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REVIEW

Possibilities and Considerations on the Use of ECMO as a Therapeutic Option for Patients with Acute Respiratory Distress Syndrome due to Viral Infections

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ABSTRACT
Management of acute respiratory distress syndrome due to viral outbreaks includes lower tidal volumes, lower inspiratory pressure, prone ventilation, and conservative fluid management. Extracorporeal membrane oxygenation (ECMO) has been proposed as rescue therapy in critically ill patients. However, in the absence of larger studies, the role of ECMO in reducing patient mortality rates remains unclear since studies that reported such effect, both during the current as well as during previous outbreaks, were based on small sample sizes, and their results are inconsistent. Furthermore, the use of ECMO might even be contraindicated in the presence of some conditions. Recurring to it has, therefore, to be discussed by qualified multi-disciplinary teams and based on a case-by-case strategy.

KEYWORDS: Extracorporeal Membrane Oxygenation; Extracorporeal Life Support; Acute Respiratory Distress Syndrome; Viral Outbreak.

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How ECMO works?
ECMO, also known as extracorporeal life support, is a form of cardiopulmonary support that may be indicated in cases of reversible acute severe cardiac or pulmonary failure unresponsive to conventional management.
Two main types of ECMO :veno-venous-ECMO, which provides respiratory support and can replace the gas exchange function of the lungs and minimize ventilator-induced lung injury, barotrauma, and oxygen toxicity; and veno-arteriel- ECMO, which provides both respiratory
and hemodynamic support[4].
ECMO does not provide direct support for organs other than the lungs or heart beyond increasing systemic oxygen delivery and mitigating ventilator induced lung injury [3].
The principle of ECMO is to collect the patient's venous blood into a pump connected to an oxygenator and restore the oxygenated and decarboxylated blood to the patient via a great vein (Veno-Veinous ECMO) or via a great artery (Veno-arteriel ECMO).
Currently, ECMO remains a complicated and high risk therapy; therefore, it requires adequate training and a well-qualified intensive care unit team

The World Health Organization Guidelines of ARDS Management
Currently, the WHO strategies on managing ARDS include lower tidal volumes (4-8mL/kg predicted body weight), lower inspiratory pressure (plateau pressure<30 cmH20), prone ventilation greater than 12 hours, and conservative fluid management. Use of ECMO has been advised for consideration in expert centers for patients who have refractory hypoxemia despite lung-protective ventilation [5].

EOLIA and CESAR Trials
The randomized EOLIA (ECMO to rescue acute lung injury in severe ARDS) trial involving patients with

severe acute respiratory distress syndrome stated that the analysis of the primary endpoint (mortality at 60 days) showed no significant benefit of early ECMO as compared with conventional mechanical ventilation; however, ECMO is safe and not associated with significantly higher mortality than standard management. When used as a rescue modality, ECMO may help improve survival in patients that would otherwise probably died [6-8].

In the CESAR trial (Randomized controlled trial and economic evaluation Controlled Trial of Conventional Ventilatory Support vs. Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure), a large multicenter randomized trial comparing consideration for ECMO versus conventional therapy for treating severe acute respiratory failure in adults, 180 patients were enrolled from 68 centers throughout the United Kingdom over a 5-year period (2001–2006). Ninety patients were randomized to consideration of ECMO, and 90 to continued conventional treatment. The results from this trial showed that the primary endpoint, survival to 6 months without disability, was significantly reduced in the ECMO group compared to the conventional treatment group (63% versus 47%; relative risk [RR] 69; (95% confidence interval [CI] 05–.097); p =.03) and support the use of ECMO in appropriately selected patients with life threatening acute respiratory failure [9-10].

Previous Experience of ECMO during Escalating Outbreaks

Since ECMO was proposed in the management of ARDS, it was considered as therapy of viral-related respiratory failure.

During the Influenza A (H1N1) pandemic of 2009, the benefits of ECMO in the management of ARDS were uncertain and controversial. Holzgraefe et al. and Pham et al. suggested that ECMO for H1N1 2009-related respiratory failure may have a favorable outcome [11,12]. Noah et al. found a mortality rate of 52.5% in ECMO group versus 27.5% in non-ECMO group [13], whereas Shinhiro et al. reported a survival rate of 35.7 % in a cohort of 14 patients and concluded that ECMO therapy for H1N1-related severe respiratory failure has very poor outcomes [14].

In turn, ECMO therapy during the Middle Eastern respiratory syndrome (MERS) outbreak appeared to be beneficial. Veno-Venous-ECMO use as rescue therapy was associated with lower mortality in severely hypoxemic patients who failed optimal ventilation strategies [15].

ECMO Use during COVID19 Pandemic

ECMO has been applied for refractory respiratory or cardiac failure secondary to severe myocarditis in COVID-19 patients [4]. WHO has recommended that consideration should be given to referring COVID-19 patients with refractory hypoxemia to expert centers capable of providing extracorporeal membrane oxygenation (ECMO) [16].

Extracorporeal Life Support Organization (ELSO) has provided selection criteria for ECMO referral. Patients who are under optimal ventilation strategies, neuromuscular blockade, appropriate PEEP, prone positioning, and pulmonary vasodilators and develop the following conditions: PaO2 /FiO2 less than 50 mmHg less than 3 hours or PaO2/FiO2 less than 60mm Hg for greater than 6 hours, or pH less than 7.20 and PaCO2 greater than 80 mmHg for less than 6 hours, may be suitable for ECMO referral whenever there is no contraindication [17].

Though there are no clinical trials of ECMO in COVID-19 patients, 11.5% of Chinese COVID-19 cases in the intensive care unit received ECMO [18]. Early cohort studies reported mortality of COVID-19- patients undergoing ECMO ranging from 42 to 94%. Zeng et al. reported a mortality rate of 41.7% in 12 COVID-19 patients with hypoxemic respiratory failure placed on ECMO [19]. In a cohort of 234 cases of COVID-19 related ARDS, 17 (7.25%) received ECMO, the mortality rate was 94.1% in ECMO group compared with 70.9% in non-ECMO group [20].

Thus, the role of ECMO in the management of ARDS-related to COVID-19 is unclear. However, we think that, in the presence of the endotheliopathy due to the infection, which activates inflammatory immune reaction and pulmonary vascular microthrombosis [19-20], the use of ECMO, which increases the inflammatory statute and the risk of coagulopathy, may be useless and even harmful.

CONCLUSION

To date, the role of ECMO in the management of ARDS–related viral outbreaks is unclear and controversial. In the absence of unanimous evidence of proven benefit, the decision to initiate ECMO in ARDS–related viral outbreak has to be discussed case by case by a high qualified multi-disciplinary team. The presence of endotheliopathy should be carefully assessed, and avoiding ECMO in its presence should be considered.

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COMPETING INTERESTS

The authors declare no competing interests with this case.

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