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Editorial

Delivering extracorporeal membrane oxygenation for patients with COVID-19: what, who, when and how?

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On 11 March 2020, the World Health Organization (WHO) declared novel coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a worldwide pandemic. Although most patients with SARS-CoV-2 are asymptomatic or experience only mild disease, approximately 14% develop severe disease associated with a high case fatality rate [1–3]. Patients with severe respiratory failure refractory to tracheal intubation, positive pressure ventilation, prone positioning, deep sedation, neuromuscular blockade and other conventional strategies might be considered for venovenous extracorporeal membrane oxygenation (VV-ECMO). The purpose of this editorial is to discuss evidence and current practices on the use of VV-ECMO in patients with COVID-19, and propose a flexible tool to support clinicians caring for such patients.

What?

Venovenous extracorporeal membrane oxygenation is the exchange of venous oxygen and carbon dioxide within an extracorporeal circuit. In severe respiratory failure, this is accomplished with an extracorporeal pump, circuit and membrane oxygenator together with percutaneous venous drainage and return cannulae [4]. Its use in very severe forms of acute respiratory distress syndrome (ARDS) is associated with a mortality benefit [5–7]. Therefore, ECMO might be considered for eligible patients with refractory respiratory failure unresponsive to conventional management [8]. Following the influenza A pandemic of 2009–2010, worldwide expertise and experience with the use of VV-ECMO increased significantly, as did clinician understanding as to which patients to accept and transfer to regional ECMO centres [9, 10]. That said, the COVID-19 pandemic presents several additional challenges for ECMO centres that may result in changes to the way in which decisions are made for referred patients and how ECMO is delivered more generally.

Who?

In England, ECMO for severe respiratory failure is commissioned centrally and delivered by five centres serving five geographical regions. Outside the SARS-CoV-2 pandemic, indications include age $\geq$ 16 years; reversible severe acute respiratory failure; Murray score $\geq$ 3.0; or uncompensated hypercapnia with pH $<$ 7.20. Relative contradictions include age $>$ 65 years; recent intracranial haemorrhage; other contra-indications to anticoagulation; and mechanical ventilation of the lungs for more than

7 days. Guidelines for pandemic ECMO usage, decision making support and triaging structure exist, but are limited [11–13].

Given the degree of SARS-CoV-2 infectivity, COVID-19 has resulted in large numbers of patients presenting to hospitals. This consumes a significant proportion of hospital resources, particularly for critical care areas [14]. Moreover, ECMO capacity at these levels of systemic stress is a finite resource and dependent on a range of external factors. As a result, the role of ECMO in a pandemic surge depends not only on the clinical characteristics of patients but also on the available resources. The use of ECMO during previous coronavirus outbreaks, including SARS and Middle East Respiratory Syndrome (MERS), was minor, particularly during SARS. Patients receiving ECMO for MERS seemed to have better survival than unmatched controls not receiving ECMO [15]. It is reasonable to assume that ECMO may provide survival benefits for selected patients with COVID-19–related severe respiratory failure, and gathering observational data will hopefully help clarify this issue.

Given the strain on resources inherent in a pandemic, ECMO may play a role until it becomes too burdensome on resources, although the timescale for this will vary from system to system [14]. Principles of precision-based clinical medicine should be applied for decisions as to which patients are likely to benefit most from ECMO during the COVID-19 pandemic. Early reports from China suggest several factors are associated with death, including: advanced age (> 65 years); the presence of comorbidities; extrapulmonary organ dysfunction; hyperinflammatory state (elevated C-reactive protein or interleukin-6); coagulation disorders (elevated D-dimer); leucopoenia; and myocardial injury [16, 17]. Patients with one or more of these risk factors are arguably less likely to survive ECMO. That said, eligible patients who develop COVID-19–related myocarditis leading to refractory cardiogenic shock may benefit from other forms of mechanical circulatory support including veno-arterial ECMO, which may confer a survival benefit in patients with non-injured lungs and fulminant myocarditis [18–20]. Use of a combination of pulmonary and extrapulmonary predictive survival models (e.g. respiratory ECMO survival prediction (RESP) and prediction of survival on ECMO therapy (PRESET) scores), if prospectively validated in COVID-19 patient cohorts, or prediction scores developed specifically for COVID-19 patients, might aid clinical decision making and precision delivery of ECMO [21]. Currently, for patients with COVID-19 referred for ECMO, many English centres use the RESP score (which should ideally be > 3) together with the clinical frailty score (which should ideally be < 3) to guide decisions. Those using mortality prediction systems should nevertheless be aware of their limitations [22]. Obesity seems to be associated with the development of severe respiratory failure in patients with COVID-19, and this presents technical challenges regarding cannulation and ongoing medical and nursing care in resource-limited settings. A body mass index > 40 $kg{\cdot}m^{-2}$ may be considered a relative contra-indication for VV-ECMO in such patients [11].

A multidisciplinary approach to patient selection is recommended involving ECMO clinicians, ECMO co-ordinators and intensive care nurses and physicians. Collaboration between ECMO centres is crucial to ensure appropriate service delivery and capacity to those patients with COVID-19–associated lung injury. Where feasible, equivocal ECMO candidates who fail to improve with conventional management during the pandemic surge, should be discussed across ECMO sites and within ECMO networks before ECMO is denied. Collaborative decision-making and consensus for borderline cases may increase the precision of clinical practice by reducing inconsistency, although such practices are not yet supported by prospective data.

When?

Ultimately, acceptance and retrieval should only be considered after all conventional strategies are exhausted [23, 24]. This includes failed trials of ventilation in the prone position and ideally < 7 days duration of mechanical ventilation. Insights from a trial investigating the use of ECMO for ARDS suggested that patients who were hypercapnic despite maximising lung-protective ventilation were the group of patients with the greatest mortality benefit [5]. In addition, this study showed that ECMO facilitated lung-protective ventilation through a reduction in mechanical power and driving pressure.

There are thought to be at least two phenotypes of hypoxaemic respiratory failure: those with normal or high compliance; and those with very low compliance together with very severe hypoxia. The mechanism of respiratory failure in these groups is uncertain, with pulmonary embolism a possible mechanism for those patients with compliant lungs. This theoretical notion is hypothesis generating and the decision to initiate ECMO or not should be based on standard criteria unless there is evidence directing the clinicians to do otherwise. In patients who are hypoxaemic with preserved pulmonary compliance, however, the diagnosis of pulmonary embolism should be considered early, ideally before the development of refractory respiratory failure requiring ECMO [25, 26]. Extracorporeal membrane oxygenation may not be

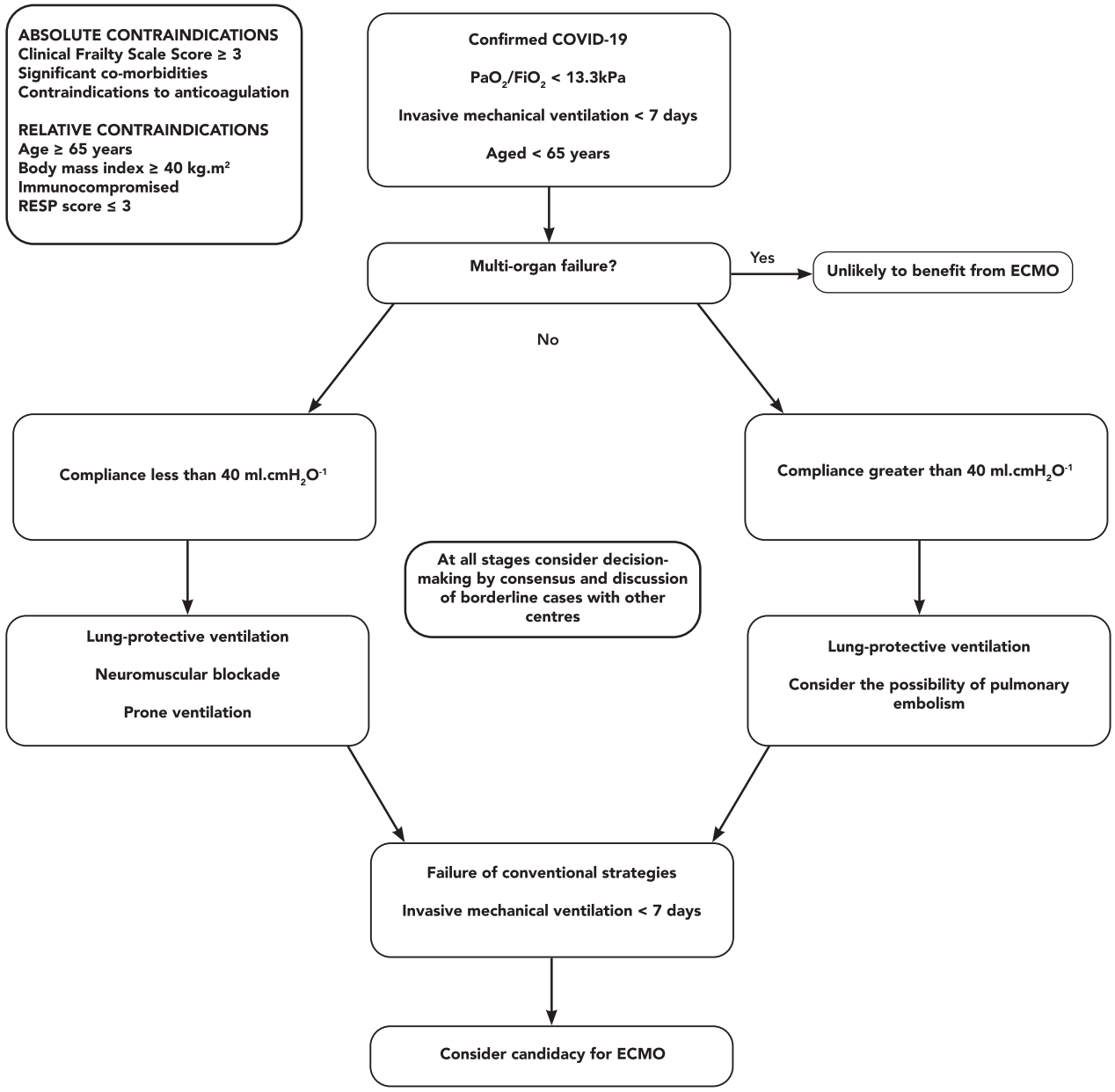

Figure 1 Proposed decision algorithm for initiation of venovenous extracorporeal membrane oxygenation (ECMO) in COVID-19–associated respiratory failure. RESP, respiratory ECMO survival prediction; PaO_2, partial pressure of oxygen in arterial blood; F_IO_2, fraction of inspired oxygen.

indicated in patients with preserved compliance until lung compliance worsens, either due to the underlying pathology or secondary iatrogenic ventilator-induced lung injury, or if hypoxaemia is severe enough to warrant the institution of ECMO.

How?

Patients who have severe respiratory failure, have been invasively ventilated for ≤ 7 days and meet general guidance criteria without extrapulmonary organ failure may be considered for ECMO [5, 11]. These criteria will likely be refined further as the pandemic progresses. Extracorporeal membrane oxygenation likely provides benefit through two mechanisms. The first is improved oxygenation at the point where conventional strategies have been exhausted [5, 27]. The second, and, likely more important mechanism for patients with low lung compliance, is facilitation of 'rest ventilation' [28].

Some centres transport ECMO candidates to an ECMO centre for assessment; expert conventional respiratory management; monitoring of clinical trajectory; and consideration for in-house cannulation and initiation of ECMO. However, in-house ECMO cannulation is resource intensive, and delaying the decision until the patient is within the centre itself enables ECMO clinicians to better assess and personalise potentially life-saving interventions short of ECMO. On the other hand, distant triage and mobile ECMO at the referring centre by retrieving ECMO clinicians for accepted candidates is common among other centres [29, 30]. This is one example of how practice between ECMO centres varies, and it is likely that other aspects of clinical management, including patient selection, may also differ [31]. Other clinical practice recommendations for ECMO use during a pandemic include avoidance of dual-lumen cannulae due to the added resource burden; central service co-ordination; avoidance of the commissioning of new centres; flexible nursing ratios; cohorting patients in open bays; avoiding the use of haemodiafiltration as compared with haemofiltration; and extending the shelf-life of primed circuits. We argue there is now enough guidance and evidence to propose a flexible decision-making aid for patients referred to ECMO centres (Fig. 1). As the COVID-19 pandemic progresses, relative and absolute contra-indications may change to ensure ethical distributive justice of resources.

Conclusion

Initiating ECMO during an outbreak of an emerging infectious disease is challenging. Patient selection based on standard criteria combined with the pulmonary mechanics profile of patients with COVID-19–associated lung injury, their response to conventional interventions, imaging and use of validated scoring systems may be the key to understanding how to fight this disease. This will potentially aid prognostication and enhance accuracy and precision before embarking on a high-risk and resource-intensive intervention.

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