



The Quagmire of Severe PARDS - To Oscillate or To Cannulate?

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ABSTRACT

In recent decades, the ventilatory management of pediatric acute respiratory distress syndrome (PARDS) has advanced remarkably. Enhancements in ventilator technology, multi-organ support strategies, and a deeper understanding of management principles have contributed to improved outcomes. However, a substantial number of children still experience hypoxemic respiratory failure that resists lung protective ventilation (LPV), even when utilizing neuromuscular blocking agents, prone positioning and recruitment maneuvers.

Keywords: pediatric acute respiratory distress syndrome

Introduction

In recent decades, the ventilatory management of pediatric acute respiratory distress syndrome (PARDS) has advanced remarkably. Enhancements in ventilator technology, multi-organ support strategies, and a deeper understanding of management principles have contributed to improved outcomes. However, a substantial number of children still experience hypoxemic respiratory failure that resists lung protective ventilation (LPV), even when utilizing neuromuscular blocking agents, prone positioning and recruitment maneuvers.

This presents intensivists with the challenge of selecting an appropriate rescue therapy. The PALICC guidelines advocate for high-frequency oscillatory ventilation (HFOV) for children with severe ARDS exhibiting a P_{plat} of 28 cm H₂O. Furthermore, they suggest considering extracorporeal membrane oxygenation (ECMO) for children with severe PARDS, particularly those with reversible causes of respiratory failure or candidates for lung transplantation. However, the timing and patient demographics that could benefit from these therapies remain inadequately defined. (1,2)

HFOV is characterized by sustained distending pressures and minimal tidal volumes (VT) (1-3 mL/breath) at a high frequency (300-900 breaths/min), utilizing rapid pressure oscillations to mitigate shear forces during the "inflate-deflate" process, ultimately enhancing oxygenation and ventilation while reducing the risk of volutrauma and atelectotrauma. The ARDS Network demonstrates that employing lower tidal volumes in ARDS patients can significantly lower mortality, and HFOV represents an optimal strategy for this approach. (3)

Gas exchange during HFOV operates through various mechanisms, including turbulence in larger airways, bulk convection, and complex flow patterns within airways. Additional physiological principles encompass Pendelluft—the movement between lung units—augmented diffusion, and the effect of cardiac action inducing gas mixing through agitation. In HFOV, both inspiration and expiration are active, leading to a decoupling of oxygenation and ventilation, where oxygenation is modulated by FiO_2 and mean airway pressure (mPaw), while ventilation is dictated by VT (amplitude) and frequency. (3)

Biologically, HFOV appears to benefit patients with less compliant lungs and heightened hypercapnia; however, clinical trials have failed to demonstrate a significant survival advantage. The pediatric literature on HFOV comprises predominantly of case series and observational studies from single centers. The OSCILLATE and OSCAR trials, which assessed HFOV against LPV in adults with moderate-to-severe ARDS, did not yield decisive evidence supporting its use as a rescue therapy when LPV is ineffective. Although one could argue that design and characteristic differences in those studies influenced outcomes, a mortality difference of 6% (35% vs. 41%) between groups points to some potential relevance. (It is crucial to note that these studies aimed to investigate HFOV as an early intervention rather than a rescue strategy). The RESTORE study indicated that using HFOV in ARDS patients correlated with a greater demand for sedation and extended hospital stays, suggesting a negative overall effect on ARDS management (4).

A recent meta-analysis incorporating eight randomized controlled trials indicated a survival benefit for HFOV (RR, 0.77; 95% CI, 0.61-0.98) and a decrease in treatment failure (RR, 0.67; 95% CI, 0.46-0.99). Nevertheless, overall survival rates were comparable, lacking risk adjustment, and revealing evident group disparities, placing limitations on the interpretability of clinical outcomes. All these findings have contributed to uncertainty regarding the role of HFOV and have led to hesitancy in its routine use for ARDS management. (5-9)

Concerns surrounding the safety and efficacy of HFOV stem not only from the limited availability of high-quality evidence but also from the potential risks reported in certain studies. Notably, tidal volumes are unmeasured and unmonitored during HFOV, raising the potential for significant volutrauma given the combination of high frequencies and unquantified volumes. Moreover, its application in hemodynamically unstable patients, particularly those with severe right ventricular dysfunction, is fraught with challenges, as the maintenance of elevated mean airway pressures and the need for deep sedation may necessitate large intravenous fluid volumes and vasoactive agents, resulting in potentially detrimental outcomes. The limitations imposed by reduced ability to conduct effective pulmonary hygiene and the risk of barotrauma in patients with specific lung pathologies further complicate the implementation of HFOV. (10-12)

Conversely, ECMO offers the potential to eliminate the need for tidal ventilation altogether. Venovenous (VV) ECMO may serve as a subsequent rescue option for select young patients experiencing reversible respiratory failure who have not responded to LPV following neuromuscular relaxation and prone positioning.

With the continuous refinement of ECMO techniques, it shows promise in selected patients with severe ARDS.

The documented experiences with HFOV and VV ECMO during the H1N1 pandemic provide valuable insights into these therapies' roles as emergency interventions for ARDS. (18-20). The CESAR study indicated that an ECMO-based protocol improved survival outcomes without severe disability. Insights from the 2009 H1N1 pandemic suggested variability in mortality rates, with ECMO recipients experiencing better outcomes. However, the EOLIA trial yielded inconclusive results regarding ECMO's advantage, particularly when initiated early. Data from pandemic studies and the EOLIA and CESAR trials suggest improved survival rates may occur when patients are referred early to specialized ECMO facilities. (13-17). Unfortunately, in many areas, access to ECMO remains limited due to high costs.

Another important concern that remains is the inability to uniformly define HFOV failure based on gas exchange metrics, that could potentially delay the activation of alternate rescue therapies like VV ECMO. The safety and efficacy of prolonged use of HFOV also remain uncertain; generally, 7 days of non-LPV treatment is considered a relative contraindication for VV ECMO (14). Consequently, valuable opportunities for patient recovery may be lost if HFOV is positioned as a bridging therapy particularly when its duration extends beyond the optimal window period to transition to ECMO

In our experience from a tertiary care centre in a developing nation, the outcomes in children with pediatric acute respiratory distress syndrome (PARDS) receiving early versus late high-frequency oscillatory ventilation (HFOV), although early HFOV was linked to significantly lower lactate levels, it did not show a survival advantage, with mortality rates at 65% for early versus 100% for late ($p=0.1$). Limitations did include the study's retrospective design, small sample size, and potential clinician bias in deciding the timing of HFOV initiation (21).

The recent Consensus Conference on Pediatric Acute Respiratory Distress Syndrome in Resource-Limited Settings (RLS) highlight 11 statements pertinent to PARDS management in these environments. They recommend integrating pulmonary and non-pulmonary ancillary therapies based on local evidence (as outlined by PALICC-2), including the implications of cost and availability (22) Further investigation into non-invasive ventilation (NIV) in respiratory failure contexts within RLS, including PARDS, is essential given that etiology, phenotype, and underlying mechanisms may differ fundamentally from those in developed nations. (23)

The ambiguity between ECMO and HFOV stems from differing clinical judgments in patient selection, with the absence of standardized protocols making it challenging to determine optimal therapy identification. The results of the individualized, physiology-based open lung HFOV approach characterized by high F and high initial $\Delta P_{proximal}$ with a liberal criterion for transitioning to HFOV represents an appealing option to explore. Too often HFOV is initiated without adequate monitoring of ventilator graphics and lung mechanics. Newer ventilators capable of measuring these lung parameters are becoming available and

may allow better monitoring. Without proper implementation, dismissing HFOV as ineffective may be premature (22).

Any endeavour to re-establish HFOV as a relevant rescue option should aim for research that (i) determines the optimal HFOV methodology and (ii) specifies patient populations that derive the most benefit. Until such substantial data are available, clinicians may continue with LPV and its adjuncts and proceed to ECMO if these options fail. The PROSpect study (ClinicalTrials.gov Identifier: NCT00180466) is set to address many of these questions.

Future research should focus on delineating which patient populations benefit most from LPV, HFOV, and VV ECMO, exploring the potential role of sub-phenotyping ARDS and prioritize evidence-based decision-making along with assessments of long-term functional outcomes (23,24).

Conclusion

Adopting lung-protective ventilation alongside adjuncts such as neuromuscular blocking agents, prone positioning, and recruitment maneuvers has proven successful for many ARDS patients. While high-frequency oscillatory ventilation may not belong in the standard repertoire of rescue therapies for ARDS, in resource-limited settings, its potential should not be dismissed prematurely. Future research should clarify the specific roles of LPV, HFOV, and ECMO, and prioritize evidence-based decision-making. Until more data emerges, ECMO should be contemplated carefully, with prompt referrals to ECMO-capable centers for patients with severe ARDS, provided no contraindications are present. Given the risk and economic aspects associated with different modalities, upcoming research should focus on delineating which patient populations benefit most from LPV, HFOV, and VV ECMO, along with assessments of long-term functional outcomes.

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