Extracorporeal Membrane Oxygenation in the Management of Respiratory Failure in the Newborn

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Extracorporeal membrane oxygenation (ECMO) has been successfully used to treat respiratory failure in over 400 newborn infants since Dr. Bartlett’s pioneering efforts and the first survivor in 1975. The key component of ECMO is the transport of oxygen into blood across a semipermeable membrane. This phenomenon was first recognized in 1944, when Kolff and Berk noted that blood became oxygenated as it passed through the cellophane chambers of their artificial kidney. The cardiopulmonary bypass concept was developed in the early 1950s. Devices used at that time were bubble or disk oxygenators with a direct oxygen–blood interface, resulting in marked hemolysis after a few hours of bypass, precluding their use for long-term problems. With the development of the first membrane oxygenator by Clowes et al. in 1956, prolonged cardiopulmonary bypass became feasible.

The 1960s and 1970s were periods for advancement in techniques and also for research into prolonged pulmonary support. It was during this time that a nine hospital collaborative study was organized by the National Heart, Lung, and Blood Institute to study ECMO therapy in adults with acute pulmonary insufficiency. Unfortunately, survival was not improved (9.5 per cent in ECMO patients and 8.3 per cent in the controls). The study had several problems: (1)
Table 1. Data From the ECMO Central Registry Summarizing the Total Infant Population in the Registry Through August 1986

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>No. of Patients</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meconium aspiration syndrome</td>
<td>191</td>
<td>85.0</td>
</tr>
<tr>
<td>Sepsis/pneumonia</td>
<td>31</td>
<td>68.0</td>
</tr>
<tr>
<td>Persistent pulmonary hypertension</td>
<td>64</td>
<td>88.0</td>
</tr>
<tr>
<td>Hyaline membrane disease</td>
<td>65</td>
<td>71.0</td>
</tr>
<tr>
<td>Congenital diaphragmatic hernia</td>
<td>69</td>
<td>59.0</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>420</strong></td>
<td><strong>78.0</strong></td>
</tr>
</tbody>
</table>

(Courtesy of John Toomasian, CCP).

the patients varied greatly as to the type and complexity of their disease processes; (2) patients were entered only when survival prediction was 10 per cent and pathologic changes in the lung were probably irreversible; and (3) intensive ventilator support was continued, which probably perpetuated lung damage.19, 21, 32 A recent study in the adult population, where pulmonary management was dramatically changed from the collaborative study design to keep the lungs “at rest,” has shown a survival of 48.8 per cent.16 Although this study was not controlled, it does indicate that further studies in the adult population should be considered with emphasis on pulmonary management and early treatment.

The ECMO experience in older children was similar to that in the adult, with many of the same problems.7, 26, 36 This important period, however, suggested that ECMO, in appropriate patients, treated early and in whom irreversible fibrosis of the lung was excluded, was technically feasible, with the potential to reverse pulmonary failure.

Unfortunately, the initial newborn population chosen for ECMO was the premature infant with hyaline membrane disease (HMD), who developed significant intracranial hemorrhage secondary to systemic heparinization, with a prohibitive mortality.11, 12, 14, 33, 37, 42 It was not until Bartlett et al. pioneered the treatment for term or near-term infants in respiratory failure3, 5 that ECMO entered its successful phase. This early work has been confirmed by Bartlett’s further work and that of others, with present-day survival rates over 70 per cent in infants with a predicted mortality of over 80 per cent (see Tables 1 and 2).2, 9, 34, 41 It must be noted that infants treated today in centers meet criteria developed from historical controls predicting an 80 to 100 per cent mortality. The only randomized controlled study using a predicted 90 per cent mortality entry criteria was recently published by Bartlett and colleagues at the University of Michigan.9 Because of his institution’s positive experience with ECMO and because of ethical concerns for withholding therapy in this population, a statistical
Table 2. Survival Statistics by Diagnosis of ECMO Patients Treated at Children's Hospital National Medical Center, Washington, D.C.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of Patients</th>
<th>Survivors (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meconium aspiration syndrome</td>
<td>49</td>
<td>45 (92.0)</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>15</td>
<td>12 (80.0)</td>
</tr>
<tr>
<td>Congenital diaphragmatic hernia</td>
<td>7</td>
<td>4 (57.0)</td>
</tr>
<tr>
<td>Sepsis/pneumonia</td>
<td>15</td>
<td>14 (93.0)</td>
</tr>
<tr>
<td>Persistent pulmonary hypertension</td>
<td>7</td>
<td>6 (86.0)</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>5</td>
<td>2 (40.0)</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>1 (50.0)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>100</strong></td>
<td><strong>84 (84.0)</strong></td>
</tr>
</tbody>
</table>

method called “play-the-winner” was used instead of the typical randomized trial. This study did show a significant survival rate in the ECMO patients but has been criticized for the statistical approach. Because of the moribund nature of this population, many centers have chosen to use historical controls to develop their criteria. Bartlett’s group is presently conducting a randomized controlled trial comparing conventional therapy with ECMO therapy in a population whose predicted survival is 50 per cent. This study may help to answer many of the questions concerning the lack of a controlled randomized study.

PATIENT POPULATION AND CRITERIA FOR ECMO

Currently, the appropriate ECMO patient population is the term or near-term infant (35 to 40 weeks’ gestation) who fails maximal ventilatory and medical support and who, by institutional criteria, has only a 20 per cent or less chance of survival.²,³⁴ The infant must be free from congenital heart disease (CHD). Because systemic heparinization is required, infants with any major bleeding disorder, including a significant intracranial hemorrhage (ICH), must be excluded. The infant’s lung disease must be potentially reversible in a 10- to 14-day period. Severe chronic lung disease cannot be reversed within the time limits of present-day ECMO therapy and therefore infants with this disorder should be excluded.

Most infants who are candidates for ECMO have, as an underlying process, persistent pulmonary hypertension (PPHN), which results in right to left shunting through the foramen ovale or the ductus arteriosus.¹⁸ This condition occurs in diseases such as meconium aspiration syndrome (MAS), sepsis, severe hyaline membrane disease (HMD), idiopathic PPHN, and congenital diaphragmatic hernia (CDH). Table 2 lists the number of infants in each diagnostic category treated at
Table 3. *ECMO Entry Criteria*

Table 3. ECMO Entry Criteria

Patient must meet all of the following criteria:

1. Weight greater than 2 kg
2. No more than 7 days of assisted ventilation
3. Reversible lung disease
4. No congenital heart disease
5. No intracranial hemorrhage or severe coagulopathy
6. Failure of maximal medical management, (100 per cent oxygen, hyperventilation, tolazoline trial)
7. Plus one of the following:

   PIP ≥ 38 plus AaDo2 ≥ 605 for 4 hours (84 per cent mortality)

* AaDo2 measured when Fio2 = 1.00
AaDo2 = Barometric Pressure (mm Hg) - 47 mm Hg - po2 - pco2

Children's Hospital National Medical Center (CHNMC) with survival rates. Maximal medical therapy varies from institution to institution: it usually includes attempts at alkalinization either by ventilatory or metabolic means (sodium bicarbonate drips) and therapy with vasodilating drugs such as tolazoline. High-frequency ventilation may be appropriate before ECMO therapy is considered. When all methods of conventional therapy have been exhausted, appropriate candidates for ECMO are those whose predicted survival is less than 20 per cent. Most institutions have found the alveolar-arterial oxygen difference, AaDo2, to be the most accurate in predicting mortality. The criteria used at CHNMC are listed in Table 3.

**ECMO EQUIPMENT**

There is no “standard” ECMO machine. The system must be designed from cardiopulmonary bypass equipment. The membrane lung used today is a silicone membrane (Sci-Med, 0.8 M2 silicone, Sci-Med Life Systems Inc., Minneapolis, Minnesota). Essential components are a tubing pack individually designed for each system; a 50-ml venous reservoir bag (also Sci-Med Life Systems Inc.); a system that monitors venous return and alarms if there is a significant drop (these are not commercially available); a 4- to 6-inch roller head occlusion pump; membrane lung; oxygen and CO2 flow meters capable of 0.01 liter flow for CO2 and 0.1 liter flow for O2; oxygen blender; heat exchanger with a heating unit.

**ECMO PROCEDURES**

The accepted ECMO procedure is venoarterial (VA) bypass. Veno-veno and single-catheter techniques hold promise but are still
in the experimental stages of development and will not be discussed (Fig. 1).¹ ²

The first step in the ECMO procedure is the preparation of the bypass circuit. It is assembled and primed with an albumin/blood mixture that is adjusted to the appropriate pH. While this is being done the infant is anesthetized with fentanyl (10–15 µg per kg) and paralyzed with pancuronium (0.1 mg per kg). The catheters are placed in the right internal jugular vein and right common carotid artery, with the venous catheter advanced such that it rests in the right atrium and the arterial catheter advanced to the entrance of the aortic arch. Catheter placement is confirmed by x-ray or ultrasound. The most common size catheters are 8 F to 10 F in the artery and 12 F to 14 F in the vein. After completion of these two procedures, the catheters are connected to the bypass circuit, while care is taken that no air is introduced during this step. The infant is slowly placed on bypass by increasing the bypass flows over a 20-minute period to where 80 to 90 per cent of the cardiac output (CO) is going through the circuit. Ventilator settings are reduced as bypass is achieved to final settings of: Fio₂ 0.21, ventilator rate 10 to 15 bpm, pressure limit 15 cm H₂O,
and PEEP 5 cm H₂O. The infant is allowed to awaken and breathe on
his or her own. All vasoactive drugs can be discontinued. The infant
must be anticoagulated and usually requires a loading dose of 100 to
150 units of heparin per kg during the cannulation procedure, with a
heparin drip of 20 to 70 units per kg per hour. Activated clotting times
(ACTs) are measured every 30 to 60 minutes, with the ACTs kept at
2 to 3 times baseline levels (240 to 280 seconds). All fluids and
hyperalimentation solutions are placed into the ECMO circuit with
the infant only requiring an arterial line to monitor blood gases and
blood pressure.

The amount of oxygen delivered to the patient on ECMO is re­
lated to the gas transfer characteristics of the silicone membrane lung.
Oxygen transfer across the membrane depends on the flow rate and
the degree of the blood's oxyhemoglobin desaturation entering the
membrane lung. Oxygen delivery expressed mathematically is

\[
\text{O}_2 \text{ Delivery} = \text{O}_2 \text{ content} \times \text{flow}
\]

where

\[
\text{O}_2 \text{ Content} = \text{O}_2 \text{ bound to hemoglobin} + \text{dissolved O}_2
\]

Therefore, to increase oxygenation one must increase the ECMO
blood flow, that is, increase the percentage of cardiac output going
through the membrane lung. The standard membrane lung size is 0.8
M², which works at maximal capacity. The average \(pO_2\) coming from
the membrane lung with an \(FiO_2\) of 1.00 across the membrane is 400
to 450 mm Hg.

Because \(CO_2\) is more diffusible than \(O_2\) and the \(CO_2\) gradient
between blood and ventilating gas is small, \(CO_2\) is efficiently removed
and must usually be added to the system to maintain a \(pCO_2\) of 40
mm Hg.

**Weaning from ECMO**

For the first 1 to 2 days, 75 to 80 per cent of the cardiac output
must flow through the circuit in order to keep the patient's \(pO_2\) be­
tween 75 to 80 mm Hg. As the infant's lungs improve, the \(pO_2\) increases
and the ECMO flow can be decreased gradually. Once the infant
reaches bypass flows equal to only 10 per cent of the cardiac output
this period is called "idling." The idling period is for 8 to 12 hours
to ensure that the patient is ready to come off. The decannulation
procedure requires that the infant be paralyzed and anesthetized. Usually
a short or intermediate neuromuscular blocker is used so that the
infant will awaken, allowing for faster extubation. The ventilator usu­
ally has to be increased at this time to \(FiO_2\)'s of 30 to 40 mm Hg, respiratory rates of 40 to 50, and pressure limits of 15 to 20 cm H₂O.
The average time to extubation at CHNMC is 28 hours with supple­
mental oxygen required for 5 to 6 days.

**ECMO Complications**

Most complications of ECMO therapy are related to the use of
heparin and its systemic effects. Bleeding from the neck operative site
ECMO IN THE MANAGEMENT OF RESPIRATORY FAILURE IN THE NEWBORN

TYPICAL SERIAL LUNG COMPLIANCE VALUES IN AN INFANT WITH MAS ON ECMO

Figure 2. Typical lung compliance changes seen in ECMO patients.

is usually minor, but if it exceeds 5 to 6 ml per hour the site should be explored. Congenital diaphragmatic hernia repairs can be extensive, and these infants, if placed on ECMO early (within 12 hours after surgery), can have significant bleeding requiring early removal from ECMO support. The most common cause of death in the ECMO patient is severe intracranial hemorrhage (ICH).2, 9, 41 In our population as with others the incidence of severe ICH is approximately 10 per cent with an overall incidence of 20 to 25 per cent if grades I and II are considered.2, 9 The preECMO asphyxia and systemic heparinization places these infants at risk for such complications, and thus heparin therapy must be monitored closely. Other bleeding complications include pulmonary hemorrhage, nasal bleeding, umbilical site bleeding, and chest tube bleeding. All of these should be treated with low ACTs (210–220 seconds) with ECMO flows kept at 80 per cent CO2, and higher platelet counts than usual (80,000 mm3 or greater).

Patent ductus arteriosus is a common finding in the second to third day of ECMO, when the right-sided pressures decrease. Most of these will close after fluid restriction and diuretic therapy. Only 1 case out of our first 100 patients required surgical ligation.

Inability to wean from the ECMO circuit can be due to a number of causes: undiagnosed cardiac disease (e.g., total anomalous pulmonary venous return, TAPVR); significant PDA; hypoplastic lungs; and mechanical factors such as loss of pump head occlusion. The most common cause is TAPVR. Lotze et al. at our institution have found lung compliance to be a good predictor of ability to wean from ECMO.
Dynamic lung compliance (CL) measurements of 0.8 ml per cm of H₂O per kg or greater predicted successful removal from ECMO.²⁹ Figure 2 depicts a typical infant's CL during ECMO. This study is now used to help diagnose undiagnosed cardiac disease and loss of pump head occlusion, for these infants may have CL levels at 0.8 or greater and still require high bypass.

FOLLOWUP AND OUTCOME

The severity of the pre-ECMO illness mandates extensive followup. Although ligation of the carotid artery has not appeared to be associated with early morbidity, there may be long-term concerns about the cerebral circulation when these children approach adulthood. Infants should be given routine post-ECMO neurodevelopmental and medical evaluations. The followup studies to date by Towne et al.⁴⁰ and Kirkpatrick et al.²⁴ are extremely encouraging with 70 to 75 per cent of the children normal. Our findings are similar. With our first 100 patients treated from June 21, 1984 through November 1, 1986, we have an 84 per cent survival rate (see Table 2). Our 12 month followup to date includes 32 of the 37 ECMO survivors available. In this group 69 per cent are normal (>90) on the Mental Index (MDI) and 67 per cent normal on the Motor Index (PDI) of the Bayley Scales, with only 2 infants showing a significant delay (MDI or PDI < 70). Although seizures occurred in 24 per cent of the infants, only 14 per cent were discharged on medications and none have had recurrent seizures with all infants off medication by 8 months of age. EEGs were routinely obtained in the first year of our program. Only 4 of 19 of these were abnormal and of these 4 infants 3 had a history of seizures either while on or before ECMO. There were no consistent abnormalities noted. By our studies it appears that right carotid artery ligation is not associated with an increased incidence of ipsilateral dysfunction on EEGs. Our neuroimaging studies by CAT scan and ultrasound done at discharge corroborate this finding. With these results, EEGs are now only obtained on infants who have had a history of seizures.

Chronic lung disease occurred in 15 of our first 100 patients, with the highest risk group being the infants with culture proven beta-streptococcal sepsis. Infants placed on ECMO late (at 7 to 8 days of age) were also at risk for chronic lung disease. The incidence of ICH in these first 100 patients was 7 per cent for severe ICH (greater than grade II) and 19 per cent for bleeds of grade I or II.

These early outcome results are encouraging with the majority of the ECMO infants functioning normally; however, more subtle attentional, learning, and language problems have not been ruled out and extensive follow-up through school age is mandatory.
THE ECMO TEAM AND REGIONALIZATION

ECMO is labor intensive and requires a large team and institutional involvement. The immediate team consists of pediatric or cardiovascular surgeons, neonatologists, perfusionists, biomedical engineering experts, ECMO technical specialists, and neonatal nursing staff members. The cardiology and radiology services, pharmacy, laboratory, blood bank, and almost all support systems in the hospital are affected and contribute to the development of a successful ECMO program. Because of the expertise required and the expense of maintaining a qualified team, this therapy should be regionalized in tertiary level pediatric centers and because this procedure is in effect prolonged cardiopulmonary bypass it should not be attempted in a hospital that does not have an appropriate cardiovascular service for backup and consultation. All infants must have congenital heart disease ruled out; therefore there must be appropriate pediatric cardiology and cardiovascular services to handle the infant transferred who has primary cardiac disease, or the patient who has TAPVR and is undiagnosed before going on ECMO (most centers have placed at least one such infant on ECMO because of the difficulty in making this diagnosis in the face of pulmonary hypertension by echocardiography).

FUTURE DEVELOPMENTS

ECMO therapy is in its infancy and can be compared to ventilator therapy of 10 years ago. The equipment used will probably be dramatically altered within the next few years. The most-needed breakthrough is a circuit to which heparin can be bonded, obviating the need for systemic heparinization. Such systems will accommodate a larger patient population, including the premature infant. These and other promising nonthrombogenic compounds are presently being tested in our and the University of Michigan's laboratories and should be considered for clinical trials in the next 3 to 4 years.

A new group of patients being treated with ECMO is the postoperative cardiac patient who requires cardiac assist for a short period. ECMO may be superior to left-heart assist devices in that it provides both right and left ventricular support. (Pennington: Unpublished data, 1986). Criteria for ECMO in the older patient are still being developed.

CONCLUSION

The use of ECMO has been successful in a significant number of term or near-term infants who are in respiratory failure. The morbidity of ECMO itself and, with careful selection of patients, the morbidity
of the disease processes appear to be acceptable. With improvements in the technique and the possibility of the development of nonthrombogenic systems, ECMO may soon become available to a much larger population of infants who presently die of their respiratory diseases.

REFERENCES


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