Extra-corporeal membrane oxygenation for paediatric respiratory failure

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Extracorporeal membrane oxygenation (ECMO) uses modified cardiopulmonary bypass technology to provide prolonged respiratory or cardiorespiratory support for patients of all ages who have failed conventional intensive care management. The use of ECMO for neonatal respiratory failure is now evidence-based following the publication of the randomised UK Collaborative Trial. ECMO use in children remains more controversial, but overall survival of 71% is possible in a group of moribund patients whose mean PaO$_2$/FIO$_2$ ratio of 61 mmHg accurately predicts death in studies of conventional ventilation. Common diagnoses for children requiring ECMO support are pneumonia and the acute respiratory distress syndrome (ARDS).

Extracorporeal membrane oxygenation (ECMO) uses modified cardiopulmonary bypass technology to provide prolonged cardiorespiratory support in the intensive care unit. ECMO is usually considered when a patient has an estimated mortality of 80% despite maximal treatment. Survival rate with ECMO is 50–95% depending on diagnosis and age group. We will discuss the principles of ECMO for paediatric respiratory failure, based on the Extracorporeal Life Support Organisation (ELSO) registry, published literature and our own experience.

History

The concept of using a pump for ‘life support’ is not new. Richardson first experimented with such a system in 1865$^1$, but was hampered by the coagulation of the blood. The discovery of heparin in 1916 by McLean$^2$ was a necessary pre-condition to the successful development of extracorporeal circulation. However, it was the death of a young woman from pulmonary embolism witnessed by Gibbon that inspired the development of cardiopulmonary bypass$^3$. Film oxygenators were not suitable for prolonged perfusion as severe haemolysis occurred after a few hours$^4$, but they did allow intra-cardiac surgery, demonstrated by the first successful clinical use of the pump oxygenator by Gibbon to close an atrial septal defect in 1953$^5$. It was the development of the
silicone rubber membrane oxygenator by Kolff, Bramson and Kolobow in the late 1950s and early 1960s that allowed prolonged circulatory support, as the separation of the blood and gas phases greatly reduced the blood damage. The first ECMO success was in 1972, when Hill et al used femoro-femoral veno-arterial ECMO to support a 24 year old man who developed ARDS following a road accident; he was supported on ECMO for 75 h.

Hill's success generated wide interest in adult ECMO leading to the US National Institutes of Health (NIH) study in the mid 1970s. This was a national multi-centre trial in which patients with severe respiratory failure who fulfilled certain 'ECM0 criteria' (fast entry—PaO₂ < 50 mmHg with FIO₂ 1 cmH₂O and PEEP > 5 cmH₂O: slow entry—PaO₂ < 50 mmHg for > 12 h with FIO₂ > 0.6 cmH₂O and PEEP > 5 cmH₂O and shunt fraction > 30%) were randomised to either receive ECMO or continue on conventional treatment. The trial was curtailed because of high mortality in both groups (91.7% conventional and 86.4% ECMO).

Although interest in ECMO waned considerably after the publication of the NIH study, two groups of researchers, Gattinoni et al in Italy, and Bartlett et al in the US believed that the fundamental principle of ECMO was correct and that greater understanding could result in better outcomes. Gattinoni, in collaboration with Kolobow, developed a low flow veno-venous system to provide extracorporeal carbon dioxide removal (ECCO₂R) to adult patients. Survivals of 48.8% were recorded which he attributed to use of low pressure and low frequency ventilation minimising barotrauma. Bartlett held similar beliefs about the importance of lung rest, but also believed that the neonatal lung had greater recuperative power than the adult. He reported the first series of successful neonatal ECMO patients in 1982. Following this lead, other groups began to experiment with neonatal respiratory ECMO. By the mid 1980s it was accepted practice for severe neonatal respiratory failure in the US. Following two modified design trials in the US and a fully randomised UK trial, it is now accepted therapy in this age group in the UK. Bartlett and other workers also began to extend their practice to include paediatric patients and, tentatively, adults, using the lessons learnt from the neonatal age group, namely low level heparinisation, avoidance of haemorrhage, lung rest and selecting patients with potentially reversible pathology. The use of veno-venous perfusion became accepted as the mode of choice for isolated respiratory failure.

Indications and contra-indications

Patients may benefit from ECMO if they have developed severe respiratory failure refractory to maximal conventional treatment,
providing that the underlying disease process is potentially reversible. Contra-indications fall into three main groups concerning: (i) the reversibility of the disease; (ii) the projected functional status and quality of life for the patient should they survive; and (iii) contra-indications to prolonged heparinisation. Conventional treatment can be considered to have failed when a-A oxygen gradient exceeds 450 mmHg for over 24 h; this level predicting death most accurately. Common diagnoses include pneumonia and the acute respiratory distress syndrome (ARDS). Pneumonia may be bacterial, atypical or viral (especially respiratory syncitial virus, RSV). ARDS may follow sepsis, massive transfusion, smoke inhalation or trauma. Often patients with sepsis present in multi-organ failure with impaired tissue oxygen delivery despite inotropic support: these patients may benefit from veno-arterial (VA) ECMO.

Absolute contra-indications are irreversible ventilator lung injury and intra-cranial haemorrhage. Irreversible ventilator lung injury due to barotrauma, volutrauma and oxygen toxicity occurs after approximately 7–9 days depending on age: younger children are more resilient. Intra-cranial bleeding is more difficult to diagnose after the fontanelles have closed. However, if a high index of suspicion is present, for example in the child with a head injury, intra-cranial bleeding should be excluded radiologically prior to ECMO. Other contra-indications include the presence of a disease incompatible with a reasonable quality of life, such as severe broncho-pulmonary dysplasia, cystic fibrosis, or other irreversible diseases, such as disseminated tumours. Extra-cranial bleeding sources are usually amenable to surgical treatment.

**Results of patients treated with ECMO**

Results from the Extracorporeal Life Support Organisation Registry (ELSO, Ann Arbor, MI, USA) and at Glenfield Hospital are given in Tables 1 and 2, respectively.

**ECMO patient management**

**Personnel**

It is essential that there is a member of staff (the ‘ECMO Specialist’) at the patient’s bedside 24 h per day who is not only competent in managing the ECMO circuit, but can also perform emergency repairs if/when it malfunctions. The specialist is usually an experienced intensive care nurse who has received additional training. Other staff include a
### Table 1  Overall results to end 1995

<table>
<thead>
<tr>
<th>Group</th>
<th>ELSO</th>
<th>Glenfield Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>% survival</td>
</tr>
<tr>
<td>Neonatal respiratory</td>
<td>11,011</td>
<td>80%</td>
</tr>
<tr>
<td>Poediatric respiratory</td>
<td>1067</td>
<td>53%</td>
</tr>
<tr>
<td>Cardiac support (poediatnc)</td>
<td>1650</td>
<td>43%</td>
</tr>
<tr>
<td>Adult</td>
<td>246</td>
<td>46%</td>
</tr>
</tbody>
</table>

### Table 2  Paediatric respiratory results at Glenfield Hospital to end of 1996

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n</th>
<th>Age (months)</th>
<th>Run (h)</th>
<th>%Veno-venous</th>
<th>PaO₂/FIO₂ (mmHg)</th>
<th>% Survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral pneumonia</td>
<td>17</td>
<td>22.4</td>
<td>261</td>
<td>59%</td>
<td>58</td>
<td>76%</td>
</tr>
<tr>
<td>RSV</td>
<td>24</td>
<td>5.9</td>
<td>169</td>
<td>71%</td>
<td>53</td>
<td>92%</td>
</tr>
<tr>
<td>Bacterial pneumonia</td>
<td>9</td>
<td>71.7</td>
<td>196</td>
<td>89%</td>
<td>49</td>
<td>89%</td>
</tr>
<tr>
<td>Aspiration pneumonia</td>
<td>3</td>
<td>12</td>
<td>274</td>
<td>100%</td>
<td>42</td>
<td>100%</td>
</tr>
<tr>
<td>Miscellaneous pneumonia</td>
<td>2</td>
<td>98.3</td>
<td>58</td>
<td>100%</td>
<td>61</td>
<td>50%</td>
</tr>
<tr>
<td>ARDS sepsis</td>
<td>8</td>
<td>53.4</td>
<td>197</td>
<td>75%</td>
<td>54</td>
<td>63%</td>
</tr>
<tr>
<td>ARDS trauma</td>
<td>2</td>
<td>106</td>
<td>222</td>
<td>50%</td>
<td>68</td>
<td>0%</td>
</tr>
<tr>
<td>ARDS miscellaneous</td>
<td>7</td>
<td>60.1</td>
<td>223</td>
<td>88%</td>
<td>61</td>
<td>75%</td>
</tr>
<tr>
<td>Near drowning</td>
<td>4</td>
<td>54</td>
<td>107</td>
<td>25%</td>
<td>141</td>
<td>50%</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>5</td>
<td>44</td>
<td>51</td>
<td>40%</td>
<td>64</td>
<td>60%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>81</strong></td>
<td><strong>34.8</strong></td>
<td><strong>191</strong></td>
<td><strong>68%</strong></td>
<td><strong>61</strong></td>
<td><strong>77%</strong></td>
</tr>
</tbody>
</table>

co-ordinator, the medical director and medical team. It is important that the director retains clinical control to ensure continuity of care. Many different skills are required to perform ECMO safely, and it is sensible to have a core team of doctors from different specialities such as cardiothoracic surgery, anaesthesia and paediatrics to provide these diverse abilities. Close liaison with other teams such as cardiology and blood transfusion is also essential.

### Cannulation

Patients must be anaesthetised and paralysed to reduce the risk of air embolism. Once the target vessels have been either exposed or initial vascular access obtained (if percutaneous cannulation is being used) a loading dose of heparin (50 U/kg) is given.

**Veno-venous cannulation**  Veno-venous or VV ECMO is the mode of choice for respiratory failure. In children weighing <6 kg, the double lumen cannula can be used. Cannulation is via the right internal jugular vein using the semi-Seldinger technique\(^20\), which does not require
ligation of the vein, and obviates the need for re-exploration of the neck for de-cannulation.

Advantages of non-ligation of the jugular vein include the drainage of de-oxygenated blood down the ipsilateral jugular vein and directly into the cannula, thereby reducing recirculation, and possibly a reduction in intracranial venous pressure which may have important advantages in terms of further reducing the incidence of intra-cerebral haemorrhage. Patients larger than 6 kg who have not started walking yet will require VA cannulation, as their femoral vessels will be too small to allow VV ECMO via two cannulae.

In two cannula VV or VA ECMO, the total flow rate in the circuit is determined by the size of the venous cannula and the height of the venous syphon (height of the bed). The best venous drainage can be obtained by the most direct route, i.e. the right internal jugular vein, which will allow the insertion of the largest and shortest drainage cannula possible. The return cannula can be inserted in either femoral vein.

There are certain facets of the Seldinger technique which become crucial if large cannulae are to be placed safely. Initial cannulation of the vein with a small cannula and confirmation of venous placement by pressure transduction removes the risk of inadvertent arterial cannulation. When dilating the track over the guidewire, great care must be taken to prevent the guidewire kinking, ensuring that the guidewire and dilator/cannula can move independently at all times. When initiating VV ECMO, low flow should be used until mixing of the patients blood and prime has occurred, otherwise infusion of large amounts of hyperkalaemic, citrated blood prime will result in hypotension or hypocalcaemic, hyperkalaemic cardiac arrest.

Veno-arterial cannulation  Veno-arterial (VA) support is indicated in the presence of haemodynamic instability for cardiac support, or when VV cannulation is not technically possible.

The right carotid artery and jugular vein are the vessels of choice although other routes have also been described. The vessels are exposed using the same approach as for the double lumen cannulae above. The jugular vein and carotid artery are encircled with ligatures proximally and distally, and heparin is given. The cephalad ligature on the artery is now tied and the cannula is inserted via an arrowhead arteriotomy. The cannula is secured with the ligatures. The tip of the cannula should lie at the orifice of the innominate artery, and not in the arch or ascending aorta. The venous cannula is inserted in exactly the same manner so that the cannula tip and side holes lie in the right atrium.
Because the carotid is not an end artery it is possible to tie it off without any short term sequelae in the majority of cases. When lesions do occur following carotid ligation they are more likely to be right sided. Risk factors for such a lesion include cardiac arrest, severe hypoxia and hypotension at the time of cannulation which results in a loss of cerebral autoregulation allowing infarction during the 3–5 min that it takes for cerebral perfusion to be re-established from the left side, thus the majority of right sided lesions could be avoided, except for approximately 10% of patients who do not have a complete circle of Willis.

Opinion regarding carotid and jugular reconstruction is divided. It is our practice to primarily re-construct only those vessels which look healthy and non-friable at the time of de-cannulation, most vessels are ligated. Jugular ligation may be more dangerous than carotid ligation as high venous pressures are thought to contribute to cerebral ischaemia by decreasing cerebral perfusion pressure. When initiating ECMO, hypercarbia should be corrected slowly, over several hours, otherwise severe cerebral vaso-constriction will result.

Advantages and disadvantages

Advantages of VA ECMO include the ability to provide circulatory as well as respiratory support, and the absence of recirculation.

Disadvantages of VA ECMO are physiological and those related to the cannulation discussed above. When the majority of the venous return is drained from the patient into the pump, right atrial pressure, right ventricular preload, pulmonary blood flow and right ventricular afterload are reduced. Reduced pulmonary blood flow leads to reduced left atrial return and low left ventricular pre-load. However, the arterial cannula is pumping blood back into the aortic arch at systemic arterial pressure and, therefore, the left ventricular afterload is high. Gradually, the left ventricle will fill from the small amount of pulmonary venous return, and veno-cordi minimi, until it has sufficient end diastolic volume to eject against the raised after-load imposed by the pump. Problems may arise, however, if left ventricular contraction is impaired, i.e. by myocarditis, as the heart will not be able to eject against the raised left ventricular afterload, and then the left ventricle will become distended with blood causing further damage. This can be prevented by venting.

VA ECMO is probably the only practical method of circulatory assist for small children.

Myocardial stun is a reversible impairment of left ventricular function related to VA ECMO. A combination of high afterload, distension and myocardial hypoxia is probably to blame. Myocardial hypoxia, as a potential cause of stun, may seem paradoxical as oxygenated blood is being pumped into the aorta. However, whilst on VA ECMO, coronary
blood flow comes largely from the left ventricle. As there is little underlying lung function this blood will be poorly oxygenated. Low pulmonary blood flow may also be responsible for the pulmonary infarcts and fibrosis seen in the post mortem material in the NIH ECMO study.

The presence of a large ductus arteriosus may cause problems on VA ECMO once the patient starts to recover and the pulmonary vascular resistance falls. High pulmonary blood flow through a large duct results in severe pulmonary oedema.

In spite of all these problems, VA ECMO remains the method of choice for inexperienced users and unstable patients particularly if circulatory support is required. VA ECMO is especially good for right sided cardiac problems. Veno-venous ECMO is the mode of choice for respiratory failure. It provides no circulatory support but can, nevertheless, still be used when there is moderate inotrope requirement (up to approximately 10 mcg/kg/min of dopamine or dobutamine).

**ECMO circuit design, equipment and priming**

ECMO circuits vary but most centres use occlusive roller pumps, usually Stockert, servoregulated with a Seabrook bladder box, Avecor silicone membrane oxygenators and Tygon S-65-HL tubing. Pressure measurement pre- and post-oxygenator is essential. Circuits are first flushed with CO₂, then washed with albumin and clear primed with Plasmalyte-A and 100 U heparin. The clear prime is displaced with blood prior to initiation of ECMO.

**Oxygen delivery, ventilation and lung management on ECMO**

The key to respiratory ECMO is the ability to maintain normal blood gases whilst resting the lungs, preventing further barotrauma. This is achieved by gentle ('rest') ventilator settings whilst on ECMO, i.e 20/10 cmH₂O, 30% O₂ and 10 breaths per minute. The high PEEP has been shown to prevent alveolar collapse allowing faster weaning. In the presence of severe barotrauma and air leaks, the lungs can be maintained static on CPAP until air leaks resolve. Blood gas tensions are controlled on ECMO by increasing extra-corporeal flow to provide more oxygenation, and increasing sweep gas flow to remove more CO₂.
**Fluid balance during ECMO**

Pulmonary oedema reduces gas exchange, and fluid restriction improves both gas exchange and outcome in a number of lung diseases. Many patients referred for ECMO have received large volume infusions during resuscitation, and may be oedematous. This is compounded by the capillary leak syndrome and low serum albumin concentration due to illness, catabolism and haemodilution. Diuresis is an important part of lung management. If haemofiltration is required, the haemofiltration circuit is attached to the ECMO circuit, avoiding the risk of dialysis catheter insertion in a heparinised patient.

**Anti-coagulation and haematology during ECMO**

Bleeding is a constant risk during ECMO, and must be prevented. Invasive procedures such as intra-muscular injections and central line insertion are avoided. Central lines, umbilical artery catheters, chest drains, etc., that are present when the patient is cannulated for ECMO are left in situ. The level of heparinisation during ECMO is much lower than during cardiopulmonary bypass (CPB). Whilst on ECMO, the ACT is kept between 160–200 s with hourly or half-hourly adjustment of heparin infusion rate, normal range 30–60 U/kg/h.

The bleeding encountered in previous reported studies of adult ECMO can be almost eliminated by tight heparin control and percutaneous cannulation. This reduces the need for red cell transfusion unless surgery is required.

When the extracorporeal circuit is exposed to the patient’s blood for the first time, plasma proteins and inflammatory cells adhere to the surface and become activated. Pre-washing the circuit with 20% human albumin solution decreases this tendency, acting to passivate the circuit to some degree. This process occurs for 2–3 days until an equilibrium is reached.

We aim to keep our patients’ platelet counts over 100,000/ml in order to reduce the risk of haemorrhage. Other factors may also contribute to thrombocytopenia (apart from activation by the circuit), such as heparin associated thrombocytopenia (HAT), anti-platelet antibodies, and disseminated intra-vascular coagulation (DIC). A DIC like picture may result from a failing oxygenator, rather than sepsis, which is more likely if the pressure gradient is increasing or the post oxygenator gases are deteriorating.

Platelet function may be preserved to some degree by infusion of the serine protease inhibitor aprotinin. Whilst aprotinin is extremely useful
to control and prevent haemorrhage during ECMO, especially if surgery is required, it makes heparin management very difficult.\textsuperscript{50-52}

The maintenance of normothermia is essential. All coagulation assays, including the ACT, are conducted at 37°C and thus have little bearing on the function of the coagulation cascade at lower temperatures. Centres advocating hypothermic cardiac ECMO have yet to document acceptable outcome data.

**Weaning from ECMO**

Patients are ready to be weaned from ECMO when their lung compliance, and chest X-ray, have improved, and when they have good blood gases on rest ventilator settings and minimum flow. Minimum flow on VV is 50 ml/kg/min and VA 30 ml/kg/min (with a lower limit of 10 rpm, or 130 ml/min for 0.25 inch tubing). At this point, the patient can be 'trialled off' ECMO for 2 h, prior to decannulation.

**Conclusions**

The efficacy of ECMO for neonatal respiratory failure is now proven, but there is still widespread scepticism about paediatric and adult ECMO. A randomised trial or a case control study may eventually resolve this issue. However, until that time, it is reasonable to offer ECMO to moribund patients with potentially reversible disease if conventional treatment is failing. The disease pattern and management of paediatric respiratory patients resembles that of adult ECMO rather than neonatal practice. Patients should be treated in experienced ECMO units as the outcome is likely to be improved, compared to ECMO provided by inexperienced users. Mobile ECMO units are now available which means that almost any patient can be transferred to a suitable unit.

**Key points for clinical practice**

ECMO should be considered to salvage children with severe, but potentially reversible, respiratory failure who are not responding to maximal intensive care. Contra-indications are intracranial haemorrhage and duration of ventilation longer than 7–9 days depending on age. Use of ECMO in experienced centres has resulted in survival of
71% of patients, almost all of whom would be expected to die by objective criteria.

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