

Extracorporeal membrane oxygenation and sepsis

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Extracorporeal membrane oxygenation (ECMO) is the use of a modified cardiopulmonary bypass circuit to provide prolonged support for severe, reversible respiratory or cardiac failure. The first successful clinical application of ECMO was reported in 1972 in an adult patient with acute respiratory distress syndrome (ARDS). Soon afterwards, ECMO was applied to patients of different ages, with the first successful report of neonatal ECMO published in 1976.^{1,2}

ECMO has a controversial history. In 1979, the first multicentre, randomised trial of ECMO for adult respiratory failure was published, showing no difference in mortality between patients supported with either conventional ventilation or ECMO.³ Many clinicians subsequently dismissed ECMO as ineffective. However, several of the centres involved in the trial had no experience in managing patients treated with ECMO, veno-arterial (VA) cannulation was used (which is not the current configuration of choice for isolated respiratory failure and may have increased the complication rate), patients lost an average of more than 2 L blood per day, and the patients treated with ECMO continued to receive high-volume mechanical ventilation, potentially perpetuating lung injury. The components of the extracorporeal circuit have evolved considerably over the past 30 years and are now safer and more effective than those used in that first trial.

At around the same time, some centres were applying ECMO to neonates with respiratory failure with considerably more success.¹ Persistent pulmonary hypertension of the newborn was recognised as the most common cause of life-threatening neonatal respiratory failure. Recovery usually occurred within several days. Two small, randomised trials in the 1980s showed improved survival in critically ill neonates who received ECMO over conventional therapy.^{4,5} However, it was not until 1996 that ECMO was convincingly shown to improve mortality in a well-designed, national randomised trial of 185 neonates with refractory respiratory failure.⁶ Subsequent analysis showed ECMO to be both cost-effective and successful to at least 4 years of follow-up.^{7,8}

ECMO has been applied in a variety of conditions other than respiratory failure, such as acute cardiac failure. Data reported to the Extracorporeal Life Support Organisation (ELSO), a group of clinicians and scientists founded in 1989 to investigate and promote ECMO, show that circulatory support is the most rapidly increasing indication for ECMO worldwide.⁹ Other relatively novel applications include using ECMO to stabilise critically ill patients in transit

ABSTRACT

Extracorporeal membrane oxygenation (ECMO) is a controversial means of life support, particularly in adults. Ongoing refinements in circuit technology and widening global experience have led to ECMO being applied to a broader group of conditions than acute respiratory failure and cardiogenic shock. Septicaemia is no longer viewed as a contraindication to ECMO. Acute respiratory distress syndrome and bacterial pneumonia are the most common conditions in sepsis that may require ECMO, although septic shock with refractory hypotension may also be an indication under certain circumstances. The last indication is generally more applicable in children than adults, because of differences in the cardiovascular response to severe sepsis seen across age groups. ECMO has a role as rescue therapy in patients with severe sepsis who would otherwise die of either hypoxaemia or inadequate cardiac output. This review describes the basic technique and application of ECMO in neonates, older children, and adults with sepsis.

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between hospitals and as a resuscitation tool during cardiac arrest.¹⁰⁻¹³

Historically, sepsis was considered a contraindication to ECMO because of concerns that the infecting organism would seed the ECMO circuit, leading to intractable bacteraemia and death. Although several reports in the 1990s refuted this assumption,¹⁴⁻¹⁷ septic shock remains a controversial indication for ECMO in most age groups. This review will elaborate on this controversy, firstly by describing the standard techniques of ECMO, then by presenting the rationale and evidence for ECMO in three groups of patients with sepsis: neonates, older children and adults.

Technique of ECMO

An ECMO circuit comprises vascular access cannulas, tubing, a pump and an oxygenator. The circuit is usually coated with a bioactive lining containing unfractionated heparin that decreases the risk of thrombus formation. In addition to reducing the amount of systemic heparin that is required, the use of heparin-bonded circuits has been associated with a reduction in some complications of ECMO, such as systemic inflammatory response and thrombocytopenia.¹⁸

Box 1. Principles of management with extracorporeal membrane oxygenation (ECMO)

The goal of ECMO is to facilitate oxygen delivery to body tissues. A given amount of blood must flow through the circuit to achieve this, with targeted flows usually 150 mL/kg/min in patients weighing < 10 kg and 2.4 L/min/m² in those > 10 kg. Targeted flows may be higher in patients with sepsis. Inotropes or vasoconstrictors may be needed as adjunctive circulatory support. Large volumes of intravenous fluid may be required to account for the effective increase in circulating blood volume, to reduce the generation of excessively negative pressures on the inlet side of the pump, and to help counteract the vasodilatory effects of the systemic inflammatory response that may be engendered by the circuit. The haemoglobin concentration is kept at a minimum of 100 g/L in older patients and above 120–140 g/L in infants. The adequacy of oxygen delivery through ECMO can be assessed by conventional means (eg, acid–base balance and urine output), as well as by measuring oxygen saturations in the venous limb of the circuit.

Ventilator settings on ECMO are generally reduced to minimise the risk of barotrauma and volutrauma and, in the case of venoarterial (VA) ECMO, to account for the reduction in pulmonary blood flow. For example, ventilator “rest” settings on ECMO might be FIO₂ 0.3, rate 5–10 breaths per minute, positive end-expiratory pressure 5–15 cmH₂O, and peak inspiratory pressure 25–35 cmH₂O. Some centres set higher FIO₂ when using peripheral VA ECMO in an attempt to maximise the oxygen content of coronary arterial blood.

To prevent clotting of the circuit, anticoagulation is given with intravenous unfractionated heparin to maintain an activated clotting

time of 1.5 to 2 times normal. This target may be temporarily lowered if there is significant bleeding. Plasma haemoglobin concentration is monitored (at least) daily to detect erythrocyte haemolysis. A high plasma haemoglobin concentration may indicate clot formation or excessively high pressures and should prompt careful review of the circuit.

In addition to maximising oxygen delivery, it is important to reduce oxygen consumption. This is facilitated in patients receiving ECMO by controlling body temperature, which is easily achieved by adjusting the set temperature of the circuit heat exchanger. Other measures, such as avoidance of overfeeding and the use of sedative drugs, are routine. Muscle relaxants should not be used unless clearly necessary.

Weaning from ECMO can be achieved in a range of ways, none of which have been shown to be superior. Once the patient's condition has been stabilised, and treatment of the underlying disease has commenced, daily trials of weaning are warranted. Ventilator settings are increased to provide full ventilatory support, the ECMO flow is gradually reduced and, in some cases, inotropes are started or increased. If systemic oxygen delivery is adequate with minimal flow through the circuit, the cannulas can be removed. An alternative strategy in patients receiving venovenous ECMO is to turn off the fresh gas supply to the oxygenator rather than to reduce extracorporeal blood flow. Monitoring ventricular performance with echocardiography while weaning can be very helpful in patients who are receiving VA ECMO. ◆

Most patients receiving ECMO require two (and sometimes three) vascular access cannulas to provide adequate flow (although special double-lumen catheters have been used in neonates for a number of years, permitting venovenous [VV] ECMO through a single cannula). VV cannulation drains blood from a large vein, typically one of the vena cavae. Blood is returned through a more centrally located venous cannula to minimise recirculation through the drainage cannula. VV ECMO results in a relatively simple system, where oxygenated blood is pumped at low pressures into the pulmonary circulation and thereby into the left ventricle. Pulsatile systemic blood flow is maintained.

VA cannulation drains blood from a vena cava and returns it through a major artery, such as the aorta, carotid (in children) or femoral arteries. This approach is associated with more complications than VV ECMO, such as vascular trauma, systemic embolisation and ischaemia. Furthermore, the resultant physiology is more complex than with VV ECMO, and there may be no net beneficial effect to cerebral or coronary oxygenation if VA ECMO is incorrectly applied. For example, if a patient with severe respiratory failure but hyperdynamic left ventricular function is placed on femoral–femoral VA ECMO (draining blood from a femoral vein and returning it through a femoral artery), then oxygenated blood will flow back up the aorta. As the left ventricle is still ejecting blood draining from the pulmonary veins, poorly oxygenated blood will flow down the

coronary and possibly the cerebral arteries. In addition, the retrograde cannulation of the femoral artery may critically compromise blood flow to that leg.

It is important that the approach for cannulation be carefully considered. In general, VV cannulation is used for respiratory failure, and VA cannulation for circulatory failure. In combined severe cardiopulmonary failure, central atrio–aortic cannulation may be necessary through a sternotomy incision.

The pumps used in ECMO are of two kinds — roller and centrifugal. The former are more commonly used in North America, the latter in Europe and Australia. The two types of pumps operate under different principles but have similar complication rates.²

Oxygenators are also of two types — membrane and hollow fibre. Historically, hollow fibre oxygenators leaked plasma, although they had favourable gas transfer characteristics. However, with the development of polymethylpentene coating (a novel substance that facilitates gas transfer but does not allow plasma leak), hollow fibre oxygenators have become the preferred type of oxygenator in many centres.^{19,20}

The clinical management of patients receiving ECMO is complex and best undertaken by a specialised team with experience in the technique.^{21,22} The basic principles of management are outlined in Box 1; more comprehensive details are beyond the scope of this article. However, it is

worth emphasising two clinical points pertinent to the use of ECMO in sepsis. First, the pharmacokinetics of most antibiotics have not been adequately studied during extracorporeal life support, and it may affect the efficacy of antimicrobial therapy. Second, the heat exchanger that warms blood passing through the oxygenator maintains the set temperature very effectively. Consequently, fever loses its utility as a clinical sign.

ECMO and sepsis

The two important manifestations of sepsis that may warrant ECMO are ARDS and septic shock. ARDS and acute lung injury are very common manifestations of sepsis in critically ill patients. If adequate ventilation cannot be achieved with conventional techniques, notwithstanding the use of inhaled nitric oxide, high-frequency oscillation, and prone positioning, then ECMO may have a role in maintaining arterial oxygenation and carbon dioxide clearance.

Septic shock has many haemodynamic manifestations, ranging from single or biventricular failure to vasodilation and impaired oxygen utilisation. In the newborn, the predominant pattern is that of persistent pulmonary hypertension of the newborn and right ventricular failure. In infants and younger children, left ventricular impairment and low cardiac output are common.²³ In older children and adults, the pattern is usually that of vasoplegic or distributive shock, often with high cardiac output. Consequently, the utility and application of ECMO in shock differs across age groups.

It is important to note that there are no universally accepted criteria to initiate ECMO. Fundamentally, if tissue oxygen delivery cannot be maintained despite optimal ventilation, inotropes and intravenous fluids, then ECMO should be considered.

ECMO in neonates

There is more evidence for the use of ECMO in neonates than in any other age group. Survival is about 80% regardless of whether the indication is respiratory or circulatory failure, but is considerably lower in congenital diaphragmatic hernias and higher in meconium aspiration syndrome.²³ The most significant randomised trial to date included 185 neonates with refractory respiratory failure, randomised to either ECMO or conventional therapy.⁶ Nineteen of these children (10%) had persistent pulmonary hypertension of the newborn secondary to sepsis, 14 of whom were randomised to ECMO. The trial was stopped early when it became apparent that the infants receiving ECMO had lower mortality. The mortality was 32% in the ECMO group and 59% in the conventional group (relative

risk, 0.55; 95% CI, 0.39–0.77). The difference in survival was seen irrespective of the primary diagnosis, although specific data on mortality in the subset of patients with sepsis were not published.

More extensive but uncontrolled data come from the ELSO database. Up to and including 2003, 19 296 neonates with respiratory failure worldwide had been supported with ECMO, of whom 2650 (14%) had sepsis. The survival to hospital discharge was 77% overall and 73% in the group with sepsis.²⁴ This is comparable to survival found at the University of Michigan in the United States, the largest ECMO centre in the world. Of the first 1000 patients treated there with ECMO, 92 were neonates with respiratory failure secondary to sepsis, 84% of whom survived.²¹ Historically, most neonates receiving ECMO had VA cannulation, but there has been a steady increase in VV cannulation (with at least 20% of this now achieved through a single cannula).⁹

The studies on neonatal ECMO deal predominantly with respiratory failure. There are no large studies specifically on cardiovascular collapse in neonates with sepsis. VA ECMO is often used in any neonate who requires inotropes at the time of cannulation, thus providing both mechanical circulatory and respiratory support. However, a recent report has challenged this practice.²⁵ In a study of 43 neonates with respiratory failure, 30 (70%) were receiving significant doses of inotropes. Twenty-six of these were supported with VV ECMO, 84% of whom survived. The remaining four who received VA ECMO had a survival rate of 75%, showing comparable mortality regardless of the cannulation site. However, the authors always used VA cannulation if the patient's mean arterial pressure remained < 35 mmHg despite the use of inotropes.

In summary, ECMO in neonates is accepted therapy in a variety of conditions, including sepsis. This is due both to the existence of randomised trials showing benefits in this age group, and to the fact that many neonatal illnesses requiring intensive care are reversible.

ECMO in children

ECMO is more controversial in children and infants older than 30 days than in the neonatal population. Survival is unquestionably lower. The reasons for this are unclear but most likely relate to the irreversible nature of many illnesses in this age group. From the ELSO data, overall survival for paediatric ECMO patients with respiratory failure is around 55%, comparable to published case series.^{21,26,27} Patients with respiratory failure from sepsis have a similar outcome. For example, by mid-2004, 290 children with bacterial pneumonia had been supported with ECMO, 157 of whom (54%) survived.⁹

The use of ECMO as mechanical circulatory support in children with sepsis was not well described until the publication of two series in the mid-1990s.^{14,15} One report was of nine patients with septic shock who had inadequate organ perfusion despite vigorous fluid resuscitation and large doses of catecholamines. All were treated with VA ECMO. Five survived to hospital discharge, demonstrating for the first time that ECMO was not contraindicated in children with sepsis with circulatory collapse unresponsive to other measures.¹⁴ The second report examined the use of ECMO in children with meningococcaemia. Four of seven children who received VA ECMO for refractory shock survived, as did four of five with ARDS who received VV ECMO.¹⁵

These results contrast with a recent report of 11 children with meningococcaemia who were supported with ECMO.²⁸ All five children with respiratory failure treated with VV ECMO survived, but only one of the six with septic shock and multiorgan failure treated with VA ECMO. Consequently, the institution that published this report no longer provides ECMO to children with multiorgan failure from meningococcaemia. However, ECMO should not be automatically discounted simply because mortality appears higher than for other indications. A similar situation exists with other infections. For example, children with pertussis severe enough to require ECMO have a very high mortality, but this should not result in their immediate exclusion from ECMO support.²⁹ It seems more appropriate to consider each patient individually rather than to have fixed rules based on the infecting microorganism. Fungal sepsis was also traditionally considered a contraindication to ECMO, but a recent report has shown that children with this condition can be treated successfully.³⁰ Consensus guidelines from the American College of Critical Care Medicine recommend that ECMO be considered as rescue therapy in children with septic shock who are unresponsive to all other therapies.²³

ECMO in adults

The use of ECMO remains the most controversial in adults, regardless of the underlying diagnosis. There are many uncontrolled case series of acute respiratory failure supported with ECMO,^{21,31} including some for specific infections such as varicella and hantavirus infection.^{32,33} However, well-designed trials of the sort that exist for the neonatal population are lacking. The survival rate in adult patients requiring ECMO for respiratory failure is around 55%, comparable to that in the paediatric population.⁹ ECMO in sepsis does not appear to be associated with higher mortality than ECMO for other indications. For example, by mid-2004 the ELSO register had recorded 186 adults with bacterial pneumonia who had been supported with ECMO, 97 of whom (52%) survived. Although sepsis-

induced ARDS is not specifically recorded by ELSO, 100 patients with ARDS not caused by surgery or trauma survived from a total of 196 (51%).⁹

There is minimal experience with ECMO for adult septic shock. Although usually characterised as distributive shock,²³ the haemodynamic response in adult sepsis is complex. Left ventricular dilation and decreased ejection fraction are common, although cardiac output usually remains high. Paradoxically, preserved ejection fractions and the inability of the ventricle to dilate have been associated with higher mortality.³⁴ Three mechanisms of death from sepsis have been described in adults.³⁵ Late deaths are typically due to multiorgan failure. Early deaths occur either from refractory hypotension and distributive shock or progressive ventricular dilation and cardiogenic shock. In the first two mechanisms of death, early intervention with ECMO might theoretically minimise oxygen consumption by controlling temperature, but otherwise be of little value. However, in the third mechanism of death, akin to septic shock in children, early intervention with ECMO might be of benefit. There is one report of an adult with distributive shock from staphylococcal septicaemia who subsequently developed severe left ventricular failure, and was treated successfully with ECMO.³⁶

ECMO is used less frequently in adults than in children. This may reflect the lack of clear evidence to guide therapy, the perceived cost of using labour-intensive, unproven therapy in critically ill patients, or a general scepticism among most of the critical care community who treat adults. In addition, many physicians who use ECMO routinely are often sufficiently convinced of its efficacy that they are unwilling to participate in a trial in which patients are randomised to either ECMO or what they perceive as almost certain death. It is for this and many other reasons that trials of any form of life support are very difficult to conduct.¹ However, a prospective randomised trial of ECMO in adult respiratory failure is currently underway in the United Kingdom. The trial design is similar to the earlier UK study in neonates⁶ and is hoped to address long-standing questions concerning the efficacy of ECMO in the adult population.

Conclusions

ECMO is a valuable form of life support that should be generally reserved as rescue therapy in those who are unsupported by other means. Whenever possible, VV cannulation should be used, as it has a lower complication rate, and the resultant physiology is less prone to miscalculation. VA cannulation should be reserved for those with severe circulatory failure or combined cardiorespiratory failure.

Although traditionally not regarded as appropriate ECMO candidates, patients with sepsis can be successfully sup-

ported. In sepsis, the most common indication for ECMO is sepsis-induced respiratory failure. Sepsis with cardiovascular collapse is a less common indication and is associated with a poorer prognosis than other conditions. Nevertheless, ECMO remains accepted therapy in the paediatric and neonatal populations.²³ It is unlikely that the use of ECMO in septic shock will be the subject of a randomised controlled trial. Clinicians treating patients who have sepsis and cannot be kept alive with conventional measures should consider referring them to an ECMO centre.

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