

Extracorporeal Membrane Oxygenation—Understanding the Evidence: CESAR and Beyond

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Presented at Perfusion Downunder, Queenstown, New Zealand, August 5–8, 2010.

Abstract: Extracorporeal membrane oxygenation (ECMO) has been used for nearly 40 years for treating life threatening respiratory failure. Two historic randomized trials in adults, conducted using outdated techniques, did not show a survival advantage. However, recent case series and a large randomized controlled trial have demonstrated good outcomes from ECMO in adults. The CESAR trial, a large, multicenter, randomized trial comparing consideration for ECMO versus conventional therapy for treating severe acute respiratory failure in adults, has recently been published. The results and implications of this controversial trial are analyzed here, and a discussion of the problems inherent in assessing complex interventions in critically ill patients is provided. Additionally, the outcomes from ECMO from pandemic H1N1 influenza in Australia and New Zealand during the winter

of 2009 are reviewed. Despite the inherent limitations of the methodology of the CESAR trial, the results support the use of ECMO in appropriately selected patients with life threatening acute respiratory failure. Treatments such as ECMO are extremely difficult to assess by randomized controlled trials. Observational data demonstrate excellent results from ECMO for treating patients with life threatening respiratory failure caused by pandemic H1N1 influenza, and have greatly influenced practice in Australia and New Zealand. Used as part of a multi-modal approach to treating acute respiratory failure in adults, ECMO is an important, potentially life saving, technique. **Keywords:** acute respiratory distress syndrome, acute lung injury, extracorporeal membrane oxygenation, extracorporeal life support, acute respiratory failure, pneumonia, adult. *JECT. 2011;43:P23–P26*

Extracorporeal membrane oxygenation (ECMO) has been used for treating severe respiratory failure in adults for nearly 40 years (1). Recently, interest in ECMO has increased. This has come about for several reasons. First was publication of the CESAR (conventional versus extracorporeal membrane oxygenation for severe adult respiratory failure) trial in 2009, which reported a substantial positive treatment effect for ECMO compared to conventional therapy in adults with life-threatening acute respiratory distress syndrome (ARDS) (2). Second was the publication of observational data demonstrating excellent outcomes from patients with pandemic H1N1 influenza treated with ECMO in Australia and New Zealand (3). Third was recent technological developments, particularly the introduction of polymethylpentene oxygenators, which have greatly improved the safety and efficacy of ECMO.

In this paper, the evidence for using ECMO for treating severe respiratory failure in adults is reviewed, with

particular emphasis on the CESAR trial. The difficulties inherent in evaluating complex treatments, such as ECMO, are also explored. The rationale, indications and contraindications, and technical aspects of using ECMO for treating severe respiratory failure in adults have recently been reviewed (4,5).

EARLY TRIALS

Following the first – and successful – use of ECMO in 1972 treating a young man with ARDS following a motor vehicle accident, in 1974 the United States National Institutes of Health initiated a randomized controlled trial (RCT) of ECMO versus conventional treatment for treating acute, severe respiratory failure. The trial involved 90 patients, 42 of whom received partial-flow veno-arterial (VA) ECMO. Both the treatment and the control groups received mechanical ventilation with high inflation pressures and low positive end-expiratory pressure (PEEP). Blood product administration in the ECMO group averaged 2.5 L/day. The results of this trial, published in 1979 by Zapol and colleagues, demonstrated a mortality of

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approximately 90% in both the treatment and control groups (6). This outcome greatly reduced enthusiasm for adult ECMO.

A second RCT of ECMO was published in 1994 involving 40 patients (7). This trial compared mechanical ventilation using an inverse ratio of inspiratory and expiratory times (a technique popular at the time) with low-flow (20–30% of normal cardiac output) veno-venous (VV) ECMO. Blood product administration in the ECMO group averaged 2.7 L/day (versus .2 L/day in the control group) of red blood cells and 2.1 L/day (versus .1 L/day in the control group) of fresh frozen plasma. The investigators had only provided ECMO to seven sheep and one human prior to commencing the study. Survival was 44% in the control group and 33% in the ECMO group.

Both of these trials have limited applicability to the modern practice of ECMO. In both trials, positive pressure ventilation with airway pressures that exceed current recommendations (8) for lung protective ventilation was used in patients receiving ECMO. Thus, one of the main potential benefits of ECMO – lung rest – was not achieved. Second, blood product administration was extremely high in patients receiving ECMO, which would be very atypical for modern ECMO for respiratory failure. Third, lower blood flows were used compared to current practices, particularly in the trial by Morris and colleagues (7). Indeed, in the Morris trial, extracorporeal blood flow was sufficient only to remove carbon dioxide. Oxygenation was achieved through a combination of low frequency mechanical ventilation (but not lung protective ventilation) and tracheal insufflation of oxygen. It is now known that hypercarbia is well tolerated in patients with ARDS, and, indeed, this is the basis of the permissive hypercarbia that is central to modern lung protective ventilation (9). Fourth, VA ECMO was used in the Zapol trial, whereas today VV ECMO is considered the appropriate form of extracorporeal support for acute respiratory failure. Fifth, mortality in both the treatment and the control arms was very high in the Zapol study (6). Finally, the inexperience of Morris and colleagues with extracorporeal support prior to commencing their study is startling, given the complex nature of the technique.

Despite the poor results from these two RCTs, good outcomes have been reported from nonrandomized case series from experienced ECMO centers, with survival rates for acute respiratory failure of 55–76% being achieved in patients with predicted mortalities of 70–80% (10–13).

THE CESAR TRIAL

In 2009, the much-anticipated results of the multicenter, randomized CESAR trial were published in the *Lancet* (2). In this trial, consideration for VV ECMO was compared with continued conventional treatment at one of 68

“conventional treatment” centers throughout the United Kingdom, for adults with severe ARDS. Patients randomized for consideration of ECMO were transported to the Glenfield Hospital, Leicester, England. Once at Glenfield patients were subjected to a standardized ARDs management protocol. Patients not responding to this protocol within 12 hours were commenced on VV ECMO. Patients randomized to conventional treatment were treated at (or transported to) one of 92 eligible “conventional treatment” hospitals throughout the United Kingdom, where they received “the best critical care practice available” as determined by the treating hospital.

Of 766 eligible patients from 148 centers, 180 were enrolled from 68 centers over a 5-year period (2001–2006). Ninety patients were randomized to consideration of ECMO and 90 to continued conventional treatment. Eligible patients were aged 18–65 years with severe but potentially reversible respiratory failure, and an acute lung injury score (from all four variables – PaO₂/FiO₂ ratio, PEEP, lung compliance, and chest radiograph appearance – and FiO₂ = 1) of 3.0 or higher, or uncompensated hypercapnia with a pH < 7.20 despite optimum conventional treatment (14). Patients were excluded if they had been on high pressure (peak inspiratory pressure > 30 cm H₂O) or high FiO₂ (>.8) ventilation for more than 7 days or had contraindications to ECMO, particularly a contraindication to limited heparin anticoagulation.

The primary end-point, 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). Average health care costs per patient were more than twice as high for patients allocated to consideration for ECMO, with a difference in cost of £40,544 (95% CI 24,799–56,288). However, consideration for ECMO was associated with a gain of .03 quality-adjusted life-years at 6-month follow-up and a lifetime predicted cost-utility of about £19,000 per quality-adjusted life-years, which is well within the range regarded as cost-effective by health technology assessment organizations.

There are several issues with the CESAR trial that warrant further discussion (15–17). First, and most important, is non-use of ECMO in the treatment arm. Twenty-two patients randomized to consideration of ECMO did not receive it. Three patients died prior to transport and two died during transport. Seventeen patients did not require ECMO following application of the standardized ARDS treatment protocol at the Glenfield Hospital. Mortality in this sub-set of 17 patients was 18%. Thus, it is important to recognize that CESAR is a trial in which standard treatment is compared to referral to an ECMO-capable hospital for consideration for ECMO. In the sense that this strategy mirrors real-world practice, this component of the trial design is reasonable.

The primary outcome variable in the CESAR trial is a composite (freedom from death or major disability at 6 months). Composite outcomes must be interpreted cautiously, and some authors recommend reporting each component of the composite separately (18). While more patients in the treatment group survived, this difference was not statistically different (RR .73, 95% [CI .52–1.03]; $p = .07$). Data in the CESAR trial were analyzed on an intention to treat basis, which is appropriate. However, when mortality data are analyzed on the basis of the treatment assigned, the difference between the groups was even less (RR .92 [95% CI .65–1.29]) (16).

The cost-effectiveness benefit has also been questioned (16), based on the authors' own admission that "the cost-utility analysis is associated with substantial uncertainty." Two further criticisms with the trial include the long recruitment period, during which time mortality from ARDS could have been expected to fall, and the fact the study was powered to an expected mortality in the conventional treatment group of 70%, which was substantially higher than the actual mortality of 50% (16).

DIFFICULTIES IN TRIAL DESIGN AND PATIENT SELECTION

The CESAR trial highlights several problems with conducting RCTs on complex treatments such as ECMO. Such trials are logistically very difficult to perform. Recruitment took 5 years and was at half the rate that was predicted (19). It is possible (perhaps likely) that the beneficial treatment effect demonstrated in the CESAR trial related to superior all round care at the Glenfield Hospital compared to that available at the conventional treatment hospitals, irrespective of whether ECMO was used (15).

Outcome from ECMO depends on much more than simply the provision of an extracorporeal circuit. Experienced ECMO centers are usually expert at conventional treatment also. For treating respiratory failure, ECMO should be part of an integrated approach to managing patients with severe ARDS (10). An integrated ARDS service should include expertise in conventional therapy (e.g., lung protective ventilation, fluid therapy, hemodynamic management), access and familiarity with other advanced respiratory therapies (e.g., high-frequency oscillation ventilation, prone positioning, inhaled nitric oxide), suitably trained and experienced health professionals (medical, nursing, perfusion), and access to ancillary services (e.g., surgeons familiar with operating on patients receiving extracorporeal support).

When clinicians attempt to define the impact of a single treatment by conducting a large multicenter RCT powered to mortality, the outcome is often a negative study. This has been the case with recent multicenter RCTs in critical care,

despite excellent trial design (20–24). Nevertheless, it is possible that some of these treatments studied (dopamine (20), high-dose renal replacement therapy (21), intensive glucose control (22), albumin fluid therapy (23), or corticosteroids (24)) do impact (positively or negatively) mortality in appropriately selected patients. Even pulse oximetry, a universally accepted monitoring tool, has not been shown to improve survival when subjected to a large RCT (25,26). Thus, demonstrating a survival benefit for ECMO over best-practice conventional treatment is likely to be very difficult.

THE AUSTRALASIAN EXPERIENCE WITH PANDEMIC H1N1 INFLUENZA VIRUS INFECTION

The impact of pandemic H1N1 influenza infection on the requirements for hospital and intensive care unit (ICU) admissions in Australia and New Zealand during the winter of 2009 was substantial (3). During a 3-month period (June 1–August 31) 722 patients with confirmed pandemic H1N1 influenza virus infection were admitted to ICUs in Australia and New Zealand, representing 5.2% of ICU bed occupancy. A high percentage, 64.6%, were mechanically ventilated and overall mortality was 14.3%. Sixty-eight patients were treated with ECMO, of whom 48 (71%) survived to hospital discharge (27). Patients receiving ECMO had a median (interquartile range) PaO₂/FiO₂ ratio of 56 (48–63) mmHg, median PEEP of 18 (15–20) cm H₂O, and an acute lung injury score of 3.8 (3.5–4.0). The median acute lung injury score in this cohort is slightly higher than patients in the CESAR trial. This intense utilization of ECMO coupled with the high rate of survival amongst a very sick group of patients greatly increased the experience and profile of ECMO amongst Australasian intensivists. Despite these data being observational, it is likely several patients treated with ECMO survived who would otherwise have died.

CONCLUSION

The question as to whether ECMO improves outcome in patients with severe life threatening respiratory failure remains unanswered. In this author's opinion, this question is unlikely to be unequivocally resolved with further RCTs. However, it seems probable that ECMO, as part of an integrated approach to managing severe ARDS, is beneficial in appropriately selected patients.

REFERENCES

1. Hill JD, O'Brien TG, Murray JJ, et al. Prolonged extracorporeal oxygenation for acute post-traumatic respiratory failure (shock-lung syndrome). Use of the Bramson membrane lung. *N Engl J Med.* 1972; 286:629–34.

2. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): A multicentre randomized controlled trial. *Lancet*. 2009;374:1351–63.
3. Webb SA, Pettita V, Seppelt I, et al. Critical care services and 2009 H1N1 influenza in Australia and New Zealand. *N Engl J Med*. 2009;361:1925–34.
4. Sidebotham D, McGeorge A, McGuinness S, Edwards M, Willcox T, Beca J. Extracorporeal membrane oxygenation for treating severe cardiac and respiratory disease in adults: Part 1—overview of extracorporeal membrane oxygenation. *J Cardiothorac Vasc Anesth*. 2009;23:886–92.
5. Sidebotham D, McGeorge A, McGuinness S, Edwards M, Willcox T, Beca J. Extracorporeal membrane oxygenation for treating severe cardiac and respiratory failure in adults: Part 2—technical considerations. *J Cardiothorac Vasc Anesth*. 2010;24:164–72.
6. Zapol WM, Snider MT, Hill JD, et al. Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. *JAMA*. 1979;242:2193–6.
7. Morris AH, Wallace CJ, Menlove RL, et al. Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO₂ removal for adult respiratory distress syndrome. *Am J Respir Crit Care Med*. 1994;149:295–305.
8. Girard TD, Bernard GR. Mechanical ventilation in ARDS: A state-of-the-art review. *Chest*. 2007;131:921–9.
9. Laffey JG, O’Croinin D, McLoughlin P, Kavanagh BP. Permissive hypercapnia—role in protective lung ventilatory strategies. *Intensive Care Med*. 2004;30:347–56.
10. Lewandowski K, Rossaint R, Pappert D, et al. High survival rate in 122 ARDS patients managed according to a clinical algorithm including extracorporeal membrane oxygenation. *Intensive Care Med*. 1997;23:819–35.
11. Linden V, Palmer K, Reinhard J, et al. High survival in adult patients with acute respiratory distress syndrome treated by extracorporeal membrane oxygenation, minimal sedation, and pressure supported ventilation. *Intensive Care Med*. 2000;26:1630–7.
12. Mols G, Loop T, Geiger K, Farthmann E, Benzing A. Extracorporeal membrane oxygenation: A ten-year experience. *Am J Surg*. 2000;180:144–54.
13. Ullrich R, Lorber C, Roder G, et al. Controlled airway pressure therapy, nitric oxide inhalation, prone position, and extracorporeal membrane oxygenation (ECMO) as components of an integrated approach to ARDS. *Anesthesiology*. 1999;91:1577–86.
14. Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. *Am Rev Respir Dis*. 1988;138:720–3.
15. Zwischenberger JB, Lynch JE. Will CESAR answer the adult ECMO debate? *Lancet*. 2009;374:1307–8.
16. Moran JL, Chalwin RP, Graham PL. Extracorporeal membrane oxygenation (ECMO) reconsidered. *Crit Care Resusc*. 2010;12:131–5.
17. Pellegrino VA, Davies AR. CESAR: Deliverance or just the beginning? *Crit Care Resusc*. 2010;12:75–7.
18. Freemantle N, Calvert M. Composite and surrogate outcomes in randomised controlled trials. *BMJ*. 2007;334:756–7.
19. Peek GJ, Clemens F, Elbourne D, et al. CESAR: Conventional ventilatory support vs. extracorporeal membrane oxygenation for severe adult respiratory failure. *BMC Health Serv Res*. 2006;6:163.
20. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med*. 2010;362:779–89.
21. Bellomo R, Cass A, Cole L, et al. Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med*. 2009;361:1627–38.
22. Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360:1283–97.
23. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med*. 2004;350:2247–56.
24. Steinberg KP, Hudson LD, Goodman RB, et al. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med*. 2006;354:1671–84.
25. Moller JT, Johannessen NW, Espersen K, et al. Randomized evaluation of pulse oximetry in 20,802 patients: II. Perioperative events and postoperative complications. *Anesthesiology*. 1993;78:445–53.
26. Moller JT, Pedersen T, Rasmussen LS, et al. Randomized evaluation of pulse oximetry in 20,802 patients: I. Design, demography, pulse oximetry failure rate, and overall complication rate. *Anesthesiology*. 1993;78:436–44.
27. Davies A, Jones D, Bailey M, et al. Extracorporeal membrane oxygenation for 2009 influenza A(H1N1) acute respiratory distress Syndrome. *JAMA*. 2009;302:1888–95.