

EMERGING TECHNOLOGY REVIEW

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Extracorporeal Membrane Oxygenation for Treating Severe Cardiac and Respiratory Disease in Adults: Part 1—Overview of Extracorporeal Membrane Oxygenation

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EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO) is mechanical support of the lungs and/or heart for a period of days to weeks by a modified heart-lung machine. There are 2 basic types of ECMO: venovenous (VV), which provides support for the lungs only, and venoarterial (VA), which provides support for both the heart and the lungs. VV ECMO is primarily used for treating severe but potentially reversible respiratory failure, and VA ECMO is primarily used for treating severe cardiac or cardiorespiratory failure. Because VA ECMO may be used as a bridge to a longer form of mechanical support or to a heart transplant, the underlying cause of the cardiac failure need not necessarily be reversible.

The Extracorporeal Life Support Organization (ELSO, www.elso.med.umich.edu/), based in Ann Arbor, MI, provides an important source of information on the indications for, outcomes from, and complications of ECMO. ELSO is an international consortium of health care professionals from over 100 medical centers that maintains a database, develops guidelines, and produces an annual report. Data from the 2008 annual report¹ are widely quoted in this article and summarized in Table 1. ELSO also publishes a textbook called *Extracorporeal Cardiopulmonary Support in Critical Care*,² but it is widely known as “the red book”; this is an excellent resource.

ECMO is a well-established therapy in pediatric patients, particularly for treating neonatal respiratory failure; a survival advantage in pediatric patients for ECMO over conventional treatment has been convincingly shown in 4 randomized trials.³

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ECMO is less commonly performed in adults than in pediatric patients and is associated with a lower overall survival (Table 1).¹ However, it is timely to review the role of ECMO in adults for 3 reasons. First, over the last decade, there have been major technological improvements in circuit components that allow ECMO to be performed relatively safely and easily for several weeks. Second, the results of several recent case series⁴⁻⁷ and 1 randomized trial⁸ have shown high survival rates with ECMO in appropriately selected patients. Finally, there is currently a global pandemic caused by a novel influenza type A virus (H1N1). Although the majority of patients infected by H1N1 suffer no major ill effects, a small proportion develop severe respiratory failure.⁹ Although firm data are not yet available, in the authors' own experience, the proportion of ventilated intensive care unit (ICU) patients infected with H1N1 influenza who go on to require ECMO is high (up to 5%-10%).

This article is divided into 2 parts. In the first part, the role of ECMO for treating severe respiratory and cardiac failure in adults is reviewed, including the rationale, indications, contraindications, and outcome from ECMO. In the second part, the physiology, technical considerations, and complications of ECMO are discussed.

RATIONALE FOR ECMO

Respiratory Support

The majority of patients who receive ECMO for respiratory failure have acute respiratory distress syndrome (ARDS), which is most commonly caused by severe pneumonia. ARDS is defined according to the American-European Consensus criteria as (1) the ratio of the partial pressure of arterial oxygen (PaO₂) to the fraction of inspired oxygen (F_IO₂) ≤200 mmHg (≤26.7 kPa), (2) the presence of bilateral pulmonary infiltrates on the chest radiograph, and (3) the absence of raised left atrial pressure.¹⁰ Causes of ARDS are listed in Table 2.¹¹

Treatment of ARDS in the 1960s through the 1980s consisted of positive-pressure ventilation (PPV) with high tidal volumes (≥10 mL/kg), high peak inflation pressures (≥40 cmH₂O), and no or low levels of positive expiratory pressure (PEEP). It is now known that this ventilatory strategy exacerbates lung injury, in part because of alveolar overdistention and shearing injury from repetitive opening and closing of the alveoli.^{12,13} By contrast, limiting the tidal volume to ≤6 mL/kg

Table 1. Cumulative Outcome From Extracorporeal Life Support (1985-January 2008) Reported by the ELSO¹

	Total Patients	Survived ECLS (%)	Survived to Discharge or Transfer (%)
Neonatal (<1 year)			
Respiratory	21,916	85	76
Cardiac	3,266	58	38
ECPR	354	63	38
Pediatric (1-16 years)			
Respiratory	3,693	64	56
Cardiac	4,036	61	45
ECPR	691	51	39
Adult (>16 years)			
Respiratory	1,416	59	51
Cardiac	825	46	33
ECPR	269	36	26

Abbreviation: ECLS, extracorporeal life support; ELSO, Extracorporeal Life Support Organization; ECPR, extracorporeal cardiopulmonary resuscitation.

to keep the plateau airway pressure ≤ 30 cmH₂O limits alveolar damage and improves mortality in patients with ARDS.¹⁴ This approach, known as lung protective ventilation, is typically combined with other ventilatory strategies, such as a decelerating inspiratory flow pattern (pressure control ventilation), high levels of PEEP (10-20 cmH₂O), a long inspiratory time, and recruitment maneuvers, in an effort to limit lung injury and improve oxygenation.¹⁵ An alternative ventilatory strategy that may be considered is high-frequency oscillation ventilation,¹⁶ although a survival benefit for this therapy in adults has not been convincingly shown.^{17,18}

Nonventilatory strategies that are used for treating ARDS include prone positioning,¹⁹ fluid restriction,²⁰ and inhaled nitric oxide. Inhaled nitric oxide improves gas exchange but has not been shown to increase survival in adults with ARDS, and its routine use is not recommended.²¹

The majority of patients with ARDS who die do so from sepsis or multiple organ dysfunction and not from respiratory failure.^{11,14} However, there are a proportion of patients with severe ARDS who, despite optimal conventional treatment, undergo progressive respiratory (or cardiorespiratory) failure and die, even though their underlying lung disease is potentially reversible. By 1 estimate, this amounts to 350 patients per year in the United Kingdom,²² which equates to 1,750 patients per year in the United States. In this circumstance, ECMO provides a period of respiratory and, if necessary, cardiac support to maintain life while allowing lung rest to minimize ventilator-induced lung injury.

Cardiac Support

ECMO is also an appropriate therapy in selected patients with life-threatening heart failure. Cardiac ECMO is typically used as an emergency rescue therapy, most commonly for failure to wean from cardiopulmonary bypass (CPB) and after a myocardial infarction or cardiac arrest. Options for mechanical cardiac support in this circumstance are either VA ECMO or a ventricular assist device (VAD). The choice depends on patient requirements (single or biventricular failure with or

without respiratory failure) and institutional experience. Similar results have been obtained for both forms of support.^{23,24} However, potential advantages of ECMO over a VAD are as follows: (1) both ventricles and the lungs are supported by a single circuit; (2) avoidance of a sternotomy, which may result in less bleeding (if peripheral cannulation is used); (3) patients can be decannulated without the need for further surgery (if peripheral cannulation is used); and (4) ECMO is cheaper and can be more rapidly instituted. VA ECMO is a particularly useful form of support when the patient's neurologic state is unknown after a cardiac arrest. If, after several days, cardiac function remains poor but neurologic recovery is good, the patient may be transferred to a longer-term VAD while he/she awaits a heart transplant. This strategy provides rational use of an expensive resource.

HISTORY AND EVIDENCE FOR ECMO

Technical Developments

ECMO, as a bedside technique performed in the ICU, was developed as an extension of CPB used in the operating room during cardiac surgery. The most important technical innovation that has facilitated ECMO has been the development of durable, efficient oxygenators that are associated with minimal blood trauma.

The first oxygenators to be used clinically were film oxygenators, in which multiple vertical discs rotate through a pool of venous blood, and bubble oxygenators, in which oxygen is bubbled through a column of deoxygenated blood.^{25,26} A major problem with these devices is the presence of a direct blood-gas interface, which contributes to intravascular hemolysis, platelet destruction, systemic inflammation, and microemboli formation. An important step was the introduction of membrane oxygenators, in which a membrane separates the blood and gas phases, thus allowing CPB to be maintained for longer than a few hours without inducing massive blood trauma. Membrane oxygenators were developed in the 1950s^{27,28} but were not introduced into clinical practice until the 1980s. From the 1980s through the early 2000s, most ECMO centers used either silicone membrane or polypropylene hollow fiber oxygenators.²⁹ Although these oxygenators are vastly superior to bubble and disc oxygenators, both have significant limitations with

Table 2. Clinical Disorders Associated With the Development of ARDS¹¹

Direct Lung Injury	Indirect Lung Injury
Common causes	Common causes
Pneumonia	Sepsis
Aspiration of gastric contents	Severe trauma with shock and multiple blood product transfusions
Less common causes	Less common causes
Pulmonary contusion	Cardiopulmonary bypass
Fat emboli	Drug overdose
Near drowning	Pancreatitis
Inhalation injury	Transfusion-related acute lung injury
Reperfusion injury after lung transplantation or pulmonary embolectomy	

prolonged use. The latest generation of oxygenators is hollow fiber oxygenators constructed from polymethylpentene (PMP). Unlike polypropylene hollow fiber oxygenators, which actually contain millions of micropores within the hollow fibers, PMP oxygenators are true, nonmicroporous, membranes, and, as such, the blood and gas phases are completely separated. PMP oxygenators have been used widely in Europe, Australia, and New Zealand for several years and have been recently been approved for use in the United States. PMP oxygenators provide substantial benefits over silicone membrane and polypropylene hollow fiber oxygenators in terms of ease of use, longevity, reduced blood trauma, and improved gas exchange.^{30,31}

Other technical advances include the widespread use of biocompatible surface coatings, which help to limit thrombus formation and inflammation,³²⁻³⁴ and the development of a new generation of centrifugal pumps, which cause less hemolysis than older-style centrifugal pumps.^{31,35,36}

Clinical Experience

The first successful human use of ECMO was reported in 1972 by Hill et al.³⁷ The patient was a young man who developed ARDS after motor vehicle trauma. He was treated with VA ECMO for 3 days and fully recovered. The comment by the authors of the institution that ECMO led "peak airway pressure to gradually fall from 60 to 35-40 cmH₂O"³⁷ is interesting in light of the current practice of lung protective ventilation.

Based on this and other early successes, in 1974 the National Institutes of Health initiated a randomized controlled trial comparing VA ECMO with conventional treatment for acute, severe respiratory failure.³⁸ Published in 1979, this trial showed a mortality of approximately 90% in both the ECMO and conventional treatment groups. This poor outcome greatly reduced enthusiasm for ECMO in adults. However, there are a number of problems with this trial that limit its applicability to current practice. First, VA ECMO was used, whereas today VV ECMO would be considered the technique of choice for treating ARDS. Second, high-pressure PPV was continued during ECMO. Thus, one of the main benefits of ECMO, lung rest, was not used. Third, blood loss in the ECMO group was very high, averaging 2.5 L/d. Finally, mortality in both groups was much higher than would be expected today.

Subsequently, in Europe, interest developed in an alternative technique of extracorporeal life support for treating respiratory failure termed low-frequency positive pressure ventilation with extracorporeal carbon dioxide removal.³⁹ With this technique, oxygenation is achieved through low-frequency PPV or apneic oxygenation using a lung protective strategy; carbon dioxide is eliminated by the extracorporeal circuit, using flows of 20% to 30% of normal cardiac output. Gattanonni et al⁴⁰ reported a survival rate of nearly 50% in a small nonrandomized group of patients who had a predicted mortality or more than 90%. A modified form of this technique was used in a randomized controlled trial by Morris et al⁴¹ published in 1994. In this study, mechanical ventilation, using an inversed ratio of inspiratory and expiratory times (a technique popular at the time), was compared with low-flow venovenous extracorporeal support. Survival was 42% in the mechanical ventilation group and

33% in the extracorporeal group. Again, this trial has several problems that limit its applicability to current practice. First, there were only 40 patients in the study, 19 in the mechanical ventilation group and 21 in the ECMO group. Second, the ventilatory strategy was similar between the treatment and control groups, exceeding current recommendations for airway pressure and failing to achieve lung rest. Third, ECMO was primarily used for treating hypercarbia, which is now known to be well tolerated in patients with ARDS. Indeed, permissive hypercarbia is an accepted consequence of lung protective ventilation.⁴² Fourth, blood loss was high in the ECMO group; transfusion requirements averaged 2.7 L of red blood cells (v 0.2 L in the control group) and 2.1 L of fresh frozen plasma (v 0.1 L in the control group) per patient per day. Finally, the trial was conducted in a center that had very limited experience with ECMO, having only provided ECMO to 7 sheep (for a total of 271 hours) and a single patient before commencing the study.

In contrast to the poor results from randomized trials, good outcomes have been reported in recent nonrandomized series from experienced ECMO centers. For respiratory failure, survival rates of 55% to 76% have been reported for patients with predicted mortalities of 70% to 80%.⁴⁻⁷ In 2007, ELSO reported 105 ECMO runs for adults for respiratory failure, with a survival rate of 52%.¹

Recently, the results of a prospective randomized study, the Conventional ventilatory support versus Extracorporeal membrane oxygenation for Severe Adult Respiratory failure (CESAR) trial, have been reported.⁸ In this trial, patients in the United Kingdom with life-threatening respiratory failure were randomized to either conventional treatment, including lung protective ventilation, in one of several "conventional treatment centers" or transfer to the Glenfield Hospital for ECMO.²² A total of 180 patients were randomized from 68 centers, 90 to ECMO and 90 to conventional treatment. The main outcome variable, survival or absence of disability at 6 months, was significantly higher with ECMO than with conventional treatment (63% v 47%; relative risk = 0.69; 95% confidence interval [CI], 0.05-0.97; *p* = 0.03). Twenty-two patients randomized to ECMO did not receive it, usually because they improved without it. One patient died as a direct consequence of ECMO because of a cannulation problem.

In contrast to respiratory failure, there are no randomized controlled trials evaluating ECMO for treating cardiac failure. Survival rates of 24% to 53% have been reported in case series.^{23,24,43-49} A recent systematic review of VA ECMO for cardiac support, which excluded cardiac surgery patients, showed a survival-to-discharge rate of 47.4% ± 4.5%.⁵⁰ A slightly higher survival rate was shown in patients with cardiogenic shock (51.6% ± 6.5%) than those with cardiac arrest (44.9% ± 6.7%). In 2007, there were 104 ECMO runs for cardiac support reported by ELSO with a survival rate of 32%.¹ In contrast, much higher survival rates of 71% to 80% have been reported in case series limited to patients with cardiogenic shock because of fulminant myocarditis.⁵¹⁻⁵³ Although overall survival from ECMO for cardiac indications is generally less than that for respiratory indications, given that ECMO for cardiac support is typically instituted in moribund patients who

otherwise have little chance of survival, the results are nonetheless impressive.

Long-term Outcome

Long-term outcome and quality of life for ECMO survivors are good. In the Glenfield Hospital Adult ECMO follow-up study, 40 adult patients who had undergone ECMO for acute respiratory failure were assessed by interview and pulmonary function testing 40.2 (range, 12-92) months after hospital admission.⁵⁴ Computed tomographic evidence of pulmonary fibrosis was identified in 6 patients. Eleven patients had a forced vital capacity <80% of predicted. However, only 6 patients reported avoiding certain activities because of physical limitation. Clinically significant anxiety was reported by 6 patients and clinically significant depression by 1 person.

In a study of long-term outcome and quality of life of patients receiving ECMO for cardiogenic shock, Short Form-36 scores, a well-validated questionnaire for assessing physical functioning along with general and emotional health, were significantly lower among ECMO survivors than matched healthy controls but higher than those reported for patients on hemodialysis, patients with advanced heart failure, or individuals recovering from ARDS. These generally favorable quality of life outcomes are mirrored by other small studies of patients treated with ECMO for ARDS⁵⁵ and cardiac failure.^{48,56}

INDICATIONS AND CONTRAINDICATIONS FOR ECMO

Respiratory Indications and Contraindications

ECMO should be considered in patients with life-threatening but potentially reversible respiratory failure who do not have contraindications to extracorporeal support. One tool for assessing the severity of respiratory failure is the Murray score, which is based on 4 criteria: (1) $\text{PaO}_2/\text{FiO}_2$ ratio, (2) PEEP, (3) dynamic lung compliance, and (4) the number of quadrants infiltrated on the chest radiograph (Table 3). A Murray score ≥ 3.0 was used for enrollment in the CESAR trial, which identifies a very sick group of patients with a predicted mortality risk >50% with conventional treatment.²² In clinical practice, the Murray score is infrequently calculated, and most clinicians rely on the $\text{PaO}_2/\text{FiO}_2$ ratio to grade the severity of pulmonary dysfunction. As simple rules of thumb and assuming extracorporeal support is otherwise appropriate, a $\text{PaO}_2/\text{FiO}_2$ ratio <100 mmHg is an indication to refer the patient to an ECMO center, and a $\text{PaO}_2/\text{FiO}_2$ ratio <50 to 70 mmHg is an indication to institute ECMO.

Irreversible respiratory failure is considered to be an absolute contraindication for ECMO because of a poor outcome in

patients undergoing lung transplantation from ECMO^{57,58} and because of the short-term nature of ECMO support compared with the normally long wait times for suitable donor lungs. Despite this, one recent report describes 3 patients who underwent successful lung transplantation from ECMO. All had very stormy postoperative courses, but all were still alive several months after surgery.⁵⁹

The assessment of reversibility must take into account the underlying cause of the respiratory failure, the patient's age and premorbid function, and the duration of mechanical ventilation. Age and duration of mechanical ventilation are independent predictors of outcome from ECMO.^{60,61} Most units consider age above 65 to 70 years to be an absolute contraindication and duration of mechanical ventilation longer than 5 to 10 days to be a relative contraindication.

Certain causes of respiratory failure typically have a short acute phase and are associated with good recovery of pulmonary function; they are therefore likely to do well with ECMO. Examples include aspiration pneumonia, asthma, near drowning, and Wegener granulomatosis. A third of the patients in the CESAR trial had 3 or more organs fail, indicating that ECMO can be successfully used in the presence of multiple organ dysfunction syndrome.⁸ In one recent study, 50% survival was reported from ECMO in patients with respiratory failure complicated by sepsis or septic shock,⁶⁰ suggesting that ECMO should not be withheld because of concomitant systemic sepsis.

ECMO may be used for treating primary graft dysfunction after lung transplantation. In one series of 297 consecutive lung transplants, 22 patients (7.9%) had primary graft failure requiring ECMO.⁶² One-year survival was 54% in the ECMO group compared with 88.6% overall. None of the 5 patients in whom ECMO was instituted beyond 24 hours after transplantation survived. By 2006, 151 cases of post-lung transplantation ECMO had been reported to the ELSO registry, of whom 63 (42%) survived to hospital discharge.⁶³

Cardiac Indications

Cardiac indications for ECMO include failure to wean from CPB, life-threatening heart failure secondary to myocardial infarction or fulminant myocarditis, and as an adjuvant to conventional cardiopulmonary resuscitation (extracorporeal cardiopulmonary resuscitation [ECPR]). The most common indication is failure to wean from CPB. Of the 825 adult cardiac ECMO runs reported to ELSO by January 2008, 658 were in postoperative cardiac surgical patients, of whom 215 (32.7%) survived.¹ The most common surgical indications were coronary artery bypass graft surgery (136 patients, 33.8% survival), heart transplant (125 patients, 39% survival), and aortic valve replacement (39 patients, 31% survival).

Indices of cardiac failure are less well defined than for respiratory failure. However, for cardiogenic shock, patients with a cardiac index <2 L/min/m², a systolic blood pressure less than 90 mmHg, and lactic acidosis despite maximal inotropic support, mechanical ventilation, and intra-aortic balloon counterpulsation may be considered for ECMO.

ECPR is an emerging indication for ECMO.^{48,49} In a recent prospective observational study of in-hospital cardiac arrest,

Table 3. Calculation of the Murray Score²²

$\text{PaO}_2/\text{FiO}_2$ (mmHg): $\geq 300 = 0$; 225-299 = 1; 175-224 = 2; and 100-174 = 4
PEEP (cmH ₂ O): $\leq 5 = 0$; 6-8 = 1; 9-11 = 2; 12-14 = 3; and $\geq 15 = 4$
Lung compliance (mL/cm H ₂ O), calculated as $\text{TV}/\text{PIP}-\text{PEEP}$: $>80 = 0$; 60-79 = 1; 40-50 = 2; 20-39 = 3; ≤ 4
Quadrants infiltrated on chest radiograph: normal = 0; 1 point per quadrant infiltrated

Abbreviations: TV, tidal volume; PIP, peak inspiratory pressure.

survival at 30 days was 34.8% with ECPR compared with 19.6% for conventional resuscitation (CI, 0.28-0.77; $p = 0.003$). Survival at 1 year was 17.4% with ECPR compared with 13.0% with conventional resuscitation (CI, 0.33-0.83; $p = 0.006$).⁴⁹

The majority of cardiac failure patients who are able to be weaned from ECMO do so within 2 to 5 days.^{23,24,47,64} This is because successful weaning usually occurs as a result of resolution of myocardial stunning, a process that is largely complete by 1 week.⁶⁵ An important predictor of failure to wean from ECMO is LV ejection fraction (EF), assessed with echocardiography on low circuit flow (ie, 1-2 L/min), early in the ECMO run. In one study, patients with an LVEF <30% after 2 days of ECMO were significantly less likely to be successfully weaned than those with an LVEF >30% (8% v 54%, $p < 0.001$).⁶⁴ Thus, unless a VAD or heart transplant is planned, there is little point in continuing ECMO for cardiac support beyond 5 to 7 days. An exception to this is patients with myocarditis who may require support for longer than 1 week.

To Facilitate Surgery or Procedures

VV ECMO may be used as an alternative to CPB to facilitate surgery or procedures involving the airway and lungs. Examples include laser resection of tracheal masses,⁶⁶ surgical reconstruction of the carina,⁶⁷ and whole lung lavage for alveolar proteinosis.⁶⁸ Extracorporeal support provides adequate gas exchange and allows an apneic, unobstructed operative field. Advantages of VV ECMO over CPB include avoiding arterial cannulation and reduced bleeding.⁶⁹

THE ECMO SERVICE

ECMO is a resource-intensive, highly technical, and demanding therapy. It requires specific equipment, appropriately trained and experienced personnel, management protocols, adequate funding, an ongoing program of quality assurance and education, and a sufficiently large referral base to ensure adequate experience. Collegial relationships between relevant specialties including critical care, cardiac anesthesiology, cardiac surgery, clinical perfusion, cardiology, and pulmonology are essential. For cardiac support, ECMO should be provided as part of a multidisciplinary heart failure program in conjunction with VADs and heart transplantation. For respiratory support, ECMO should form a component of an integrated

approach to treating ARDS, including advanced ventilatory and nonventilatory therapies.⁴ ELSO has developed guidelines for the institutional requirements for ECMO centers (<http://www.else.med.umich.edu/guide.htm>), which address issues such as the size and structure of the ICU, physical facilities and equipment, and staff training and continuing education. ELSO recommends that ECMO centers should be located in tertiary centers with a referral base able to support a minimum of 6 ECMO patients per year.

Referring and Transporting Patients

Because a significant proportion of patients requiring ECMO will be from outside the treating ICU, ECMO centers should develop guidelines for who to refer for extracorporeal support. Ideally, patients should be referred with less severe forms of cardiac or respiratory disease than are appropriate for commencing ECMO. This is particularly so for respiratory failure in which a period of several hours or even days may elapse between the development of severe respiratory failure and the need for ECMO. Thus, ideally, patients should be referred and transported to an ECMO center before they become too unstable. However, transporting very sick or unstable patients using conventional means of cardiorespiratory support inevitably leads to patients dying in transit. One option to minimize this risk is to establish a mobile extracorporeal support service.^{70,71} With mobile ECMO, a team is dispatched to the referring hospital where ECMO is instituted, and the patient is transported to the ECMO center on extracorporeal support.

SUMMARY

ECMO has been used for treating severe cardiac and respiratory failure for over 30 years, particularly in children in whom its role is well established. Early trials of ECMO for respiratory support in adults were disappointing. However, a recent case series and 1 randomized trial, which more closely mirror contemporary practice, have shown high rates of survival. Furthermore, recent technical developments have greatly improved the ease of use of ECMO such that it can be performed safely for a period of several weeks. ECMO should be performed in centers with the appropriate experience and expertise using clear selection criteria. Guidelines should be established for the referral and transport of appropriate patients to regional ECMO centers.

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