Current Status of Extracorporeal Membrane Oxygenation for Severe Respiratory Failure

Shingo Ichiba and Robert H. Bartlett

University of Michigan Medical Center, Ann Arbor, Michigan, U.S.A.

Abstract: Extracorporeal membrane oxygenation (ECMO) for respiratory failure was reviewed. ECMO progressed from laboratory research to initial clinical trials in 1972. Following a decade of clinical research, ECMO is now standard treatment for neonatal respiratory failure refractory to conventional pulmonary support techniques worldwide. The application of neonatal ECMO has been extended with improved outcome to premature and low birth weight infants as well as older children and adults.

Extracorporeal membrane oxygenation (ECMO) refers to the use of prolonged extracorporeal circulation for temporary support of the failing heart or lungs. The first successful ECMO support case was done by Hill et al. in 1971. Reports of several other successful cases soon followed. In 1974, the Lung Division of the National Heart and Lung Institute proposed a multicenter prospective randomized study of ECMO in adult respiratory failure. This study began in 1975. In that year a meeting on prolonged extracorporeal support was held outside of Copenhagen. The plans for the NIH-ECMO study were reported and reviewed at that meeting. The first successful newborn infant with ECMO was also reported on at the meeting.

NEONATAL ECMO

Bartlett, Gazzaniga, and his colleagues at the University of California–Irvine treated the first successful neonatal ECMO patient in 1975. This was soon followed by other successful neonatal cases. The technique for newborn infants was fairly standardized including the ECMO technique and recognition of persistent pulmonary hypertension as the primary underlying pathophysiology. In 1979, the first neonatal ECMO seminar was held at the University of California–Irvine, demonstrating the circuit, technology, and concept of the ECMO team and specialists. In 1980, the neonatal ECMO project moved to the University of Michigan. By the end of 1986, 715 newborn cases had been treated in 18 centers with excellent survival results reported from each center. The Michigan group carried out a prospective randomized study in newborn infants between 1982 and 1984, using a statistical technique called randomized play-the-winner, in which assignment to one treatment or the other is randomized but influenced by all previous patients in the study. Statistical significance is reached when there is a significantly larger group of patients in one arm of the study compared with the other (1). O’Rouke et al. carried out a prospective randomized study comparing ECMO and conventional medical therapy in neonates with persistent pulmonary hypertension of the newborn between 1982 and 1983 (2). They proved that the results with ECMO were better than conventional therapy.
ECMO became standard care for severe neonatal respiratory failure in 1986-87. In 1988, venovenous bypass using a double lumen catheter became available with excellent outcome (3). The current technique of ECMO includes venoarterial access via the right internal jugular vein and right carotid artery, heparin titration based upon whole blood activated clotting times (ACT), and "lung rest" at low ventilator settings (4). The extracorporeal circuit consists of a collapsible bladder in the venous line (providing control of a roller pump) and a solid silicone rubber membrane oxygenator (Avecor, Inc. Minneapolis, MN). Blood is circulated through a heat exchanger and then returned to the patient. Sweep gas flow to the oxygenator typically consists of a mixture of 100% oxygen, carbogen (95% oxygen and 5% carbon dioxide) to maintain Paco₂ between 30 and 40 mm Hg. Anticoagulation is achieved by constant heparin infusion, maintaining the ACT between 180 and 200 s. Platelet counts are maintained above 100,000/mm³. The hematocrit values are kept above 40%. Initial bypass flow is about 80-100 ml/kg/min in the venoarterial bypass mode and 100-120 ml/kg/min in the venovenous mode. Patients are weaned according to SVO₂ and Pao₂ values. On initiation of bypass, ventilator settings are decreased to an inspired oxygen concentration of 30%, peak airway pressure <30 cm of H₂O, PEEP usually maintained at 5 cm of H₂O, and a respiratory rate of 10 beats/min.

The active groups formed a study group in 1989 called the Extracorporeal Life Support Organization (ELSO). ELSO maintains the registry, conducts courses, holds an annual meeting to share experience, and represents the membership to the community. Schumacher et al. reported a cost-effectiveness study demonstrating that the early use of ECMO does not increase hospital cost or utilization and suggests a lower morbidity rate (5). The application of ECMO is now being extended to premature and low birth weight infants (6). A follow-up study reported that 80% of survivors were healthy children. The remaining 20% have some degree of pulmonary or neurologic impairment. Death or disability is caused by perinatal neurologic injury or pulmonary hypoplasia (7). In 1994, there were nearly 100 ECMO centers throughout the world. Over 9,000 newborn infants have been treated with ECMO with an 81% overall survival rate (Table 1) (8). Bleeding was the most frequent complication. ECMO is now standard treatment for severe neonatal respiratory failure. The availability of ECMO has made the evaluation of other innovative methods of treatment, such as late elective repair of diaphragmatic hernia, and new pulmonary vasodilators, such as nitric oxide (9) possible.

**TABLE 1. Percent survival by primary diagnosis for neonatal ECMO**

<table>
<thead>
<tr>
<th>Primary diagnosis</th>
<th>University of Michigan* (n = 470)</th>
<th>International registry (n = 9,258)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAS</td>
<td>97% (165/170)</td>
<td>93% (3,173/3,395)</td>
</tr>
<tr>
<td>RDS/HMD</td>
<td>88% (809/91)</td>
<td>84% (879/1,051)</td>
</tr>
<tr>
<td>Pneumonia/sepsis</td>
<td>83% (6578)</td>
<td>76% (1,091/1,431)</td>
</tr>
<tr>
<td>CDH</td>
<td>66% (45/68)</td>
<td>58% (1,057/1,808)</td>
</tr>
<tr>
<td>PPHN/PFC</td>
<td>92% (35/38)</td>
<td>83% (1,008/1,209)</td>
</tr>
<tr>
<td>Air leak syndrome</td>
<td>0% (0/1)</td>
<td>72% (31/43)</td>
</tr>
<tr>
<td>Other</td>
<td>75% (18/24)</td>
<td>78% (250/321)</td>
</tr>
<tr>
<td>Overall</td>
<td>87% (408/470)</td>
<td>81% (7,489/9,258)</td>
</tr>
</tbody>
</table>

* Includes initial 45 cases treated at the University of California-Irvine. Data from the ECMO registry report of the ELSO as of July 1994.

**PEDIATRIC AND ADULT ECMO**

An NIH-sponsored study of ECMO in adult patients was completed in 1979 and reported (10). Although there were many problems with this study, this was the first attempt at a prospective randomized study of the ECLS technique in which the end point was death. Some centers had no prior experience before their first study patient. Bleeding complications were major with average blood loss exceeding 2 L/day. Although the purpose of ECMO is lung rest, many of the patients remained on high ventilator settings under the venoarterial bypass mode. The study was planned for 300 patients, but it was terminated after 92 patients were entered because the survival in both groups was less than 10%. Autopsy revealed that extensive and irreversible pulmonary fibrosis was uniformly formed, indicating that the major problem was underlying parenchymal lung disease. As the result of this study, clinical research on ECMO in adult patients essentially stopped in the United States in 1979. Gattinoni and his colleagues in Milan started using a new method for extracorporeal life support with the following hypothesis. First, the purpose of ventilation is to excrete carbon dioxide. Oxygenation can be achieved by inflation and airway oxygenation alone. Second, progressive lung injury in acute respiratory distress syndrome (ARDS) is caused in part by ventilator-induced high pressure or overdistension injury of the most normal alveoli. Third, if the emphasis should be on carbon dioxide removal to eliminate the need for high pressure ven-
tilation, this could be accomplished with veno-
venous access using relatively low blood flow and a
large membrane lung surface area. Fourth, this sys-
tem would allow for normal pulmonary blood flow,
even if the lung is severely injured with large
amounts of transpulmonary shunting. They used
these principles in venovenous extracorporeal gas
exchange with low-frequency positive pressure
ventilation in a variety of adult patients selected by
the same criteria used for the NIH ECMO study.
They reported their study with 49% survival in 1986
(11). These results have been corroborated in many
European centers, and similar results were reported
by the Kumamoto group in Japan.

Based on these reports and our experience with
neonatal ECMO, our institute began to reevaluate
ECMO in adult patients with cardiopulmonary fail-
ure in 1988. The ECMO technique for adult patients
is the same as neonatal ECMO, including the veno-
enous and venoarterial bypass mode with lung
rest. Selection criteria for respiratory failure in
adults with 90% or greater mortality risk includes
transpulmonary shunt greater than 30%, static com-
pliance lower than 0.5 ml/cm of H2O/kg, and a dif-
fusely abnormal chest roentgenogram in four quan-
drants despite optimal conventional therapy (12).
Bleeding was the most frequent complication. Indi-
cators of irreversibility of lung injury in these pa-
tients were elevated pulmonary artery pressures
(75% or greater of systemic pressure), decreased
capillary exchange, lung compliance, and a diminution of
transpulmonary gas exchange. Patients with more
than 5 pre-ECMO ventilation days had a signifi-
cantly higher mortality risk compared with those
ventilated for less than 5 days. The elevated pulmo-
nary artery pressure/systemic pressure ratio, trans-
forming growth factor β (TGF-β) activity in the
Broncho alveolar lavage fluid (BALF), and mea-
surement of oxygen transfer across the native lung
during ECMO may be good early predictors for the
reversibility of lung injury. As of July 1994, 48 pa-
tients with severe respiratory failure have been
treated with ECMO with 30 survivors (63%) at the
University of Michigan (Table 2) (8). The difference
in the results of modern ECMO and those of the
1970s, when the NIH-ECMO study was performed,
may in part be due to better case selection, veno-
enous perfusion, and improvement in the technol-
gy of long-term perfusion (12). Advances in critical
care techniques today may improve the survival
from respiratory failure.

For older children (between 1 month and 18 years
of age) who have failed conventional mechanical
ventilation, ECMO has also been proposed and uti-
lized as a rescue therapy. As of July 1994, 754 pe-
diatric cases have been treated with ECMO therapy
with an overall survival rate of 49% (Table 3) (8).
Our institute has experienced 62 cases with an over-
all survival rate of 66% (8). In the near future, rou-
tine use of heparin-coated equipment will reduce
the complication associated with systemic heparin-
ization and blood material interaction.

TABLE 2. Percent survival by primary diagnosis for
pediatric ECMO

<table>
<thead>
<tr>
<th>Primary diagnosis</th>
<th>University of Michigan (n = 62)</th>
<th>International registry (n = 754)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial pneumonia</td>
<td>100% (3/3)</td>
<td>44% (28/63)</td>
</tr>
<tr>
<td>Viral pneumonia</td>
<td>73% (16/22)</td>
<td>53% (120/225)</td>
</tr>
<tr>
<td>Intrapulmonary hemorrhage</td>
<td>100% (1/1)</td>
<td>64% (7/11)</td>
</tr>
<tr>
<td>Aspiration</td>
<td>67% (4/6)</td>
<td>61% (45/74)</td>
</tr>
<tr>
<td>Pneumocystis</td>
<td>0% (0/0)</td>
<td>42% (5/12)</td>
</tr>
<tr>
<td>ARDS</td>
<td>0% (0/0)</td>
<td>32% (6/19)</td>
</tr>
<tr>
<td>Other</td>
<td>66% (19/29)</td>
<td>46% (162/350)</td>
</tr>
<tr>
<td>Overall</td>
<td>66% (41/62)</td>
<td>49% (373/754)</td>
</tr>
</tbody>
</table>

ARDS, adult respiratory distress syndrome. Data from ECMO
registry report of the ELSO.

ARDS, adult respiratory distress syndrome. Data from ECMO
registry report of the ELSO.

TABLE 3. Percent survival by primary diagnosis for
adult ECMO

<table>
<thead>
<tr>
<th>Primary diagnosis</th>
<th>University of Michigan (n = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial pneumonia</td>
<td>14% (1/7)</td>
</tr>
<tr>
<td>Viral pneumonia</td>
<td>88% (7/8)</td>
</tr>
<tr>
<td>Aspiration</td>
<td>67% (2/3)</td>
</tr>
<tr>
<td>ARDS</td>
<td>70% (16/23)</td>
</tr>
<tr>
<td>Other</td>
<td>57% (4/7)</td>
</tr>
<tr>
<td>Overall</td>
<td>63% (30/48)</td>
</tr>
</tbody>
</table>

ARDS, adult respiratory distress syndrome. Data from ECMO
registry report of the ELSO.

ECMO has become standard treatment for severe
neonatal respiratory failure in our institute and
worldwide. The application of ECMO is now being
extended to premature and low birth weight infants
as well as older children and adults. The outcome of
ECMO for adult and pediatric patients in our insti-
tute showed that it was a reasonable therapy for
patients with severe respiratory failure who failed
to recover with conventional medical therapy.
Technical advances will lead to a better outcome
with much easier and safer use of ECMO in the future.

Acknowledgment: Supported in part by grants from the
National Institute of Health and the William Randolph
Hearst Foundation.
REFERENCES


