Extracorporeal Membrane Oxygenation for Nonneonatal Acute Respiratory Failure

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Hypothesis: Extracorporeal membrane oxygenation (ECMO) is effective in nonneonatal acute respiratory failure under certain circumstances.

Design: Retrospective medical record review.

Setting: The intensive care unit of a tertiary care hospital.

Patients: Thirty-four nonneonatal patients (mean age, 22 years; range, 8 days to 56 years), with ratios of the PaO₂ to the fraction of inspired oxygen persistently below 70, who were treated with ECMO after maximal ventilator therapy had failed (mean time of ventilator therapy, 6.9 days; range, 1-41 days). The mean ECMO duration was 304 hours (range, 56-934 hours). Patients were grouped into 7 categories based on their diagnosis: sepsis or sepsis syndrome (n = 3), bacterial or fungal pneumonia (n = 10), viral pneumonia (n = 5), trauma or burn (n = 2), inhalation injury without burn (n = 1), immunocompromised state (due to transplantation or chemotherapy) (n = 8), and acute respiratory failure of unknown origin (n = 5).

Main Outcome Measure: Survival to hospital discharge following ECMO therapy.

Results: Overall survival was 53% (18 patients). All 6 patients (100%) with viral pneumonias or isolated inhalation injuries survived. Of 13 patients with bacterial pneumonia, sepsis, or sepsis syndrome not complicated by multiorgan failure, 10 (77%) survived. In contrast, all but 1 of the immunocompromised patients died. Survival in patients who were intubated for less than 9 days before ECMO was 64%, whereas survival fell precipitously to 22% for patients who experienced mechanical ventilation for 9 or more days before the implementation of ECMO. Finally, the proportion of patients who died while receiving ECMO therapy was greater when the ECMO duration exceeded 300 hours (62% vs 38%; P<.05).

Conclusions: Nonneonatal survival with ECMO therapy is strongly dependent on the diagnosis. Pre-ECMO intubation for less than 9 days had little effect on survival. Survival rates decreased when the length of time of receiving ECMO exceeded 300 hours.

PATIENTS AND METHODS

Between February 1, 1990, and April 30, 1998, 34 patients aged 8 days to 56 years with refractory ARF were consecutively treated with venoarterial or venovenous extracorporeal lung support in the neonatal, pediatric, and adult intensive care units at the Massachusetts General Hospital, Boston. Patients were identified retrospectively by reviewing office records from the pediatric surgical service ECMO database. The hospital medical record for each patient was reviewed, and pertinent information was recorded. A favorable outcome was defined as patient survival and discharge from the hospital.

Patients were considered for enrollment using a modification of Extracorporeal Life Support Organization criteria11; all patients were treated with ECMO after severe ARF developed and maximal ventilator therapy that required prolonged oxygenation with 100% oxygen failed. The patients had mean ± SD ratios of PaO₂ to the fraction of inspired oxygen of 85.0 ± 22.9 for survivors and 56.9 ± 4.8 (P=.27) for nonsurvivors. They were considered for ECMO therapy only after all septic foci had been drained, pulmonary air leaks were managed with thoracotomy tubes, and all identified infections were treated with appropriate antibiotic therapy.

Patients were separated into 2 groups: survivors (n = 18) and nonsurvivors (n = 16). The characteristics for these patients—age, the duration of ECMO therapy, ventilatory support variables before ECMO therapy, and laboratory values—are shown in Table 1.

Ventilator management while receiving ECMO was directed at limiting airway pressures by maintaining peak inspiratory pressures of less than 30 cm H₂O and PEEP between 20 and 24 cm H₂O. Large air leaks were treated with no PEEP and minimal ventilation until they resolved. Anticoagulation maintained activated clotting times at 180 ± 20 (mean ± SD) seconds for all patients.

Statistical analyses on the data presented in Table 1 were performed using the Student t test. To determine whether age was a significant predictor of outcome, analysis of variance was performed.

The purpose of this retrospective study is to report the results of the ECMO experience in nonneonatal patients with severe ARF. In addition, the data presented here provide confirmatory evidence that ECMO can be beneficial in this patient population. Finally, this report may aid in the design of more appropriate selection criteria for critically ill patients with ARF for whom conventional therapy has failed.

RESULTS

Thirty-four nonneonatal patients received ECMO support during the 8 years that were reviewed. The male-to-female ratio was 5:9 for the survivors and 13:3 for the nonsurvivors. Of the 34 patients with ARF, 21 (62%) received lung function and were weaned from extracorporeal support. Of these, 18 patients (53%) survived and were discharged from the hospital. Of patients who were weaned from ECMO and subsequently died, 1 patient died of complications from an underlying congenital heart lesion, and 2 patients who were previously treated with bleomycin sulfate had gradually progressive respiratory failure. The mean age for the group as a whole was 22 years (range, 8 days to 56 years). The age of the patients in the survivor group ranged from 8 days to 53 years (mean, 19.8 years) compared with the patients in the nonsurvivor group, whose age ranged from 2 months to 56 years (mean, 24.6 years). The mean of the 2 groups did not differ significantly; however, a bimodal distribution was observed when patient age was plotted against the frequency of survival (Figure 1). Furthermore, there was a significant increase in survival of patients in the later peak (P<.05) as the ECMO experience progressed through the 8 years (Figure 2).

The total number of days during which the patients were treated with assisted ventilation before ECMO therapy varied from 1 to 41 days (mean, 6.9 days). The duration of ECMO ranged from 56 to 934 hours (mean, 304 hours). The proportion of patients who died while receiving ECMO was greater when the ECMO duration exceeded 300 hours (8/13 [62%] vs 8/21 [38%]; P<.05). Survival by the duration of mechanical ventilation preceding ECMO is shown in Figure 3. Patients who received ventilatory support for fewer than 9 days had a significantly better outcome (P<.05).

For all categories, differences between the survivors and nonsurvivors were not significant, with the exception of the number of hours that PEEP exceeded 8 cm H₂O and the number of units of packed red blood cells transfused before and during the implementation of ECMO. Patients were grouped into 7 categories based on their primary discharge diagnosis: sepsis or sepsis syndrome (n = 3), bacterial or fungal pneumonia (n = 10), viral pneumonia (n = 5), trauma or burn (n = 2), inhalation injury without burn (n = 1), immunocompromised state (due to transplantation or chemotherapy) (n = 8), and ARF, unknown origin (n = 5). Survival for each group is shown in Table 2.

COMMENT

Respiratory insufficiency in nonneonatal patients is usually self-limiting. In the few patients in whom fulminant respiratory failure develops, however, reported mortality exceeds 50%. If pulmonary failure progresses in this group, and conventional management schemes are exhausted, mortality rates approach 90%.12 Experimental models1 suggest that the irreversible progression to death in nonneonatal patients is caused in part by the iatrogenic damage of the lung occurring with prolonged positive-pressure mechanical ventilation needed to overcome the ventilation-perfusion mismatches resulting from parenchymal shunting. Management strategies have been designed13 to improve oxygenation and minimize the mechanical damage associated with high alveolar pressure. These include low-volume and high-frequency ventilation, reversed inhalation to exhalation ratios, pressure-
controlled ventilation to maintain peak inspiratory pressures under 40 cm H$_2$O, permissive hypercapnia, and inhaled nitric oxide. All strategies are designed to promote optimal ventilation and perfusion, to minimize positive pressure–related parenchymal damage, and to afford the greatest capacity for recovery of the already-insulted lung.\textsuperscript{14,15} Still, the mortality of the patients not responding to these therapies exceeds 50%, and alternative methods of support have been studied.

Poor survival in adults was initially reported by Zapol et al\textsuperscript{16} after an ambitious multicenter, randomized ECMO trial. Subsequently, the application of ECMO in this population was forestalled. At the same time, however, Bartlett et al\textsuperscript{17} showed dramatic successes in the treatment of refractory neonatal ARF by ECMO. There is little debate regarding its efficacy in these patients, as it has been shown\textsuperscript{18} to improve survival rates to 80% in patients with a predicted mortality of 90%. Soon thereafter, Gattinoni et al\textsuperscript{19} reported improved survival for adults with ARF using extracorporeal removal of carbon dioxide. The Extracorporeal Life Support Organization and its registry, as well as others,\textsuperscript{8,13,20} have since reported a combined survival for the nonneonatal, noncardiac group of patients.

Table 1. Patient Characteristics, Arterial Blood Gas Values, and Laboratory Values\textsuperscript{*}

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survivors (n = 18)</th>
<th>Nonsurvivors (n = 16)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>19.8 ± 3.9</td>
<td>24.6 ± 4.3</td>
<td>.46</td>
</tr>
<tr>
<td>Time on ECMO therapy, h</td>
<td>250.0 ± 42.1</td>
<td>366.0 ± 72.7</td>
<td>.16</td>
</tr>
<tr>
<td>Pre-ECMO ventilation</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ventilatory support, d</td>
<td>4.8 ± 2.5</td>
<td>9.3 ± 0.8</td>
<td>.08</td>
</tr>
<tr>
<td>Positive end-expiratory pressure (PEEP), cm H$_2$O</td>
<td>46.4 ± 3.0</td>
<td>53.8 ± 4.7</td>
<td>.18</td>
</tr>
<tr>
<td>Positive inspiratory pressure (PIP), cm H$_2$O</td>
<td>13.6 ± 1.1</td>
<td>15.8 ± 1.2</td>
<td>.19</td>
</tr>
<tr>
<td>Fio$_2$ &gt; 0.9, h</td>
<td>32.3 ± 9.7</td>
<td>74.3 ± 43.8</td>
<td>.33</td>
</tr>
<tr>
<td>PEEP &gt; 40 cm H$_2$O, h</td>
<td>37.7 ± 9.7</td>
<td>134.5 ± 55.9</td>
<td>.08</td>
</tr>
<tr>
<td>pH</td>
<td>42.7 ± 6.6</td>
<td>177.8 ± 58.4</td>
<td>.02</td>
</tr>
<tr>
<td>Pre-ECMO arterial blood gas values</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>PaO$_2$, mm Hg</td>
<td>7.30 ± 0.02</td>
<td>7.32 ± 0.03</td>
<td>.57</td>
</tr>
<tr>
<td>PaCO$_2$, mm Hg</td>
<td>78.8 ± 20.4</td>
<td>53.9 ± 3.5</td>
<td>.26</td>
</tr>
<tr>
<td>Alveolar-arterial gradient</td>
<td>61.4 ± 5.5</td>
<td>60.8 ± 5.7</td>
<td>.94</td>
</tr>
<tr>
<td>Fio$_2$.0.9, h</td>
<td>531 ± 30</td>
<td>559 ± 21</td>
<td>.46</td>
</tr>
<tr>
<td>Pao$_2$/Fio$_2$ ratio</td>
<td>85 ± 23</td>
<td>57 ± 5</td>
<td>.27</td>
</tr>
<tr>
<td>Laboratory values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-ECMO PRBC transfusion, U</td>
<td>2.3 ± 0.9</td>
<td>9.6 ± 3.2</td>
<td>.03</td>
</tr>
<tr>
<td>PRBC transfusions on ECMO therapy, U</td>
<td>15.5 ± 4.6</td>
<td>41.7 ± 9.6</td>
<td>.02</td>
</tr>
<tr>
<td>Pre-ECMO WBC count, × 10$^9$/L</td>
<td>18.0 ± 1.9</td>
<td>15.7 ± 3.7</td>
<td>.57</td>
</tr>
<tr>
<td>Pre-ECMO hematocrit, %</td>
<td>34.0 ± 1.3</td>
<td>33.7 ± 1.6</td>
<td>.87</td>
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<tr>
<td>Pre-ECMO platelet count, × 10$^9$/L</td>
<td>215 ± 40</td>
<td>170 ± 37</td>
<td>.42</td>
</tr>
<tr>
<td>Pre-ECMO serum creatinine, µmol/L (mg/dL)</td>
<td>66.0 ± 8.8 (0.8 ± 0.1)</td>
<td>97.2 ± 17.7 (1.1 ± 0.2)</td>
<td>.09</td>
</tr>
</tbody>
</table>

\textsuperscript{*}Data are given as mean ± SEM. ECMO indicates extracorporeal membrane oxygenation; Fio$_2$, fraction of inspired oxygen; PRBC, packed red blood cell; and WBC, white blood cell.

Figure 1. Patient survival (percentage) by age. The Massachusetts General Hospital (MGH), Boston, experience was compared with the Extracorporeal Life Support Organization (ELSO) database.

Figure 2. Survival by year of extracorporeal membrane oxygenation (ECMO) therapy and age of patient. Each circle represents a patient who survived therapy with ECMO and was discharged from the hospital.
tients of greater than 50%. The growing neonatal experience, together with reports of successes in adults, has led to an expanded use in patients other than neonates. In addition to longer treatment periods, the improvement in survival is thought to have been most influenced by the development of newer technologies, management strategies, and a better understanding of which patients may benefit from these technologies. Guidelines have been established to aid in the selection of patients who would be the most appropriate candidates for ECMO. These were defined as those who had “severe but reversible” ARF.21 Despite changes in protocols and improvement in outcomes, several controversies remain as to how ECMO should be implemented so that risks are outweighed by benefits and outcomes are better than they would be if conventional therapies were applied.

Recently, several investigators13 have studied the outcomes for nonneonatal patients with ARF based on the cause of their respiratory failure. Similarly, we reviewed our patient base and placed each into 1 of 7 categories based on their discharge diagnosis (see “Results” section). As other groups have suggested, we observed that several disease states portend better outcomes, whereas the course of others is unchanged by ECMO therapy. Overall survival in our institution was 53% (18 patients). More interestingly, survival in patients presenting with isolated viral pneumonias, isolated inhalation injuries, or with sepsis or sepsis syndrome with ARF but not complicated by multiorgan failure was 100% (9 patients). In contrast, 1 (12%) of the 8 patients who were immunocompromised either as a result of chemotherapy for the treatment of cancer or by immunosuppression for organ transplantation survived to hospital discharge. Although 2 of the 7 nonsurvivors were weaned from extracorporeal support and the cannula removed, they subsequently died of a progressive respiratory failure thought to be related to their past bleomycin therapy. Therefore, as many have thought, these patients may not be suitable candidates for ECMO therapy. Similarly poor outcomes were seen for patients with ARF complicated by multiorgan failure or precipitated by trauma or burns.

In this series, the disease process appeared to be significantly effective in identifying those patients with “reversible” lung injury in whom ECMO may be of benefit. Most authors agree that limiting lung injury before and during ECMO is of paramount importance when considering whether a patient is capable of survival. Identifying patients earlier in their “reversible” disease progression, and thereby limiting the well-characterized pre-ECMO ventilatory insult, should improve survival. Pranikoff et al20 showed that pre-ECMO mechanical ventilation exceeding 5 days was a poor prognostic indicator in adults. Our data suggest that there is no significant difference in survival in those patients who had had up to 9 days of pre-ECMO ventilatory support and that a lesser but substantial percentage of patients who receive mechanical ventilation for longer than 9 days will survive to discharge after ECMO therapy.

Early in the ECMO experience, Zapol et al16 considered the appropriate duration of ECMO therapy in adults to be equivalent to that seen by investigators treating neonates. Most authors at that time failed to take into account any possible differences in the resilience of the damaged lung parenchyma that may be expected in the nonneonates compared with neonates. The results reported by Zapol et al, therefore, as many have come to realize, came early in the ECMO learning curve and underestimated the time necessary for the return of lung function in the nonneonatal group. The centers that participated in the National Institutes of Health–sponsored adult trial allowed only 5 days of ECMO, and if no improvement was seen, it was considered futile and discontinued. Since then, the average time of extracorporeal support in nonneonatal patients has been better defined, the mean ± SD duration of ECMO for these patients now being reported as 10.3 ± 6.8 days.22 The cannulation time for our patients ranged from 2.3 to 38.9 days (mean, 12.6 days). More important, the difference in the mean cannulation time of the survivors (10.4 days) from that of the nonsurvivors (15.3 days) is apparently not significant. The proportion of patients who died while receiving ECMO, however, was greater when the ECMO duration exceeded 12.5 days (8/13 [62%] vs 8/21 [38%]; P < .05). Still, 5 of the 18 patients in the survivor group had ECMO durations exceeding 300 hours.

When considering a patient with ARF of unknown origin, age may prove to be a useful prognostic indicator. When the age of the patients in this series was plot-


30s had a higher likelihood of survival. What’s the problem with being in the 10- to 30-year age group?

The second question is, you’ve shown us that single-organ failure, that is, the lung, and short-term patients do best. Do you have absolute contraindications to the use of ECMO? And how about age? Are about two thirds of the people in this audience beyond the age limit and would you write us off or would you give us a chance with ECMO in the final analysis if it were a single-organ lung failure?

The third question is, when you cross that threshold of 300 hours or 13 days, when and how do you decide to turn off the ECMO?

Pardon Kenney, MD, Boston: Your survival data are obviously impressive. I have a quality-of-life question. How many of your survivors required permanent ventilators, and how many of them actually ended up in a chronic care hospital? How many of these patients have been referred? Are they all based at the Massachusetts General Hospital originally? Can these patients be transported for ECMO, and when would you do that?

Dr Masiakos: To answer Dr Hendren’s questions, we find that these diseases cluster by ages, and we suspect that they cluster because of disease predispositions. The group that you speak of, the 10- to 30-year-olds, contains the sickest patients. They are the ones who have fungal sepsis, are immunocompromised after their lung transplants, and are most likely to present with multiorgan failure after trauma. They typically do the worst.

To your second question about the absolute contraindications: The first contraindication is head injury. Children or adults who present with head trauma or intracranial hemorrhage are refused. Irreversible lung damage, as seen by biopsy with indications of pulmonary fibrosis, is also a contraindication. Finally, a patient with an underlying fatal disease like metastatic cancer or end-stage acquired immunodeficiency syndrome would be refused as well.

Age is not an absolute contraindication, and I know you all hate me for saying that, however, it’s a patient by patient evaluation and we assume enrollment criteria based on what we find on their lung pathology report.

To your last question, the 300-hour threshold: There’s no good way to tell a patient’s parents or family members that their life support is going to be withheld or withdrawn. We observe the patients day to day, and if there’s no evidence of lung recovery after the second or third week, the patients are offered a lung biopsy. If fibrosis is seen on lung biopsy, we consider that to mean irreversible lung damage, and at that point, we suggest that ECMO be discontinued.

The quality-of-life issues: None of the patients who were survivors after receiving ECMO therapy had poor quality of life, none of them were institutionalized, and none continued to need ventilation therapy for their disease. After they recovered, they would be terminated from ECMO and then subsequently be terminated from ventilator support.

To your question about ECMO referrals, it’s imperative to understand that lung damage predisposes these patients to poor outcomes. We suggest that the patients be transferred to an institution where ECMO can be provided if in a short amount of time the patient is deemed not recoverable by the current conventional therapies. To get a patient there promptly results in fewer problems in the transfer than when the patient decompensates later.

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The Archives of Surgery will give priority review and early publication to seminal works. This policy will include basic science advancements in surgery and critically performed clinical research.