CESAR: deliverance or just the beginning?

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Extracorporeal membrane oxygenation (ECMO) has been used for over 44 years as a rescue therapy for severe acute respiratory failure that is refractory to mechanical ventilation.[1] The process of establishing the clinical efficacy for this use has a long and fascinating history due to the unique ethical[2] and logistical challenges inherent in this form of support and the patient populations with this disease. In the 1970s[3,4] and 1980s,[5] uncontrolled observational reports suggested clinical benefits with the use of extracorporeal support, but these were not realised in subsequent randomised controlled trials (RCTs).[6,7] Over the past 40 years, the nature of extracorporeal lung support has evolved and changed. Major developments have included (a) a change in the mode of support from venoarterial to venovenous; (b) variation in the degree of support, from partial to complete; (c) emergence of an appreciation of ventilator-induced lung injury and protective lung ventilation; (d) a substantial reduction in ECMO circuit- and pump-induced complications; (e) a change in staffing and circuit monitoring practices in ECMO care; and (f) a broadening of patient populations considered appropriate for ECMO. These changes have allowed more intensive care units to provide ECMO, and the capacity and preparedness to provide ECMO seem to have increased remarkably in Australia and New Zealand.[8,9] A recent observational study suggested that, in experienced centres, mortality can be reduced without causing long-term harm.[10]

In 2001, the CESAR (Conventional Ventilation or ECMO for Severe Adult Respiratory Failure) trial[11] in the United Kingdom commenced enrolment. This study is, to date, the largest prospective adult ECMO trial conducted, with 103 referring hospitals and a single experienced ECMO unit having enrolled 180 patients. The much anticipated results were published in 2009, and the intention-to-treat analysis showed that significantly more patients allocated to consideration for treatment including ECMO survived to 6 months without disability when compared with those allocated to conventional management (relative risk [RR], 0.69 [95% CI, 0.05–0.97]; $P = 0.03$). This is a relatively large treatment effect, albeit with borderline precision and with a sample size that was less than initially planned. Reasonable concerns with regard to the basis of the efficacy, the quality of respiratory care in the control arm and the generalisability of the findings outside the UK have been raised.[12]

To what extent has the CESAR trial justified a role for ECMO support in patients with severe acute respiratory failure, and particularly acute respiratory distress syndrome (ARDS)? In this issue of the Journal, Moran and colleagues have updated their quantitative meta-analysis of RCTs of ECMO for ARDS and have shown that there is no significant effect on mortality.[13] As they have stated, "we conclude from this analysis that a null effect of ECMO is not excluded and there is only weak evidence for efficacy". In addition, they carefully examine the CESAR trial design, conduct and analysis, making several insightful comments about trial methodology, and in particular the stopping rules for RCTs. They then challenge the conclusion that ECMO is a justified form of support in adults with severe ARDS and call for further trials.

What can we take from the updated meta-analysis? Does it provide greater objectivity and generalisability, or is it misleading? The first and most obvious concern is the degree of clinical diversity in the three studies included in the meta-analysis. Is it reasonable to compare these interventions as "ECMO"? The clinical diversity is not merely due to the technical evolution of extracorporeal devices over the past 40 years, but also to the nature of the support itself. In the first ECMO RCT trial,[6] published in 1979, venoarterial ECMO was used to support respiratory failure, as insufficient experience with venovenous ECMO existed at the time. There was (not surprisingly) little appreciation of the need to provide protective lung ventilation in either trial arm. Consequently, acute lung injury was likely exacerbated by the introduction of ECMO (causing a reduction in pulmonary blood flow) and the maintenance of lung ventilation. As the patient population had mixed acute respiratory failure, there was little concordance with the ARDS patients enrolled in the CESAR trial. Conventional-arm care was associated with 90% mortality at 13 days, indicating that the features of this patient population and their therapy were very different from those of the CESAR population. Finally, although difficult to justify, the array of membrane oxygenators used in the 1979 study in no way resembled current components and almost certainly would have introduced more complications than in subsequent studies.

In the second study,[7] published in 1994, the form of extracorporeal lung support used was "conceptually different to ECMO"[5] and was used to provide partial lung support only, to facilitate another mode of lung ventilation: low-frequency positive-pressure ventilation. This was intended to provide lung rest by reducing lung motion to 3–5 sighs per minute and maintaining high positive end-expiratory pressure to preserve the functional residual capacity. The lung extracorporeal support, termed "extracorporeal CO_2 removal", was incapable of providing sup-

port for hypoxaemia, as circuit blood flow was only intended to reach 20%–30% of venous return. Oxygenation was primarily achieved by apnoeic oxygenation assisted by an intratracheal catheter.

In summary, the two older trials of "ECMO" included in the meta-analysis by Moran et al do not represent current extracorporeal oxygenation in terms of mode, extent of support and ventilator management. And although the meta-analysis techniques described seem extremely sophisticated, they cannot be expected to overcome what appears to be excessive heterogeneity, making interpretation extremely difficult. Discrepancies between meta-analyses and large RCTs are common,[14] so which should take precedence for clinical decision-making? Certainly the relatively small size of the meta-analysis (involving a total of 310 patients [a figure not mentioned by Moran et al and an important omission]) should raise caution, as smaller meta-analyses seem to be more useful for generating hypotheses for future research than for making firm conclusions about the clinical efficacy of medical interventions.[15]

Moran et al also express concern about the design and cost-effectiveness analysis of the most recent trial. The use of a composite endpoint (death or disability at 6 months) as the primary outcome measure in the CESAR trial had a significant effect on the final outcome and conclusions of the study, as the relative risk for the single endpoint of 6-month mortality was not significant (RR, 0.73 [95% CI, 0.52–1.03]; $P=0.07$). Caution when interpreting composite endpoints is appropriate.[16] In this instance, the primary endpoint was adapted for an adult population from the endpoint used in a UK neonatal ECMO trial,[17] in order to include outcomes of similar clinical importance and to address existing clinical concerns.

The mortality assumptions made by the CESAR investigators — and thus, sample size calculations (which affected the observed clinical effect in terms of precision) — are limitations of the CESAR trial. However, these did not affect the treatment effect observed. The sample size was reduced after 2 years and the study still required 5 years to recruit 180 patients, despite the withdrawal of all government funding for adult ECMO for respiratory support outside the trial within the UK (population 55 million). The proposed recruitment rate of 80 patients per annum was more than twice the realised rate.[18] We can only assume that investigators went to great lengths to maximise enrolment.

Clearly, the precise contribution of ECMO to the observed beneficial treatment effect remains debatable in view of possible differences in mechanical ventilation between study groups and the incomplete requirement for ECMO in the treatment arm. Despite this, the investigators have expressed confidence in the clinical effectiveness of ECMO

for severe acute respiratory failure on the basis of their results. Readers will draw their own conclusions.

How should intensivists view the place of ECMO for respiratory failure in 2010, and do we need further multicentre RCTs? ECMO is not a simple intervention. In clinical practice, ECMO outcomes depend on many factors, such as local expertise, staffing and training processes, program leadership, and supporting teams such as surgical teams, perfusionists and other health care teams. Multicentre RCTs conducted in centres without formally established and well organised ECMO clinical services may not achieve the full benefit (and may increase the harm) that the technology can deliver.[19] The benefits from complex care processes (such as ECMO and medical emergency teams) are not always apparent when assessed by multicentre RCTs.[19,20] Nevertheless, a French-led multicentre trial of ECMO for adults with severe ARDS is soon to commence.

While awaiting the next instalment, clinicians might reflect on the outcomes reported from the use of ECMO in Australia and New Zealand during the recent influenza A(H1N1) pandemic.[8] We recently updated the final outcomes of this cohort and have reported that ECMO was associated with a hospital survival rate of 75%.[21] Although we fully recognise that observational studies can be influenced by selection and other forms of bias, there seems little doubt that, based on the severity of illness documented, this patient group would probably have had a significantly lower survival rate if ECMO had not been used. We therefore contend that ECMO is likely to be life-saving if used in appropriately selected patients with ARDS, and that RCTs (and indeed meta-analyses) may not be the most appropriate tools to determine the efficacy of such a complex intervention.

For the moment, the use of this therapy will remain driven by enthusiasts, most of whom would have taken heart from the fact that the treatment effect observed in the CESAR trial reflects the benefits derived from an experienced, well led and well staffed ECMO clinical service. Others will need more convincing.

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