Extracorporeal Membrane Oxygenation

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Extracorporeal life support has evolved from a need for improved methods of gas exchange and cardiac support for patients with severe respiratory or cardiac failure, or both. Its development has been linked to that of cardiopulmonary bypass technology used in the operating room for cardiothoracic surgery. The first oxygenators to be widely used were bubble oxygenators, characterized by a direct blood-gas interface. Although effective, hemolysis limited the duration of safe exposure (1). The subsequent development of membrane oxygenators with a physical separation between the blood and gas phases minimized hemolysis and introduced the potential for long-term support (2). Membrane oxygenators are now used in many variations of extracorporeal life support, including venoarterial (VA) and venovenous (VV) extracorporeal membrane oxygenation (ECMO), extracorporeal carbon dioxide removal (ECCO₂R), and intravascular oxygenation (IVOX). This review will discuss all of these technologies but will focus primarily on the technique, history, and clinical indications for VA ECMO.

Venoarterial Extracorporeal Membrane Oxygenation

Venoarterial ECMO describes a circuit in which blood exits from the venous system, is oxygenated and ventilated, and is then returned to the arterial circulation (Figure 1). A drainage (venous) cannula is placed into the right atrium via the right internal jugular vein, which is distally ligated. Blood flows from the right atrium via gravity to a bladder and then onward to an occlusive blood pump. The bladder, with a volume of 30–50 mL, adds capacitance to the system, acts as a safeguard against inconsistent venous return, provides an access site for sampling and blood and drug administration, and "traps" any air entrained in the venous limb of the circuit. The occlusive, nonpulsatile blood pump is servoregulated to the pressure of the venous return. Venoarterial ECMO flows are usually directed to achieve approximately 100 mL·kg⁻¹·min⁻¹, that is, one-half to two-thirds of the patient's cardiac output. This flow, although usually adequate and easily achieved in neonates, is more problematic in adults. Venous drainage is the greatest limitation to ECMO flow, and, as such, it is important to cannulate the right atrium with the largest venous catheter possible (12–14F for neonates, 16–22F in children, and up to 28F in adults). After the pump, the blood enters the membrane oxygenator, which is a silicon envelope coiled around a spool and then encased in a plastic sleeve. The membranes are rated for gas transfer capability, which is a function of surface area: from 0.4 m² for a neonate to 3.5–4.5 m² for an adult. Fresh gas flows through the inside of the envelope while blood travels outside in a countercurrent direction. The sweep gas is responsible for delivering oxygen and washing out carbon dioxide; its composition and flow rate are adjusted in response to arterial blood gases; the usual fraction of inspired oxygen (FIO₂) ranges from 40% to 100%, with 1%–5% CO₂ added to maintain normocarbia. After the oxygenator, blood passes through a countercurrent heat exchanger and is then returned to the ascending aorta by way of a single end-hole catheter. At the time of cannulation, the arterial catheter is advanced through the right common carotid artery, which is ligated distal to the catheter.

There is a safety bridge connecting the proximal venous and distal arterial tubing, which is used to ensure continued circulation of blood through the membrane in the event that temporary discontinuation of ECMO is necessary. Normally occluded, the bridge can be opened while the catheters proximal to the patient are clamped, effectively separating the patient from the circuit.

Before cannulation, the circuit is primed with crystalloid and albumin, followed by heparinized blood corrected to normal pH and calcium concentration. The standard circuit volume, including the prime, is 500–650 mL in a neonate and as high as 2400 mL in the older child and adult. The patient and the circuit are

Accepted for publication June 1, 1992.
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then heparinized by a continuous infusion maintaining an activated clotting time of 200-240 s (1.5-2 times normal). This maintains a balance between catastrophic clot formation and bleeding complications.

While on VA ECMO, the native lungs participate little in gas exchange; therefore, the ventilator is set at "rest" settings. Although the more conventional settings would include room air, rate of 4 breaths/min with a peak inspiratory pressure of 20 cm H₂O, and positive end-expiratory pressure of 5 cm H₂O, some authors have reported improved native lung recovery with the use of higher positive end-expiratory pressures in the range of 12-14 cm H₂O (3). The ECMO flows maintained in any particular patient are chosen to support adequate gas exchange and mean arterial pressure. While on ECMO, the goal is Pao₂ 60-100 mm Hg and Paco₂ 30-45 mm Hg. Hypocarbia is not routinely attempted.

The duration of ECMO support is a function of both the patient's rate of recovery from the underlying disease and from the frequent development of near complete opacification of the lung fields as seen by chest radiograph after the initiation of ECMO support. The etiology of this "whiteout" is poorly understood; however, it corresponds to a period of markedly decreased lung compliance during which time the patient's ability to exchange gas by way of the lungs is nearly impossible to support in the absence of ECMO (4,5). The decision to wean from ECMO is made when the lung compliance and radiographic image improve and the right-to-left shunt has decreased. The ECMO flow is slowly decreased while the patient’s ability to support adequate gas exchange is tested. When the patient can demonstrate gas exchange with acceptable levels of conventional support, the ECMO catheters are removed, and routine conventional ventilatory support is continued.

Extracorporeal membrane oxygenation was first attempted in the early 1970s in a select population of adult patients with acute respiratory failure (ARF) refractory to conventional therapy (4,6,7). The first adult survivor was reported by Hill et al. in 1972 (8), and over the next 5 yr >150 adults were supported with ECMO with a reported survival rate of 10% (7). In response to these early reports, the National Institutes of Health sponsored a multicentered study to compare the effects of ECMO and conventional mechanical ventilation (CMV) in an adult population with terminal ARF. Ninety-six patients with an 80% predicted mortality were selected and randomized to CMV or ECMO. Unexpectedly, the results showed no difference in survival rates, with 8.7% survival with CMV and 9.3% survival rate with ECMO (6).

Critics of this study claimed that the study entry criteria selected too heterogeneous a group of patients who, at the time they met study entry criteria, already had irreversible lung damage either from their primary disease or secondary to their ventilator management. They proposed that earlier institution of ECMO might have prevented pulmonary fibrosis, thus improving survival (4,7). The study also imposed a 5-day run limit on the use of ECMO in patients without clearly defined improvement. It is possible that this led to the premature termination of what might have proved to be an effective means of support. However, this study essentially halted the use of ECMO in adults with ARF. In retrospect, these results may not be applicable to the use of ECMO in the 1990s. During the period of the National Institutes of Health study, many patients were victims of an extremely virulent form of influenza virus with resultant pulmonary necrosis, limiting the possibility of reversible lung pathology. Also, compared to the newer, more efficient ECMO circuits, the circuits used during the 1970s captured much less of patients' cardiac output and relied much more on their lungs to achieve oxygenation and ventilation.

Neonatal Extracorporeal Membrane Oxygenation

A new population of neonatal patients with reversible lung disease have emerged as candidates for
ECMO. There are a number of obvious differences between potential adult and neonatal ECMO patients. Adults supported with ECMO often had ARF from destructive primary lung disease or from adult respiratory distress syndrome, which may result in severe parenchymal injury and fibrosis (9). In contrast, neonatal ARF is usually secondary to an abnormality of the pulmonary vasculature, immaturity of the surfactant system, or a chemical pneumonitis with small-airway obstruction, as in meconium aspiration (10). It is unusual for the neonate to have a primary destructive pulmonary process. This gives the neonate a higher likelihood of having reversible lung disease. Despite this advantage, the neonate, as well as the adult, is still subject to secondary lung damage from mechanical ventilation associated with barotrauma and elevated levels of inspired oxygen. Therefore, it would not only be important to select patients with reversible lung processes, but also to identify these patients early in the course of their disease and therapy before irreversible iatrogenic damage can occur. Fortunately, the usual natural history of neonatal respiratory failure makes it possible to identify infants with increased predicted mortality within the first few days of life, before major ventilator toxicity has occurred.

Each of these factors contributed to the success of neonatal ECMO. After a number of scattered case reports (11-15), in 1982 Bartlett et al. (16) published the first series of neonatal patients as a phase I study evaluating the safety and efficacy of ECMO support in infants. An experience of ECMO support in 45 infants during 1974-1982 was reported. The patient population was broad, with gestational ages of 27-44 wk and birth weights of 1-5.2 kg. The investigators tried to identify patients with a <10% chance of survival by devising a scoring system called the Neonatal Pulmonary Insufficiency Index in the first 24 h of life or by the attending neonatologist's clinical assessment that the patient was about to die with routine management. Patient diseases included respiratory distress syndrome, meconium aspiration syndrome (MAS), persistent fetal circulation, and sepsis. The overall survival was 50% and, by diagnosis, respiratory distress syndrome 43%, meconium aspiration syndrome 68%, persistent fetal circulation 60%, and sepsis 25%. Clearly the survival was considerably greater than the anticipated 10%, and the authors concluded that ECMO was effective and had improved outcome compared with conventional management.

As a result of cooperation among neonatal ECMO centers, the national experience has been continuously collected since 1981 in the national ECMO registry. This registry is sponsored by the Extracorporeal Life Support Organization and was created for the purpose of capturing the ECMO experience to track growth, success, or failure. Although patient reporting is voluntary, it is estimated that the registry captures at least 95% of the ECMO cases in the United States. However, because the registry includes different institutions, it reflects different degrees of local expertise with implementing and maintaining ECMO as well as different modes of conventional ventilatory support, and different criteria for predicting anticipated mortality. This results in a very heterogeneous population. In 1988, Toomanian et al. (17) reported the first formal review of the registry: 715 infants treated at 18 centers between 1980 and 1987 were included. These infants met their own institutional criteria for 80% predicted mortality. With ECMO support, 81% survived.

Inclusion and exclusion criteria for neonatal ECMO have been formulated to include patients with a high predicted mortality and a reversible pulmonary process, and to exclude patients with a physiologic process that would not benefit from ECMO, or an underlying condition that would greatly increase the inherent risk of ECMO (Table 1). Specific entry criteria for neonates include an 80% predicted mortality, at least 34 wk completed gestation, and a minimal weight of 2 kg. The exclusion of infants <35 wk of gestation results from an early limited ECMO experience in which premature infants had massive intraventricular hemorrhages (IVH) (18,19). Neonates are also excluded if they have sonographic evidence of a significant IVH (4), with most ECMO centers accepting patients with grade I IVH (hemorrhage into the germinal matrix) and some centers accepting patients with IVH of grade II severity (extension of the hemorrhage into the ventricles). The inherent risk is that with systemic heparinization, the hemorrhage will increase in severity. Extracorporeal membrane oxygenation is not a cure for lung or heart disease; rather, it is a form of cardiopulmonary support while the patient's underlying pathophysiologic process abates. Therefore, infants are excluded if the hypoxemia is secondary to congenital heart disease or

Table 1. Inclusion/Exclusion Criteria for Neonatal Extracorporeal Membrane Oxygenation

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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<tbody>
<tr>
<td>1. 80% predicted mortality with conventional therapy</td>
<td>1. Sonographic evidence of significant massive intraventricular hemorrhage (&gt;grade I)</td>
</tr>
<tr>
<td>2. 34 wk completed gestation</td>
<td>2. Previous mechanical ventilation of &gt;10 days</td>
</tr>
<tr>
<td>3. Minimal weight 2 kg</td>
<td>3. Hypoxemia secondary to congenital heart disease</td>
</tr>
<tr>
<td>4. Other anomalies precluding survival</td>
<td>4. Other anomalies precluding survival</td>
</tr>
</tbody>
</table>
if they have other anomalies precluding reasonable survival. To identify these infants, all prospective ECMO candidates must first undergo a cardiac echocardiogram. In addition, to avoid supporting infants with preexisting ventilator damage, >10 days of previous mechanical ventilation is usually considered an exclusion criterion.

The greatest problem with patient selection has been the questionable validity of indicators of predicted mortality based on historical experience. The criteria presently used were formulated from retrospective chart reviews of infants with persistent pulmonary hypertension of the newborn (PPHN) (18,20–22). Most indicators use some measurement of oxygenation: alveolar-arterial oxygen difference, oxygenation index, and Pao2 (Appendix). Oxygenation index is the most commonly applied predictor, with an 80% predicted mortality identified by oxygenation indices ranging from 0.40 to 0.55 at various centers. It is important that every center determine what is most accurate at their own institution. Despite best efforts, historical control data provide a number of problems and inaccuracies. Historical data evaluate the care given during a prescribed time, and its relevance to current management is questionable. The use of historical controls has been criticized for potentially overestimating mortality. Cole et al. (23) reported that when retrospective ECMO criteria were prospectively applied to a neonatal population, the predicted 80% mortality was in reality only 23%, using only conventional mechanical ventilation. Dworetz et al. (24) from Yale reported a similar study and found only a 17% true mortality.

There have been two prospective randomized studies designed to overcome the limitations and criticisms of historical control populations and advances in CMV. The first by Bartlett et al. (25) compared ECMO with conventional management in patients with a predicted 80% mortality. The study design utilized play-the-winner randomization, which resulted in only 1 patient receiving CMV and 11 patients receiving ECMO. All the ECMO patients survived, but the conventionally treated patient died. This study was published in support of ECMO but was accompanied by much criticism (26). In a second study, O’Rourke et al. (27) again compared ECMO and conventional therapy. This study used an adaptive design; the first stage of 50:50 randomization was followed by a second stage with all patients receiving the “better” therapy. Initially, 10 patients were supported conventionally and 6 survived; whereas of the 10 patients receiving ECMO, all 10 survived. An additional 19 patients were supported with ECMO, with only one death. This study also supported ECMO, but like that of Bartlett, has been criticized for study design (28,29). Despite the limitation of patient selection and paucity of controlled studies, ECMO is now considered standard care for many full-term neonates with pulmonary diseases.

Presently there are 5479 neonates enrolled in the registry, with an overall survival rate of 83% and a disease breakdown as shown in Table 2. What becomes clear from this is that survival is a function of primary diagnosis, with infants with meconium aspiration syndrome and PPHN experiencing a higher survival rate, and infants with congenital diaphragmatic hernia a much lower survival rate. Although ECMO “run times” are not standardized, some expected time frames do exist. The average run for all neonates is 5.5 ± 2.5 days, with meconium aspiration syndrome and PPHN usually lasting 5 days, neonatal sepsis 5–7 days, and congenital diaphragmatic hernia 7–14 days.

There are many interventions associated with ECMO that increase risk of morbidity. These include ligation and cannulation of the right common carotid artery and right internal jugular vein, systemic heparinization, exposure to blood products, being sick enough to meet entry criteria, and exposure to and possible failure of any of the component parts of the ECMO circuit.

The most frequent complication is bleeding. The most common sites of bleeding include the neck cannulation site, the central nervous system (CNS), and the tracheobronchial tree. Although systemic heparinization and alterations in normal platelet number and function are thought to be responsible for much of this observed bleeding, the etiology of CNS hemorrhage appears to be multifactorial. Possible additional factors include alteration of the normal arterial and venous cerebral circulations (30), the return of unfiltered blood to the systemic circulation, and systemic hypertension. Central nervous system hemorrhage is certainly the most problematic, with a reported 15% incidence in most centers (17,31). During ECMO, serial cranial ultrasound scans are ob-

### Table 2. Extracorporeal Life Support Organization Registry; Neonatal Entries as of October 1991

<table>
<thead>
<tr>
<th>Disease</th>
<th>No. of patients</th>
<th>Survived (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAS</td>
<td>2067</td>
<td>93</td>
</tr>
<tr>
<td>RDS/HMD</td>
<td>788</td>
<td>85</td>
</tr>
<tr>
<td>CHD</td>
<td>996</td>
<td>61</td>
</tr>
<tr>
<td>Pneumonia/sepsis</td>
<td>752</td>
<td>77</td>
</tr>
<tr>
<td>PPHN</td>
<td>792</td>
<td>88</td>
</tr>
<tr>
<td>Other</td>
<td>184</td>
<td>79</td>
</tr>
<tr>
<td>Total</td>
<td>5479</td>
<td>83</td>
</tr>
</tbody>
</table>

MAS, meconium aspiration syndrome; RDS, respiratory distress syndrome; HMD, hyaline membrane disease; CHD, congenital diaphragmatic hernia; PPHN, persistent pulmonary hypertension of the newborn.
tained to detect CNS hemorrhage, and ECMO is discontinued in the presence of large or expanding hemorrhage.

Results from the ECMO registry disclose an 11%–30% incidence of CNS injury, leading to anything from subtle to devastating damage (32). Long-term neurologic follow-up of the ECMO survivors has been hindered by the young age of this population and the lack of a comparable control group. The results are limited to reports from several institutions. Towne et al. (33) published one of the first reports from the early ECMO experience at the University of California, Irvine. A 1–14-yr evaluation of 18 patients was reported: 13 (72%) had normal growth and development; 3 (17%) had moderate neurologic deficit; and 2 (11%) were severely injured. More recent clinical experience has been reported from Washington, D.C. (Children’s National Medical Center), University of Virginia, and University of Michigan. The Children’s National Medical Center studied 42 consecutive patients over a 2-yr period (31). The patients were evaluated with cranial ultrasound while on ECMO, computer tomography studies of the head before discharge, and neurodevelopmental tests and neurologic examinations at 1 yr of age. Despite the fact that 17 (41%) of the patients had abnormal radiographic findings by cranial ultrasound and computed tomography, only 9 (21%) of the children were delayed, 8 (20%) had suspect examinations but were not delayed, and the remaining 25 (59%) patients had normal neurologic examinations. Krummel et al. (34) evaluated six patients and reported five (83%) normal 1–3 yr after ECMO. Andrews et al. (35) reported the follow-up of their first 14 survivors: 9 (64%) had normal motor development; 10 (71%) had normal mental ability. Two more recent studies have interpreted their data by comparison with previously reported morbidity statistics among neonates with severe respiratory failure treated with conventional therapy (36,37). Essentially, they reported no statistical differences between the developmental outcome of ECMO survivors and conventionally treated neonates.

Renal complications also occur commonly during ECMO. The development of renal failure, thought to be suggestive of the development of either pre- or intra-ECMO multisystem organ failure, carries a predicted mortality of >80% shown in one study (38). Hypertension, manifested as systolic pressure >100 mm Hg while on ECMO, is another commonly observed phenomenon, with an incidence as high as 58% in one study (39). The occurrence of hypertension does not correlate with plasma renin levels, colloid volume infused, or milliequivalents of sodium delivered. Possible etiologies include an increase in cardiac stroke volume, preexisting myocardial dam-

age in the nonhypertensive patients, or an alteration in the patient’s ability to handle sodium or water.

To circumvent the complications associated with carotid ligation, some centers are attempting carotid artery reconstruction. A recent study, published in 1991, utilized noninvasive magnetic resonance imaging and ultrasound to demonstrate patency of the right common carotid artery in 14 of 18 infants undergoing reconstruction (40). Infants were considered ineligible for this procedure if they demonstrated neurologic abnormalities before decannulation or if they had undergone reexploration for excessive bleeding at the cannulation site. Six-month follow-up was obtained in only seven of the infants; however, the patency rate was 100%.

The registry review (17) also pointed out the importance of the institution’s previous experience with ECMO. The patient data were analyzed to see whether outcome improved with technologic experience. Survival of the first 10 patients at all centers was 73.5%, compared with 83.7% if the first 10 patients were excluded. This difference could not be explained by any differences in pre-ECMO characteristics of these patients. Of note, the first 10 patients had a higher incidence of complications (2.26 per patient) compared with later patients (1.6 per patient).

The current status of neonatal ECMO can best be described as controversial and changing. The national experience has steadily grown over the past years. The results of that experience suggest a very high survival rate, and short- and long-term follow-up studies suggest a tolerable morbidity. However, like so many therapies aimed at critically ill patients, ECMO has not undergone the rigors of a large conventional, prospective, randomized study to prove or disprove efficacy. What makes this increasingly difficult is that as ECMO technology has improved, so has CMV, and perhaps these improvements may diminish the disparity in patient outcome from these two methods of support.

The main change in CMV is a progression toward “gentle,” less aggressive ventilator support. The mainstay of conventional management of PPHN has been to maximize pulmonary vasodilation by maintaining relative hyperoxia and inducing both a respiratory and metabolic alkalosis (41,42). However, this approach exposes the infant’s lungs to 100% oxygen and often markedly elevated airway pressures. Some clinical investigators believe that not only does this approach inflict significant damage to the lungs, but that there is no clearly proved benefit (43,44). These clinicians suggest the use of low airway pressures and Fio2 to maintain just adequate arterial blood gases: Pao2 50–60 mm Hg and Paco2 <60 mm Hg. Wung et al. (45) from Columbia University have been one of the proponents of this “gentle” therapy. In
1985, they reported 90% survival without the use of ECMO in term neonates with severe respiratory failure. In addition, they also suggest that their method of ventilation results in a much lower incidence of bronchopulmonary dysplasia. Proponents of ECMO state that the risk of residual lung disease in ECMO patients (0%-8%) compares favorably with those treated with conventional mechanical therapy (up to 35%), and some individuals speculate that earlier ECMO intervention may help to eliminate chronic lung disease altogether (18,35,46). These reports do demonstrate dramatically the institutional and chronologic heterogeneity of CMV and the potential problems in utilizing ECMO criteria developed in one institution at a fixed time.

Pediatric Extracorporeal Membrane Oxygenation

As the technology for neonatal ECMO became routine in many pediatric centers, ECMO was soon applied to older children who were thought to be at risk for dying of pulmonary disease. In most situations, it has been offered as a "last resort" or rescue therapy on an individual case basis (8,47-51).

The existing experience of pediatric ECMO for ARF is documented in several small clinical reports and in the Extracorporeal Life Support Organization registry (48,50,52). As of October 1991, 285 pediatric patients have been reported in the registry. There are no specific entry criteria for pediatric ECMO. Typically, ECMO is reserved for those patients with an anticipated 100% mortality, as judged by their physician. The heterogeneity of patient age, development, and etiology of disease makes it even more difficult to define this population compared with neonates.

In the older child, ARF is caused by a number of diseases, which, although different, may share some common pulmonary pathophysiology. Unlike the neonate with PPHN, many of the acute respiratory diseases in children are associated with direct air-space injury, with necrotizing alveolitis, and with deposition of fibrin (53,54). In addition, most older children are exposed to longer periods of ventilatory support before meeting criteria for CMV failure. As a result, the older child has a much higher probability of iatrogenic injury from elevated airway pressure and oxygen exposure. In addition, while most lung diseases share a final common pathophysiology, the inciting event can be remarkably different. It is not clear that ARF from hydrocarbon ingestion is the same as ARF from viral pneumonia or near drowning. Also, because pediatric patients represent a wide spectrum of ages, and because the child's lungs continue to grow, mature, and remodel during the first years of life, one wonders whether equivalent injuries have the same morbidity and mortality in a child aged 10 mo compared with one aged 10 yr.

The natural history of ARF in older children is poorly understood. Specifically, is death caused by inadequate gas exchange? Studies of adult patients with ARDS show that <20% of these patients die of respiratory failure (55,56). The majority die of multi-system organ failure, and mortality is particularly elevated in the presence of sepsis or malignancy, or both. Similar studies in pediatric patients are scant, but the existing evidence supports the same findings (57-59). This is in sharp contrast to the neonate with PPHN who often succumbs to hypoxemia. Therefore, in the older child can maintenance of gas exchange change the natural course of the disease? Should ECMO be offered earlier before multi-system organ failure occurs, or should it be a contraindication for ECMO?

To date, most pediatric ECMO has used the same technologic approach as routine neonatal VA ECMO, with cannulation of the right internal jugular vein and the right common carotid artery. The risks of ECMO in the older patient are similar to those in the neonate. Although there is anecdotal evidence that the older child has more hemorrhagic complications with pulmonary and cannulation site bleeding, there appear to be fewer CNS hemorrhagic complications (60).

Cardiac Extracorporeal Membrane Oxygenation

Venoarterial ECMO has also been used to support cardiac function in pediatric patients with cardiovascular dysfunction. The majority of these patients are children who develop low cardiac output syndrome or severe pulmonary artery reactivity, or both, after surgical repair of congenital heart defects. There are also a few children who have been placed on ECMO preoperatively, and others with myocarditis or cardiomyopathy in whom ECMO has provided a bridge to cardiac transplant or hemodynamic support until their myocardial function resolves.

As of the end of 1991, 494 children have been supported with ECMO for acute cardiovascular failure. The majority (90%) of these patients were placed on ECMO after surgical repair of congenital heart disease; the remainder had cardiac failure from myocarditis or a cardiomyopathy (52). The overall survival rate is reported to be 47%. A few patient series have been reported (61-65), and a number of patterns have emerged. The average duration of ECMO support in these patients was much shorter than for ARF patients. Pennington et al. (66) reported an average
ECMO duration of <4 days in survivors and noted that those requiring >7 days subsequently died. Another observation was that survival correlated with the time of ECMO initiation; patients who required ECMO support either in the operating room or within the first six postoperative hours experienced a high mortality of >90%, whereas those who demonstrated more perioperative stability and were placed on ECMO at >4 h had an improved outcome. This dramatic difference may represent the fact that the group requiring early ECMO intervention had greater myocardial damage or that they suffered more hemorrhagic complications, or both, as a result of the resumption of systemic heparinization before adequate hemostasis.

The indications for ECMO as postoperative support are poorly defined. Similar to the pediatric ARF population, there have been no retrospective or prospective controlled studies. The heterogeneity of the population makes it difficult to identify predictors of mortality. Most clinicians select ECMO candidates on the basis of evidence of decreased end-organ perfusion and the failure of pharmacologic support of the circulation. Dosage of inotropic agents, elevation of right or left atrial pressures, decreased mixed venous oxygen saturation, metabolic acidosis, decreased urine output, and increased serum levels of liver enzymes are all factors used to select patients. Investigators have reviewed their experience with selected groups of patients to predict mortality and to guide patient selection for ECMO. As an example, Klein et al. (65) reported in a retrospective chart review that there was a <3% survival in postoperative cardiac patients, who at 8 h after bypass required >10 µg·kg⁻¹·min⁻¹ of dopamine and had <2.0 mL·kg⁻¹·h⁻¹ urine output. Obviously, these findings vary with the types of cardiac diseases studied, the preoperative status of the patients, the surgical repair, and the institutional approach to inotropic management. These results must be evaluated independently in each institution, and regardless of the indicators used, it is important to identify these ECMO candidates before the development of irreversible end-organ failure and cardiac arrest. Two clear prerequisites for postoperative ECMO include a successful surgical repair and cardiac anatomy compatible with ECMO cannulation. Contraindications for postoperative ECMO include irreversible neurologic damage and active uncontrolled bleeding at the surgical site.

The ECMO procedure in acute cardiovascular failure is similar to VA ECMO used for ARF. The flow rates required to support perfusion are often greater: 100–200 mL·kg⁻¹·min⁻¹. This emphasizes the need for very large venous catheters. Transthoracic cannulation is often used to allow larger catheters; however, the main disadvantage of this is the difficulty in assessing and treating cannula site bleeding.

During ECMO, the blood returning at high flow rates to the ascending aorta can increase left ventricular afterload. This can have a negative impact on those patients with left or biventricular failure. Decompression of the left side of the heart can be achieved through placement of a left atrial or left ventricular catheter (65,66). Although this may help unload the left ventricle, it is obviously more invasive and provides added risks.

Other forms of extracorporeal oxygenation and support have evolved from the original techniques and applications of VA ECMO. These include VV ECMO, ECCO₂R, and IVOX.

Venovenous Extracorporeal Membrane Oxygenation

In VV ECMO, blood is drained from the right side and returned to the right side of the circulation. This can be accomplished with either a single- or double-catheter system. In the double-catheter system, one catheter is used for drainage and the other for return (67,68). Most commonly, outflow is through a right atrial catheter, and blood is returned to the femoral vein (68). Unfortunately, with this system there is recirculation when some of the oxygenated blood returned via the femoral vein is captured by the outflow catheter in the right atrium and is recirculated through the ECMO circuit.

Various types of single-catheter VV ECMO have been attempted. The most promising is a double-lumen catheter that allows continual outflow through the proximal port and inflow through the distal port (69). Despite the two ports, there is some recirculation of oxygenated blood. Another single-catheter system uses a single-lumen catheter. Similar to dialysis systems, there are separate infusion and outflow times that are controlled by a tidal flow system (70,71).

Regardless of which system is used, VV ECMO has some basic differences compared with VA ECMO. Perhaps most important is the fact that VV ECMO does not support cardiovascular function. Second, the patient’s Pao₂ is lower in VV ECMO than in VA ECMO; this reflects the fact that there is some degree of recirculation of oxygenated blood back into the ECMO circuit. Because the efficiency of gas exchange is less than in VA ECMO, often the patient’s lungs have to be used to augment oxygenation. This obviates the ability to totally rest the lungs, which may cause further lung injury and impact the ability of the patient’s lungs to heal. Despite these differences, many centers are now involved in neonatal VV ECMO, and in some institutions it is the treatment of choice over VA ECMO.
Extracorporeal CO₂ Removal

Another approach to extracorporeal gas exchange is extracorporeal CO₂ removal (ECCO₂R). This mode of support dissociates oxygenation and carbon dioxide elimination into essentially two separate functions. The lungs are used for oxygenation, and the ECMO circuit maintains ventilation or removal of carbon dioxide. Because the circuit only supports ventilation, a relatively small fraction of the cardiac output is obligated to go through the ECMO circuit. This can be accomplished by using VV ECMO, either with a single catheter placed in the internal jugular system or via a two-catheter system, using a combination of the jugular-to-femoral or femoral-to-femoral systems. Oxygenation is then supported by the lungs. Low-frequency positive pressure ventilation is used and incorrectly called “apneic oxygenation.” In the described series, a catheter delivers low-flow 100% oxygen at the level of the carina, while the ventilator delivers 4–12 breaths/min with peak pressures of 40–50 cm H₂O and peak end-expiratory pressures of 8–15 cm H₂O. While the patient is on this support, systemic heparinization is required (72).

The advantage of this system, as well as VV ECMO, over more routine VA ECMO is the fact that the arterial system does not need to be accessed. This is particularly important in consideration of the fact that the standard arterial approach involves cannulation and ligation of the common carotid artery in the infant and child.

ECCO₂R requires the patient’s lungs for oxygenation. This implies that ECCO₂R should be instituted before impairment of gas exchange is too severe. If the lungs cannot support any oxygenation, ECCO₂R is not an option.

In 1986,Gattinoni et al. (72) reported the results of ECCO₂R in 43 patients who, in their estimation, had an expected mortality of >90% with conventional therapy. These patients were placed on ECCO₂R as rescue therapy. Thirty-one (72.8%) showed improvement in lung function, and 21 (48.8%) survived. Although this was an uncontrolled study, it was stated that ECCO₂R was a safe and effective method to support gas exchange and that it should be considered as an alternative to standard methods of mechanical ventilation (72).

Intravascular Oxygenation

A new investigational method of gas exchange is the intracorporeal intravenous mechanical gas exchange system, which has been referred to by the acronym IVOX. The concept is simple: a small-diameter hollow fiber membrane oxygenator is placed into the inferior vena cava, thereby obviating the need for an extracorporeal circuit. The oxygenator is introduced via a sheath placed through a common femoral venotomy. The oxygenator is advanced in a cephalad direction with the distal tip lying in the superior vena cava or the right atrial appendage. Once inserted, the oxygenator unfurls, exposing the expanded surface area necessary for gas exchange. The oxygenator has a double-lumen gas transport tube that allows for an inflow and outflow limb. Oxygen passes through the inflow limb, driven either by positive pressure or by suction, and provides oxygenation and washes out carbon dioxide. The oxygenators are made in three different sizes, with surface areas that range from 225 to >9000 cm² with external diameters of 1.8–10.8 mm. Gas exchange is a function of the oxygenator surface, the sweep gas through the oxygenator, the mixed venous Po₂ and Pco₂, and the patient’s cardiac output. The oxygenator surface in IVOX cannot entirely support gas exchange, and similar to ECCO₂R, the patient’s lungs must be used (73,74).

The IVOX system has successfully supported gas exchange in 20–40-kg dogs and 60-kg sheep. There have been no reportable complications. There was little or no hemodynamic effect on central venous pressure or cardiac output after insertion. There has been no evidence of gas emboli or bubbling; and, finally, neither clotting nor thrombi deposition was observed in any of these animals. Of note, all animals were fully heparinized.

Under surveillance of the Food and Drug Administration, clinical trials are in progress to test the efficacy of IVOX in adults. In the phase II trial, IVOX is being offered to patients with at least a 90% predicted mortality from continued conventional methods of support (75).

Summary

Extracorporeal membrane oxygenation is still a relatively new technology that has recently achieved recognition after initial clinical disappointment in the late 1970s. At present, it is considered standard therapy for the full-term infant with PPHN who fails CMV and extraordinary, heroic therapy for older children and adults with ARF or cardiac failure, or both. Currently, the emphasis is on developing new technologies for increasing safety and effectiveness. Areas of interest include heparinless circuits, carotid artery reconstruction, improved monitoring, and expanding applications of VV ECMO. As ECMO becomes safer and more effective, it is believed that new and expanding patient populations will emerge to include premature infants, earlier intervention in term infants, and more liberal application to pediatric and adult populations.
Appendix

1. Oxygenation index (OI):

\[ OI = \frac{MAP(100)}{PaO_2 - PaCO_2} \]

where MAP = mean alveolar pressure; \( PaO_2 \) = arterial oxygen tension.

2. Alveolar/arterial oxygen difference (A\(aD_O_2\)):

\[ AaDO_2 = PAO_2 - PA_CO_2 \]

where \( PAO_2 \) = alveolar oxygen tension; \( PA_CO_2 \) = arterial CO_2 tension; and \( R \) = respiratory quotient difference.

References

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