e. ICU mortality) than any ventilator strategy that targets any specific Vt [6]. Whether this can be confirmed when applying newer concepts of protective ventilation (e.g. limitation of driving pressure) remains unclear.

Furthermore, long-term neurodevelopmental outcome remains largely unknown.

2. Positive end-expiratory pressure (PEEP) and lung recruitment strategies

Although characteristics of the respiratory system of the small child with acute hypoxic respiratory failure (i.e. low chest wall elastance, low functional residual capacity) would call for PEEP titration for improving oxygenation and compliance with a minimal risk for side effects [7, 8], little knowledge on how to guide PEEP titration or other recruitment manoeuvres exists.

3. High frequency oscillation

High frequency oscillation ventilation (HFOV) for paediatric acute respiratory distress syndrome (PARDS) is not uncommon, despite the lack of paediatric data showing a long-term outcome benefit as well as negative outcome data in adults. A retrospective paediatric data analysis [9] showed increased mortality with HFOV when mainly used as a rescue strategy, but post hoc analysis of the RESTORE trial showed no effect of HFOV on mortality [10]. Whether early intervention HFOV and with which strategy applied might be effective and/or superior to

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conventional mechanical ventilation (CMV) in PARDS remains unanswered.

4. Prone positioning

The single paediatric randomized controlled trial (RCT) [11] that investigated, in a heterogeneous group of mild to severe PARDS patients, the effect of prone positioning on outcome showed no benefit. The conclusion of this study should be used with caution as the study design mandated the use of HFOV for those with more severe lung disease. Whether the finding from adults that proning is most beneficial with severe ARDS would also apply to severe PARDS remains unknown.

Assisting spontaneous breathing

5. Neuromuscular blockers

Muscle relaxation in the early phase of severe ARDS might be beneficial. Nothing is known on this topic in children with the exception that neuromuscular blockade may result in an improved oxygenation index [12].

6. Patient–ventilator synchronization

Despite advancements of various flow-triggered modes, which should allow for improved patient–ventilator synchronization, ineffective inspiratory triggering is still a predominant cause of patient–ventilator asynchrony [13]. Furthermore, no data are yet available showing that better patient–ventilator synchronization has an effect on outcome.

7. Level of support (including proportional assist)

The optimal level of support during assistance of spontaneous breathing remains unknown. Adult findings indicate that pressure preset ventilation might be potentially harmful, as a result of larger effective transpulmonary pressures, during assistance of spontaneous breathing efforts [14]. For methods that allow for proportional assist support in relation to patient effort and improved patient–ventilator synchronization [e.g. neurally adjusted ventilatory assist (NAVA)] [13, 15], it remains unclear how much support should be provided to reduce work of breathing for an individual patient.

Non-invasive respiratory support

8. Non-invasive respiratory support

Early application of non-invasive positive pressure ventilation (NIPPV) in paediatrics improves breathing pattern, respiratory muscle unloading and gas exchange [16]. However, many paediatric NIPPV studies used continuous positive airway pressure (CPAP) as the NIV mode. This troubles an understanding of the true effects of NIPPV as well as which patients would best qualify for NIPPV. Definitive evidence is lacking with regard to the effects of NIPPV or CPAP on relevant outcome measures in children [17].

9. High flow nasal cannula (HFNC)

High flow nasal cannula in children is a relatively safe, well-tolerated and feasible method for delivering oxygen. It reduces work of breathing [18]. However, to date, there are no convincing data indicating that HFNC might be equal or superior to CPAP or that it might help to prevent intubation in children with moderate-to-severe respiratory distress.

Weaning from mechanical ventilation

10. Weaning from invasive mechanical ventilation

In children, limited guidance exists regarding weaning and extubation. Two reasons are the short duration of MV [1] and low extubation failure rates (2–20%) [19]. Various weaning concepts, including spontaneous breathing trials and closed-loop weaning, have failed to show superiority over clinical judgment [19, 20]. Yet, no single or combination of variables, including respiratory mechanics, gas exchange and patient ability to maintain work of breathing, reliably predicts weaning success [19].

Major topic	Top 10 items	Unproven concepts	Existing major observations	Data quality	Unknown/untested
Lung protective ventilation	(1) Low Vt or pressure limitation	Low Vt of 5–6 mL/kg IBW will improve outcome	No or even inverse relationship between Vt size/IBW and outcome Direct relationship between peak inspiratory pressure level and outcome	One meta-analysis assessing various cut-off Vt values, otherwise only retrospective or prospective observational studies	Is limiting distending pressures important and if yes to which level?
	(2) PEEP and lung recruitment strategies	PEEP titration according the oxygenation response or lung recruitment will improve outcome	PEEP can improve oxygenation and compliance in acute hypoxic respiratory failure and is well supported, especially by small children	Only observational studies No short- or long-term outcome studies	Is there a place for PEEP titration protocols? Are transpulmonary pressure measures important and might they help for targeting PEEP?
	(3) HFOV	HFOV as an early intervention will improve outcome	Rescue HFOV may not be beneficial for improving outcome	No adequately powered RCTs One retrospective data analysis from the Virtual PICU database	Is there a role of HFOV for lung protection in early or late, mild or severe PARDS?
	(4) Prone positioning	Prone positioning will improve outcome		One RCT including mild to severe PARDS patients: HFOV and CMV were used	Does prone position improve outcome in children with severe ARDS?
Concepts of assisting spontaneous breathing	(5) Neuromuscular blockade	Neuromuscular blockade for 24–48 h will improve outcome in severe ARDS	None	N/A	Does neuromuscular blockade for 24–48 h improve outcome in children with severe ARDS?
	(6) Patient–ventilator synchronization	Optimized patient–ventilator synchronization will improve outcome	So far, no difference in relevant outcome parameters between untriggered and triggered ventilator modes could be documented	Several RCTs, but of small size with the exception of neonatal trials One meta-analysis in children Several Cochrane meta-analyses for neonates	Does synchronization have an impact on outcome?
	(7) Level of support (including proportional assist)	Avoiding large Vts is important in spontaneous breathing ventilator-assisted children NAVA is lung protective	None	N/A	Are the sometimes observed excessive large Vts in spontaneous breathing ventilator-assisted children dangerous? How to dial in best NAVA support levels?
Non-invasive respiratory support in acute hypoxic and/or hypercapnic respiratory failure	(8) NIPPV	Avoiding intubation is improving outcome	Early application of NIPPV improves breathing pattern, respiratory muscle unloading and gas exchange The use of NIPPV the first day of mechanical ventilation is a risk factor for prolonged mechanical ventilation	Few observational studies 1 Cochrane meta-analysis	Does the use of NIPPV impact relevant outcome parameters? Which patient will benefit from NIPPV instead of invasive mechanical ventilation?
	(9) HFNC	HFNC is better than CPAP	HFNC is not superior, but even inferior to CPAP to prevent intubation in children with moderate-to-severe respiratory distress	2 RCTs	HFNC for which patient, when and in which setting?

Major topic	Top 10 items	Unproven concepts	Existing major observations	Data quality	Unknown/untested
Weaning from invasive mechanical ventilation	(10) Weaning and extubation readiness testing		No single or even combined measure of respiratory mechanics, gas exchange or patients work of breathing can reliably predict extubation success Passing the air-leak test does not predict extubation success in patients with upper airway obstruction	Small observational studies 1 subgroup analysis from an RCT designed to evaluate sedation strategies 1 concise review	Are weaning strategies important for intubated children, and if yes in which conditions?

Conclusions

To date, the practice of paediatric MV is predominantly based on anecdotal experiences, institutional belief and, to a certain degree, extrapolation of adult-based data. This is clearly an unwanted situation for such a commonly practised intervention in the paediatric critical care environment. Therefore, we must define objective assessments of clinically relevant outcome measures, better identify patient and disease groups to be studied for the effect of a tailored intervention, and consider using accumulated clinical information (e.g. adaptive design methodology) to create convincing evidence given the difficulties of small patient numbers and, therefore, often insufficient power for a definitive RCT.

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