Editorial

Half-empty or half-full?—interpretation of the EOLIA trial and thoughts for the future

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The inability to provide adequate cardiovascular and pulmonary support in acutely ill patients led to the concept of using cardiopulmonary bypass as temporary mechanical support to patients failing conventional medical treatment (1). Early efforts were plagued with severe bleeding and hemolysis, however, until the advent of the membrane oxygenator by Clowes in 1956 (2). While trials of extracorporeal membrane oxygenation (ECMO) in adults found no survival benefit over conventional care, use of ECMO in infants demonstrated a survival benefit (3). The H1N1 influenza outbreak, coupled with the availability of low-resistance oxygenator devices, cannulas with improved flow dynamics and centrifugal pumps which created less hemolysis, resulted in a significant rise in the use of adult ECMO, and demonstrated a survival benefit (4,5).

Other modalities have been evaluated for improvement in outcomes in patients with severe respiratory failure, with the acute respiratory distress syndrome (ARDS) network trial of low tidal volume ventilation (adjusted for plateau pressures less than 30 cmH_2O) shown to decrease mortality (6). Studies of positive end-expiratory pressure (PEEP) and alternative modalities such as high frequency ventilation have also been evaluated but failed to demonstrate an improvement in mortality in randomized trials (7). Combining interventions and ventilation management algorithms have also had variable results. Grasso and colleagues evaluated the benefit of utilizing the stress index to adjust PEEP on an individual basis, and while no large change in outcome was noted, inflammatory mediators, which may impact lung injury, were reduced in this report (8). While theoretically evaluating the stress index may be of benefit during ARDS ventilator management, patients may still develop hypercapnia or hypoxia which cannot be reversed. Recent work and metanalyses have found that prone positioning may also be of benefit. Prone positioning has improved oxygenation and survival in multiple reports, and is now recommended for patients with severe respiratory failure as an early intervention (9-11). Neuromuscular blockade during the early phase of severe respiratory failure has also shown benefit (12,13).

Secondary effects of mechanical ventilation, coupled with hypoxia, may induce organ failure outside the lung itself. High intrathoracic pressures can cause elevated pulmonary vascular resistance, which can then decrease right ventricular performance. Additionally, patients with ARDS may develop contractile dysfunction independent of afterload (14). Diminished cardiac output can lead to need for high levels of volume resuscitation or vasoactive medications, which may contribute to inadequate tissue oxygenation and set off the multiple organ dysfunctions often seen in patients with severe ARDS. The ability to provide oxygenation, ventilation and hemodynamic support with the use of ECMO may allow a decrease in ventilator settings and vasoactive medications and mitigate some of the associated complications encountered during the management of ARDS (15,16).

In order to determine whether ECMO would reduce mortality associated with ARDS, a multicenter randomized

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controlled trial (CESAR) was conducted in the UK. The CESAR trial found that 6 months survival was dramatically improved in those patients randomized to ECMO. The trial, however, was criticized for the fact that some patients referred to the ECMO center improved without receiving ECMO support and that those patients randomized to conventional mechanical ventilation (CMV) were not mandated to a specific algorithm of ventilator management (17). To help answer some of the critics of the CESAR trial, Combes and colleagues constructed a multicenter international randomized controlled trial of ECMO versus CMV. The EOLIA trial randomized patients to ECMO or a CMV arm, recruited 249 patients over a 6-year period and was recently published in the *New England Journal of Medicine* (*NEJM*). Patients received venovenous ECMO support using recent ECMO technology with centrifugal pump, hollow-fiber oxygenators and cannulas (Maquet-Getinge, Germany). All patients on ECMO received a mechanical ventilation strategy with plateau pressures maintained below or equal to 24 cmH_2O. The control (CMV) arm utilized a high PEEP, high recruitment strategy while limiting the tidal volumes to 6 cc/kg adjusted to maintain plateau pressures to less than 30 cmH_2O. A rescue ECMO arm for crossover from CMV was allowed if hypoxemia with arterial saturations <80% for >6 hours persisted in spite of a trial of prone positioning, recruitment maneuvers and inhaled nitric oxide or inhaled prostacyclin. The treating physician also had to feel that there was no irreversible multi-organ failure and that ECMO might change the outcome.

The trial was stopped after approximately 75% recruitment when the monitoring board determined the primary endpoint of a 20% decrease in mortality in the ECMO group was not going to be achieved. Mortality was reduced 11% in favor of the ECMO group (35% *vs.* 46%) while the relative risk was 0.76 (CI: 0.55–1.04) and did not reach statistical significance. Of note, 28% (35/125) of control patients received rescue ECMO in a crossover arm. The crossover patients had a higher plateau pressures, lower respiratory system compliance and radiographically more extensive disease. In addition, these patients had higher serum lactates and rising vasopressor support. Prior to crossover 7 patients were noted to have severe right heart failure and required venoarterial ECMO, with 9 patients suffering cardiac arrest and 6 undergoing ECMO during active CPR. These patients had the highest mortality rate of 57%. Pre-determined secondary analysis of death by day 60 in the ECMO group and as either crossover to ECMO from CMV or death in control group patients found that relative risk was 0.62 (CI: 0.47–0.82, P<0.001) and that mortality was 35% in the ECMO group and 58% in the control arm. Other secondary analyses (ventilator-free days, renal failure, and cardiac failure) were also in favor of ECMO patients. Bleeding requiring transfusion and thrombocytopenia were greater in the ECMO group.

So, where do the results of the EOLIA trial leave us? To those who already believe that ECMO can help save lives, it confirms that ECMO plays an important role in support of patients with severe respiratory failure. To those who do not accept ECMO as a helpful modality, it may do little to change their opinion. Several things from EOLIA are clear however: to those who fear use of ECMO, this study confirms that it is not associated with an increase in death in patients with severe respiratory failure. In addition, although study design allowed for an "ethical" crossover for CMV patients to ECMO, this feature had a major impact on the trial outcome. It is important to note that 28% of patients were "crossed-over"—implying that almost a third of clinicians felt that patients under their care, despite interventions such as prone positioning, neuromuscular blockade and "lung-protective ventilation", felt that their patients were going to die without ECMO as a rescue maneuver. Another feature of the trial was that death in the CMV group was less than predicted—and that in the control arm, over 90% of patients received prone positioning and all received neuromuscular blockade. Thus, it would seem that control group patients received what currently are best recommendations for care of severe respiratory failure—and still almost one third of patients were failing and ECMO was the next intervention chosen by the bedside clinician. This is similar to "real life"—clinicians use what is best available for their patients and then look for other modalities which may have additional benefit. As 39% of the patients in EOLIA were transported from non-ECMO sites, having a strong relationship with an ECMO center that can provide transport of patients on ECMO is needed.

Another point to be mentioned is that study enrollment was 0.06 pts/unit/month, and it is estimated that total planned enrollment might have taken over 15 years to complete. As the trial itself took over 10 years from conception to completion, changes in care of severe respiratory failure patients would seem to have decreased mortality over this period, although death rates remain high (40–55% in most series). Changes in management that occur during a RCT as large as EOLIA is an additional

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obstacle in performing trials of complex diseases which affect only a small portion of the overall population. Failure to recruit enough patients has stalled other trials, and while the monitoring board for EOLIA used appropriate statistical methods to halt the trial without completion of enrollment, the trend towards improved outcomes with the ECMO patients makes one wonder what results would have been if 100% enrollment was reached. This aspect of the trial was also commented on in the editorial which accompanied the EOLIA publication in the *NEJM* (18).

It is unlikely that another RCT of ECMO will be undertaken—given that the EOLIA trial took almost 10 years from conception to completion—but it does provide new and important data. What the EOLIA trial demonstrates is that in patients who are not responding to recommended therapies for severe respiratory failure (low pressure, low tidal volume ventilation, trials of prone positioning, neuromuscular blockade, pulmonary vasodilators) ECMO should be considered early on, as responses to these interventions can be assessed within a few hours to days and ECMO can provide additional support which can be beneficial. One last caution involves the current rapid expansion of ECMO programs throughout the world. While ECMO can be a life-saving modality, it does require expertise and training to provide optimal care. The ECMO centers within EOLIA were well-experienced and had mobile ECMO capacity as well. Any center providing ECMO should make adequate training and education mandatory prior to implementing it as a patient care service. Further, all patients receiving ECMO should be entered into an international database [the Extracorporeal Life Support Organization (ELSO) registry] with outcomes and complications reported. Benchmarking center performance against other sites with similar patient volumes and populations is also available within the ELSO registry.

Further investigation and collaboration will be required to refine the best patient population for ECMO, and how to reduce complications such as bleeding and thrombosis. We congratulate the EOLIA investigators in adding important information to the ECMO field. As future data becomes available, perhaps the glass will one day be full.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Bartlett RH, Andrews AF, Toomasian JM, et al. Extracorporeal membrane oxygenation for newborn respiratory failure: forty-five cases. Surgery 1982;92:425-33.
2. 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.
3. Andrews AF, Roloff DW, Bartlett RH. Use of extracorporeal membrane oxygenators in persistent pulmonary hypertension of the newborn. Clin Perinatol 1984;11:729-35.
4. Park PK, Dalton HJ, Bartlett RH. Point: Efficacy of extracorporeal membrane oxygenation in 2009 influenza A(H1N1): sufficient evidence? Chest 2010;138:776-8.
5. Randolph AG, Vaughn F, Sullivan R, et al. Critically ill children during the 2009-2010 influenza pandemic in the United States. Pediatrics 2011;128:e1450-8.
6. Brower RG, Matthay MA, Morris A, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342:1301-8.
7. Brower RG, Lanken PN, MacIntyre N, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med 2004;351:327-36.
8. Grasso S, Terragni P, Mascia L, et al. Airway pressure-time curve profile (stress index) detects tidal recruitment/hyperinflation in experimental acute lung injury. Crit Care Med 2004;32:1018-27.
9. Dalton HJ. There and back again: does prone positioning have any value in respiratory failure? Crit Care Med 2002;30:1658-9.
10. Gattinoni L, Marini JJ. Prone positioning and neuromuscular blocking agents are part of standard care in severe ARDS patients: we are not sure. Intensive Care Med 2015;41:2201-3.
11. Sud S, Friedrich JO, Adhikari NK, et al. Effect of prone positioning during mechanical ventilation on mortality among patients with acute respiratory distress syndrome: a systematic review and meta-analysis. CMAJ 2014;186:E381-90.

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12. Schmidt M, Bailey M, Sheldrake J, et al. Predicting survival after extracorporeal membrane oxygenation for severe acute respiratory failure. The Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score. Am J Respir Crit Care Med 2014;189:1374-82.
13. Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010;363:1107-16.
14. Greyson CR. Pathophysiology of right ventricular failure. Crit Care Med 2008:S57-65.
15. Fan E, Gattinoni L, Combes A, et al. Venovenous extracorporeal membrane oxygenation for acute respiratory failure : A clinical review from an international group of experts. Intensive Care Med 2016;42:712-24.
16. Agerstrand CL, Bacchetta MD, Brodie D. ECMO for adult respiratory failure: current use and evolving applications. ASAIO J 2014;60:255-62.
17. 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 randomised controlled trial. Lancet 2009;374:1351-63.
18. Hardin CC, Hibbert K. ECMO for Severe ARDS. N Engl J Med 2018;378:2032-4.

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