The Treatment with ECMO of Persistent Fetal Circulation following Repair of Congenital Diaphragmatic Hernia

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Abstract

Efforts in the animal laboratory over the last four years have been directed toward exploration of the use and improving the techniques of extracorporeal membrane oxygenation (ECMO), anticipating that with greater refinement ECMO might find wider application. As a result of this laboratory experience, the first clinical trials at Children's Hospital of Pittsburgh were undertaken.

Four neonates having undergone repair of a congenital diaphragmatic hernia and developing a persistent fetal circulatory pattern have been supported with prolonged (3 to 9 days) extracorporeal membrane oxygenation between December of 1979 and July of 1980, and three have survived. This encouraging experience indicates that the pattern of persistent fetal circulation in the newborn who has undergone repair of a diaphragmatic hernia can be successfully managed with ECMO even when efforts to lower pulmonary hypertension and improve oxygenation with vasodilators (tolazoline, phenothiazine, acetylcholine, prostaglandin E1) have been ineffective. The effectiveness and safety of ECMO is convincing enough to warrant its consideration as therapy for congenital diaphragmatic hernia and persistent fetal circulation prior to the use of vasodilators.

Introduction

Newborn infants with a congenital diaphragmatic hernia (CDH) can develop lethal respiratory failure after operative repair. Mortality appears to be due to a persistent fetal circulation associated with an elevated pulmonary vascular resistance. Right to left ductal and preductal shunting develop leading to progressive hypoxemia.1 If the pulmonary vascular resistance can be lowered, then survival will be improved.2

Extracorporeal membrane oxygenation (ECMO) has been useful in the treatment of CDH with persistent fetal circulation and other cases of neonatal respiratory failure.3 Much effort in our animal laboratory over the past four years has been directed toward developing the techniques of ECMO. As a result of this favorable laboratory experience, the first clinical trials at Children's Hospital of Pittsburgh were undertaken.

Between December 1979 and August 1980, four neonates post-repair of a congenital diaphragmatic hernia with persistent fetal circulatory pattern were supported with ECMO. Three have survived. By improving oxygenation and lowering pulmonary vascular resistance, right to left shunting is reversed and normal circulation re-
turned. The effectiveness and safety of ECMO make it a reliable alternative for treatment of respiratory failure in this setting.

Methods and Materials

Our ECMO circuit was first tested on neonatal lambs (weight = 4–8 kg.). Personnel were recruited from the research laboratory, perfusion team and intensive care nursing staff. The animal experiments allowed for training in the management of extracorporeal circuit priming, oxygenator gas and blood flow selection, and patient heparinization, phlebotomy and drug administration. Lectures in conjunction with a laboratory workshop were required. This in vivo application was responsible for an efficient and uncomplicated transition to the clinical setting.

The technique of prolonged extracorporeal circulation for the neonate was nearly identical to that described by Bartlett with few modifications. Venoarterial perfusion was achieved by gravity drainage from the right atrium via cannulation of the internal jugular vein and return of arterialized blood to the aortic arch via the right carotid artery. The circuit consists of a bladder mechanism which servo-regulates the pump when venous drainage is inadequate, a heat exchanger to maintain normothermia, and a Sci-Med Kolobow membrane oxygenator. The 0400-A oxygenator was found to be preferable for neonates weighing 3–4 kg because ventilation of the oxygenator with 100% oxygen maintained normocarbia unlike the 0800-A oxygenator which required a mixture of carbon dioxide and oxygen to avoid hypocarbia. Air was evacuated from the circuit by flushing with carbon dioxide after which a vacuum was applied to the gas phase of the oxygenator. A balanced crystalloid solution with 12.5 grams of albumin per 500 cc. of prime was infused and subsequently replaced with fresh whole blood. The hematocrit was between 30% and 40%. Sodium, potassium, calcium and glucose were normal. The pH was adjusted with Tris buffer, and 100% oxygen was used to ventilate the oxygenator prior to the initiation of bypass.

The extracorporeal flow was regulated to approximately 90% of the cardiac output (120 cc/kg/min.). Blood products were infused until the desired flow was achieved. Radial artery $p_O_2$ was maintained at 80–100 torr. As pulmonary function improved, the blood flow rate was decreased while the oxygenator $Fi_O_2$ was maintained at 70%. Crystalloid solutions were only used to administer heparin and to flush access lines; the volume did not exceed maintenance requirements (100 cc/kg/24 hours) and insensible losses from the oxygenator (7 cc/M²/hr.). Edema was treated with furosemide (1 mg/kg/6 hrs.). Fresh frozen plasma, packed red cells and platelets were used to replace sampling losses and to maintain extracorporeal flow.

An initial dose of heparin (200 units/kg) was given and the whole blood activated clotting time (ACT) was maintained at three times the control value with a continuous heparin infusion (approximately 100 units/kg/hr.). Platelets were administered when counts were below 70,000. Positive pressure ventilation was reduced to 40% fraction of inspired oxygen ($Fi_O_2$), a peak inspiratory pressure (PIP) of 20–30 cm of H₂O, a positive end-expiratory pressure (PEEP) of 2–4 cm of water, and a rate of 6–8 per minute. These settings reduced atelectasis and oxygenated the blood which escaped to the pulmonary vasculature.

Pulmonary function was evaluated daily by discontinuing extracorporeal support and reinstituting mechanical ventilation with 100% oxygen at a PIP of 20–30 cm. of H₂O, PEEP of 2–4 cm of H₂O, and a rate of 20–30/minute. As pulmonary function improved, $Fi_O_2$ was gradually reduced to 40% during this test period. When the arterial gases remained satisfactory at $Fi_O_2$ of 40%, support was continued for 12 hours and weaning was begun. The cannulae were then removed and mechanical ventilation instituted.

Case Reports

Case 1. A 4.0 kg. boy of 42 weeks gestation developed mild respiratory distress one hour following birth. A left diaphragmatic hernia was diagnosed and repaired at six hours of age. The preoperative acidosis and hypoxia were improved at the conclusion of the operation (Table I).

Twelve hours following surgery, he was extubated but required re-intubation at 36 hours of age for recurrent acidosis and hypoxia. Right-to-left
TABLE I
Arterial Gases During Hospital Course of Case 1

<table>
<thead>
<tr>
<th>Day</th>
<th>Time</th>
<th>Radial Artery</th>
<th>Ventilator</th>
<th>Rate (breaths/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>pO₂ (torr)</td>
<td>pCO₂ (torr)</td>
<td>pH</td>
</tr>
<tr>
<td>1</td>
<td>Preop</td>
<td>40</td>
<td>84</td>
<td>6.99</td>
</tr>
<tr>
<td>1</td>
<td>Postop</td>
<td>213</td>
<td>32</td>
<td>7.34</td>
</tr>
<tr>
<td>2</td>
<td>Extubation</td>
<td>100</td>
<td>35</td>
<td>7.40</td>
</tr>
<tr>
<td>2</td>
<td>Reintubation</td>
<td>58</td>
<td>33</td>
<td>7.24</td>
</tr>
<tr>
<td>2</td>
<td>Tolazoline</td>
<td>193</td>
<td>35</td>
<td>7.33</td>
</tr>
<tr>
<td>3</td>
<td>Pre-ECMO</td>
<td>58</td>
<td>40</td>
<td>7.29</td>
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<tr>
<td>4</td>
<td>ECMO</td>
<td>89</td>
<td>34</td>
<td>7.41</td>
</tr>
<tr>
<td>7</td>
<td>Post-ECMO</td>
<td>189</td>
<td>34</td>
<td>7.54</td>
</tr>
<tr>
<td>12</td>
<td>Post-extubation</td>
<td>73</td>
<td>43</td>
<td>7.45</td>
</tr>
</tbody>
</table>

Legend: Data are from a 4.0 kg neonate with a Congenital Diaphragmatic Hernia with Persistent Fetal Circulation. Extracorporeal Membrane Oxygenation (ECMO) was maintained for 67 hours. F₁O₂, Inspired oxygen fraction. PIP, Peak inspiratory pressure. PEEP, Positive end-expiratory pressure.

Ductal shunting was evident (radial artery pO₂ of 159 with an umbilical artery pO₂ of 36). Tolazoline (2 mg/kg/hr) was reinstituted and produced a temporary response. The ductus closed at 60 hours (radial artery pO₂ of 193 with umbilical artery pO₂ of 192). At 72 hours of age, he was again acidotic and hypoxic. Higher doses of tolazoline, and acetylcholine all failed and ECMO was instituted at 80 hours of age. Cardiopulmonary resuscitation was necessary on three occasions during the six hours prior to ECMO.

ECMO was maintained for 67 hours. Mechanical ventilation was required for five days post-ECMO. A diffuse encephalopathy evidenced by hypotonia and poor feeding was supported by electroencephalography. Because of the absence of complications during ECMO, the pre-existing hypotension and cardiac arrests were felt to be responsible for the neurological damage. He was discharged from the Children's Hospital of Pittsburgh at the age of 47 days. At three months of age his neurological status had improved significantly.

Case 2. A 3.8 kg girl of 41 weeks gestational age developed respiratory distress at birth. A left diaphragmatic hernia was repaired at 24 hours of age. Immediately after operation her acidosis and hypoxia were corrected but hypoxia associated with ductal shunting from right-to-left returned at 24 hours post-operatively. Tolazoline (2 mg/kg/hr) and prostaglandin E₁ (0.1 mg/kg/hr) were transiently effective. The previous favorable experience prompted the institution of ECMO at 48 hours post-operatively.

Within 12 hours of extracorporeal support the ductus closed (radial artery pO₂ 153 and umbilical artery pO₂ 141). After 48 hours of ECMO mechanical ventilation was resumed and terminated four days following ECMO. She was discharged at 30 days of age with no neurological deficit. She continued to be well two months later.

Case 3. A 3.5 kg girl of 43 weeks gestational age required immediate resuscitation at birth, and was transported to Children’s Hospital of Pittsburgh. A left diaphragmatic hernia was repaired. Cardiopulmonary resuscitation was required 12 hours following the operation. Prostaglandin E₁ (0.1 mg/kg/hr) therapy was begun and right-to-left shunting through a patent ductus was evident 20 hours postoperatively (radial artery pO₂ 297 and umbilical artery pO₂ 88). Respiratory failure was evident at 24 hours postoperatively and tolazoline (2 mg/kg/hr) was added but proved to be ineffective. ECMO was instituted at 48 hours after surgery.

Following 24 hours of ECMO a decision was made to ligate the patent ductus, (radial artery pO₂ 136 and umbilical artery pO₂ 23). Persistent bleeding at the thoracotomy site necessitated termination of anticoagulation and extracorporeal support at 42 hours. Improved function at four hours post-ECMO was transient and hypoxia led to death at 37 hours following ECMO.

Case 4. A 3.2 kg boy of 42 weeks gestation developed respiratory distress at birth. A right diaphragmatic hernia was repaired at 8 hours of age. He was reintubated at 16 hours post-operatively. Right-to-left ductal shunting was evident (radial...
artery pO₂ of 148 with an umbilical artery pO₂ of 48). Prostaglandin and tolazoline therapy failed and ECMO was instituted at 56 hours of age.

ECMO was maintained for 76 hours without incident. The ductus closed within 8 hours of initiation of ECMO (radial artery pO₂ of 136 and umbilical artery pO₂ of 129). Mechanical ventilation was required for 3 days and he was discharged at 32 days of age.

Results

Four neonates were supported with prolonged extracorporeal membrane oxygenation (ECMO) at Children's Hospital of Pittsburgh between December of 1979 and August of 1980. All developed progressive hypoxemia associated with persistent fetal circulation after operative repair of a congenital diaphragmatic hernia. Death was imminent for all if conventional therapy had been continued. Three lived with one mortality complicated by bleeding from the thoracotomy incision for ductus ligation. Otherwise, incisional, gastrointestinal, and intracerebral hemorrhage, sepsis, necrotizing enterocolitis, or renal failure did not occur. One child had a diffuse encephalopathy due to pre-existing cardiac arrests and prolonged hypotension; the magnitude of his neurological deficit is uncertain since his visual, auditory, and muscular function are normal at four months of age.

The three surviving children were supported for 67, 48, and 76 hours followed by 3.5 days of mechanical ventilation. The ipsilateral hypoplastic lungs expanded to fill the hemithoraces and appeared normal radiographically.

A patent ductus in three children closed spontaneously at 8 and 12 hours of ECMO. In one neonate (Case 1) the ductus was patent until 60 hours of age when it closed spontaneously before the institution of ECMO. The single death can be attributed to premature termination of ECMO necessitated by hemorrhage due to the thoracotomy for ligation of the ductus 24 hours following the institution of ECMO. Survival was possible had the support been continued for an additional 24 or 48 hours.

Platelet consumption was managed with intermittent platelet transfusions, and no significant consumptive coagulopathies occurred. Rebound thrombocytopenia following ECMO occurred as late as 48 hours after terminating support but resolved prior to discharge.

Discussion

Respiratory insufficiency can be a fatal complication when associated with persistent fetal circulation in infants who have undergone repair of a congenital diaphragmatic hernia. Pharmacologic agents capable of reversing pulmonary arteriolar vasoconstriction have shown little success.4,5 ECMO is a reliable alternative to drug intervention. Diversion of the cardiac output into the extracorporeal circuit reduces right-to-left shunting. Right sided pressures are decreased and systemic hypoxemia and acidosis are corrected. This support eliminates many potent pulmonary vasoconstrictors and allows expansion of alveoli. Pulmonary function returns toward normal and mechanical ventilation with low oxygen concentrations, low peak inspiratory pressures and low ventilatory rates can be initiated. The safety and effectiveness of ECMO demonstrated here warrant its early application for persistent fetal circulation following repair of congenital diaphragmatic hernia.

References