The Therapeutic Window for Oxygen

Extracorporeal membrane oxygenation (ECMO) is used as a rescue therapy for patients unable to achieve acceptable physiologic status despite maximum support. In patients with severe ARDS or pediatric ARDS, along with preserved cardiac function, venovenous (VV) ECMO is a therapeutic option to support gas exchange and minimize ventilator-induced lung injury while treating the patient's underlying condition. In 2017 Barbaro et al¹ published a review of neonatal and pediatric data from the Extracorporeal Life Support Organization (ELSO) registry. Between 2009 and 2015, a total of 21,907 reported ECMO cases had survival to hospital discharge of 61%. For the 9,280 subjects considered to be in the pediatric group (age 29 d to 17 y), survival to discharge was 60% in the respiratory cohort, 57% for cardiac subjects, and 43% in extracorporeal cardiopulmonary resuscitation cases. The same report highlighted an increased proportion of pediatric respiratory failure patients treated with VV ECMO compared with venoarterial ECMO; in 2009, 41% of cannulations were VV, which increased to 59% by 2015.¹

One of the most important questions surrounding the use of VV ECMO is how to maximize lung recovery. The 2017 ELSO adult guidelines² recommend the use of “lung rest” settings regardless of whether the patient is on venoarterial or VV ECMO. Typical rest settings include long inspiratory time, low plateau pressure (< 25 cm H₂O), low F_{IO₂} (< 0.30), and titrated PEEP. This post-cannulation version of lung protection is well described, but there is considerable variability in practice. In a 2014 survey of ELSO centers,³ the majority (77%) reported lung rest to be the primary goal of mechanical ventilation during ECMO. However, only 81% of participating centers reported using tidal volumes ≤ 6 mL/kg, including 34% who used ultraprotective tidal volumes ≤ 4 mL/kg. It stands to reason that, if it is important to avoid ventilator-induced lung injury prior to cannulation, maintaining lung-protective ventilation during VV ECMO is a critical management strategy.

In this issue of RESPIRATORY CARE, Friedman et al⁴ contribute an article reporting on their multicenter retrospective cohort study including subjects ages 14 d to 18 y treated

with VV ECMO between 2011 and 2016. Overall survival to ICU discharge was 68%. They noted variability in mechanical ventilator practices, though there was a clear trend toward the use of lung-protective settings. The key finding was that no ventilator parameter was associated with mortality except for F_{IO₂}. The authors rigorously controlled for underlying disease, severity of illness, ventilator settings,

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and ECMO settings when evaluating the impact of F_{IO₂}. The clearest illustration of this impact comes in Figure 2, a scatter plot of the S_{pO₂} and ventilator F_{IO₂} during ECMO. The points were divided into quadrants based on high or low S_{pO₂} and high or low F_{IO₂}, with high defined as S_{pO₂} > 85% and F_{IO₂} > 0.50. Survival to ICU discharge was significantly different based on quadrant (*P* = .002). As expected, the high S_{pO₂}/low F_{IO₂} group had the highest survival at 81%. What is particularly striking was that the high S_{pO₂}/high F_{IO₂} group showed diminished survival at 60%.⁴

Critical care providers have been increasingly aware of the harmful effects of high concentrations of inspired oxygen. As early as the 1940s, clinicians recognized an association between oxygen levels and retinopathy of prematurity.⁵ It has been demonstrated in the adult literature and confirmed in a pediatric study that hyperoxia is associated with increased ICU mortality following resuscitation from cardiac arrest.^{6,7} There is also evidence that hyperoxia has adverse effects on neurologic outcomes in traumatic brain injury.⁸ In the respiratory literature, it is well documented that using high levels of oxygen results in reactive oxygen species and tissue damage. It also results in absorption atelectasis, which can ultimately lead to ongoing alveolar injury.

Most lung-protective strategy guidelines include the use of PEEP for alveolar recruitment and tolerance of oxygen saturations between 88% and 92%. The purported rationale is to minimize exposure to supplemental oxygen and the potential for oxygen-mediated lung injury. While high concentrations of oxygen have demonstrated pulmonary toxicity, there is little discussion in the literature about the potential risks of oxygen at what are typically considered non-toxic concentrations. Specifically, the dose-response effect of lower oxygen concentrations has not been extensively studied. The current work implies that the therapeutic window of oxygen may be much narrower than previously assumed.

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The work of Friedman et al⁴ highlights the importance of meticulous management of every component of the lung-protective approach, including F_{IO_2} . It reminds us that the gap between survivor and nonsurvivor may be narrowed if F_{IO_2} is no longer regarded as an “easy button,” rather than a potent therapy with a specific therapeutic range. It remains an active point of debate whether higher pressure or oxygen is more toxic. In this particular patient cohort, with an average PEEP of 10 cm H_2O , it is hard to argue that higher F_{IO_2} was needed to combat otherwise unacceptably high ventilator settings. Instead, the data indicate that either our therapeutic goals for S_{pO_2} may be inappropriately high, or we are choosing the wrong knob to turn, or both. While prospective studies of F_{IO_2} management during VV ECMO are needed, it would be wise to treat oxygen with the same respect we have shown for pressure when considering lung protection. Currently the overall survival rate in pediatric ECMO patients is around 60%. We cannot afford to miss any opportunity for improvement.

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