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LESS IS MORE IN INTENSIVE CARE

Saying no until the moment is right: initiating ECMO in the EOLIA era

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The use of extracorporeal membrane oxygenation (ECMO) for refractory acute respiratory distress syndrome (ARDS) has increased considerably over the last decade [1]. The main reasons for this were the apparent benefits of ECMO during the influenza A(H1N1) pandemic of 2009 and the publication of a randomized trial ('Conventional ventilation or ECMO for severe adult respiratory failure' or CESAR) in the same year showing reduced mortality in patients treated in an ECMO-capable centre [2, 3]. The methodology of the CESAR trial, however, was criticized because of the lack of standardized management in the control arm and because 25% of patients in the treatment arm did not actually receive ECMO. This led to a new trial, 'ECMO to Rescue Lung Injury in Severe ARDS' (EOLIA) [4].

EOLIA had a number of strengths including its international, multicentre design and strict inclusion criteria. The primary outcome was 60-day mortality. Thirty-five percent of the treatment group had died by day 60 vs 46% of the control group (95% CI 0.55–1.04, $p = 0.087$). There was substantial cross-over (28%) from the control to the treatment arm. This was only permitted in patients with no irreversible multiorgan failure and arterial oxygen saturations (SaO_2) < 80% for > 6 h despite mandatory prone positioning, recruitment manoeuvres and pulmonary vasodilators. The secondary endpoint—death or crossover to ECMO—occurred in 57% of the control group (95% CI 0.47–0.82, $p < 0.001$). Those in the control group who eventually received ECMO had more advanced critical illness and hypoxia at the time of ECMO initiation, one-quarter of them suffered cardiac arrest, and they ultimately had higher mortality. For a subgroup of patients, EOLIA effectively compared early versus late ECMO, with significantly better outcomes in the early group.

The dramatic increase in ECMO for ARDS alluded to above occurred prior to publication of the EOLIA trial. It is possible that the prevailing enthusiasm for ECMO, comparable to many other areas of intensive care medicine [5], may lead to it being initiated too early. While ECMO is safer than in previous eras [6], it is still associated with significant risks, in particular bleeding [4, 7] and nosocomial infection [8, 9]. Other simpler interventions for ARDS should be employed before ECMO is considered but there is evidence that this is not practiced across much of the world.

The use of prone positioning was demonstrated in a randomized trial to be associated with reduced 90-day mortality (Hazard ratio for death, 0.44 (95% CI 0.29–0.67)) and less need for ECMO (1% vs 2.6%) [10]. A subsequent meta-analysis also demonstrated lower mortality in moderate-to-severe ARDS patients who were prone for > 12 h/day [11]. Nonetheless, prone positioning does not appear to be commonly used, with only 16% of patients with severe ARDS being proned in two recent studies [12, 13]. It is noteworthy that 90% of the control group in EOLIA was proned vs 66% of the treatment group and some advocate that even patients on ECMO may have better outcomes when proned [14]. While prone positioning is contraindicated in some ARDS patients, such as those with multitrauma or pregnancy, it is not contraindicated in the majority. It seems misguided to utilize ECMO in ARDS without a trial of prone positioning and it is much simpler and cheaper to try the latter first. The relative investments in building a respiratory ECMO program are not comparable in scope, evidence, or expense to prone positioning.

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Other strategies for managing patients with severe ARDS have been more controversial, such as the use of neuromuscular blockade. A randomized trial demonstrated reduced mortality with 48 h of early neuromuscular blockade [15] but a larger, more recent trial did not replicate these findings [13]. Routine neuromuscular blockade is no longer advocated but should still be used on a case-by-case basis.

One lesson from EOLIA was that ECMO should be used in severe ARDS only after the current best, evidence-based practices have been attempted [16]. It is important to establish as early as possible when these interventions fail, however, because delaying ECMO when it is indicated may lead to life-threatening hypoxia, progressive organ failure, and the risk of cardiac arrest. The conditions which had to be met in EOLIA to crossover from the control to the treatment group were a necessary part of the trial and relied on pre-trial clinical equipoise with regard to the merits of ECMO in this setting. Given the results of the trial, we do not recommend waiting until patients' $SaO_2 < 80\%$ for 6 h before initiating ECMO.

When should we say 'no' to ECMO? The answer requires distinguishing between 'no, never' and 'no, not yet'. The exclusion criteria in the EOLIA trial included those patients mechanically ventilated for > 7 days, pediatric patients, pregnant patients, those with morbid obesity, and those unlikely to survive despite ECMO [4]. With the exception of the final criterion, these should not be regarded as a list of contraindications to ECMO. Some groups not enrolled in the trial, such as pregnant women with ARDS, can be successfully supported with ECMO and have acceptable outcomes [17] but there is greater uncertainty about the precise role of ECMO in these patients. The list of absolute contraindications to which the reply would be 'no, never' is relatively short and centres on irreversible lung diseases for which transplantation is not feasible [7], or when the referral for ECMO has been made too late and the patient has suffered irreversible organ damage.

When should we say 'no, not yet'? If the patient has no contraindication to proning, any further discussion about ECMO should generally be deferred until proning has been attempted. If the patient does not have sufficiently severe respiratory failure as to meet the inclusion criteria for ECMO used in EOLIA, it is also reasonable to defer ECMO. This should only be done in the correct setting, however, such as when the patient is being managed in an experienced ECMO centre. Patient referrals from non-ECMO centres will need to be made earlier, particularly when the centre does not perform prone positioning, otherwise the interhospital transport team may have to cannulate equivocal cases simply in order to facilitate safe transfer [16].

Since the publication of EOLIA, at least three further studies have lent credible support to the use of ECMO in carefully selected patients with refractory ARDS [11, 18, 19]. It may be tempting to deploy ECMO without having first tried other approaches to management, but this temptation should be resisted. Less is more. Start with the basics such as prone positioning [10, 11] and avoiding harmful mechanical ventilation [20] before considering an expensive, complex and high-risk therapy such as ECMO [21].

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