

Clinical Applications of Extracorporeal Membranous Oxygenation: A Mini-Review

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The clinical usage of extracorporeal membranous oxygenation began more than 40 years ago. Although the indications for its use have expanded over the years, it has been challenging to conduct randomized controlled trials to prove that extracorporeal membranous oxygenation is more effective than traditional approaches. Through a review of retrospective reports and data from registries, we attempted to evaluate the appropriateness of its application for acute respiratory distress syndrome, cardiopulmonary resuscitation, postcardiotomy cardiogenic shock, and sepsis. Our investigation revealed that using extracorporeal membranous oxygenation when readily available is appropriate for all patients with cardiopulmonary resuscitation or postcardiotomy cardiogenic shock, and for selected patients with acute respiratory distress syndrome or sepsis.

Key Words: Acute respiratory distress syndrome • Cardiopulmonary resuscitation • Extracorporeal membranous oxygenation • Postcardiotomy cardiogenic shock • Sepsis

INTRODUCTION

ECMO, or extracorporeal membranous oxygenation, is considered to be one of the most important breakthroughs in the development of extracorporeal life support to date. The extracorporeal life support system was developed in the early to mid-1990s for use during open heart surgery.¹ In the early systems, blood came into contact with air directly for oxygenation, which would extensively denature protein in a matter of hours and prohibit long-term usage. In the 1960s, Kolobow improved the membranous oxygenator using dimethylsiloxane to construct a membrane between the air and

blood.² After the success of the membranous oxygenator, long-term use of the extracorporeal life support system became possible, and ECMO claimed its place in the history of extracorporeal life support.

The first successful use of ECMO was reported by Dr. Hill in 1972.³ A 24-year-old male patient with sub-arterial transection of the thoracic aorta from blunt trauma developed respiratory failure four days after successful repair of the thoracic aorta. Venous-arterial ECMO with peripheral cannulation was used for 75 hours and the patient recovered. Subsequent to that case, ECMO was used for patients with acute respiratory distress and postcardiotomy cardiogenic shock (PCS), and then the procedure was expanded to patients during cardiopulmonary resuscitation (CPR) and various other causes of circulatory or/and respiratory compromise. The results were encouraging and will be discussed in this mini-review.

ACUTE RESPIRATORY DISTRESS SYNDROME

Dr. Hill's first success in 1972 and subsequent re-

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ports were so encouraging^{4,5} that clinical trials of ECMO were conducted for the treatment of acute respiratory distress syndrome (ARDS) in both neonatal⁶ and adult⁷ populations. The results in the neonatal group, reported by Bartlett in 1985, were excellent with all 11 neonates randomly chosen for ECMO support surviving and only one of them suffering an intracranial hemorrhage. In 1989, O'Rourke reported a 97% survival rate in the ECMO group compared to 60% in the non-ECMO group of newborns with persistent pulmonary hypertension.⁸ In 1996, the UK neonatal ECMO trial group reported a significant increase in survival rates of an ECMO group compared to a non-ECMO group (68% vs. 41%) of neonates with severe respiratory distress.⁹ With the improvement of perinatal care and modern respiratory care, the number of neonates needing ECMO each year for respiratory distress continues to decrease, and the survival rates have remained between 60-70% in the last decade, according to the Registry of the Extracorporeal Life Support Organization (ELSO).¹⁰

On the other hand, the first ECMO clinical trial on adult respiratory distress syndrome undertaken in 1979 reported similar survival rates for ECMO patients and control patients; 9.5% and 8.3%, respectively.⁷ A second randomized clinical trial published in 1994, which used ECMO for carbon dioxide removal in patients with ARDS, was also discouraging.¹¹ Despite these two trials, the enthusiasm for treating ARDS with ECMO continued. Not only did the concept of conventional treatment evolve but the ECMO durability also improved. In the first clinical trial, ECMO support was used for only five days due to equipment limitations, limiting patient recovery; currently, prolonged ECMO support for a month or more is technically possible.¹⁰ In a cohort study reported in 1997, Peek showed a 66% survival rate of ARDS patients receiving ECMO after conventional treatment failed.¹² This encouraging result led to the CESAR trial,¹³ which was reported in 2010. ECMO was incorporated as a treatment option in the CESAR trial for the ECMO group, and not for the conventional group. The results showed a decrease in rates of mortality and severe disability six months after randomization in the ECMO group (36.7% vs. 52.9% with $p = 0.030$), and the authors concluded that transferring ARDS patients to centers experienced with the ECMO procedure would increase the chance of survival. Though the benefit of

ECMO was vaguely expressed, it is clear that ECMO can play a role when conventional therapy for ARDS fails.

In pediatric patients, a 22% improvement in survival rates was observed when ECMO was used in a multi-center retrospective cohort study reported in 1996, which included 331 patients from 32 hospitals.¹⁴ This good result was challenged by an 89% survival rate achieved using high-frequency pressure-control ventilation with high positive end-expiratory pressure¹⁵ reported in the same year. Subsequently, the role of ECMO has remained as more of a salvage procedure since then for pediatric patients.¹⁶

POSTCARDIOTOMY CARDIOGENIC SHOCK

ECMO was used for PCS in the early 1970s. The first successful case was reported in 1972, and that patient was weaned off ECMO support within two days.¹⁷ Good functional recovery with a good chance of returning to normal work functions was reported in early studies.¹⁸ Bhat reported a 30-day survival rate of 33% for infants weighing three kilograms or less and requiring ECMO after cardiac surgery,¹⁹ and identified renal replacement therapy as the only independent factor of poor survival by multivariate analysis. Alsofi reported a 50% survival rate using ECMO support after repair of congenital heart disease,²⁰ though provision of a ventricular assist device was believed to provide a better chance of a positive prognosis than ECMO.

In the adult population, a study undertaken by Ko²¹ at our institution found that 60.5% of patients were weaned off ECMO, but only 23.1% survived to discharge. Dialysis for acute renal failure was found to be a significant risk factor for mortality in patients weaned off ECMO. Similar results were also reported by Slottoch,²² with a weaning rate of 62% and a 30-day mortality rate of 70%. Rastan reported the largest cohort of 517 consecutive adult patients treated with ECMO for PCS.²³ The weaning rate was 63.3% and 24.8% survived to discharge. Rastan also identified age in excess of 70 years, diabetes, preoperative renal insufficiency, obesity, logistic EuroSCORE greater than 20%, and operative lactate value greater than 4 mmol/L, as the risk factors for hospital mortality. The survival rates at six months, one year, and five years were 17.6%, 16.5%, and 13.7%, respectively.

The results of ECMO on PCS were not satisfactory, and miniaturized ventricular assist devices (VADs) were developed to overcome these emergent circumstances. In RCOVER I, a miniaturized left VAD was implanted into 16 patients for PCS, and the survival rates at 30 days, three months, and a year were 94%, 81%, and 75%, respectively.²⁴

Although some medical professionals recommend using VAD instead of ECMO for patients with PCS,²⁵ Chamogeorgakis reported a retrospective study comparing ECMO to miniaturized VADs and found no difference between the in-hospital survival rates, weaning rates, bridge to long-term support, or transplantation and limb complications.²⁶ VADs could unload the left ventricle, and ECMO could not. That might represent a niche for VADs but at this point, ECMO is still the most well-developed mechanical circulatory support for patients with PCS.

EXTRACORPOREAL CARDIOPULMONARY RESUSCITATION (ECPR)

Emergent extracorporeal circulatory support for circulatory arrest was performed in the 1960s and 1970s,^{27,28} but the results were disappointing. A portable cardiopulmonary bypass machine was produced in the late 1960s, and the survival rates using ECPR were 68.4% for acute pulmonary embolism and 12.5% for cardiac patients as reported in 1976 using this machine.²⁹ During the following years, the successful rate of ECPR remained low. In 1990, Reichman³⁰ reported that only 15.8% of patients survived to discharge, and an even worse result (3.4%) was reported by Hartz in the same year.³¹ Although these results were disappointing, the enthusiasm for improving ECPR results continued.

Survival rates following in-hospital cardiac arrest (IHCA) and out-of-hospital cardiac arrest (OHCA) remained low in both pediatric (36.8% and 4.4%) and adult groups (22.7% and 6.7%).³² The ELSO registry reported that survival rates in the neonatal ECPR population, the pediatric ECPR population, and the adult ECPR population were 40%, 41%, and 29%, respectively.¹⁰ This group of patients would not have survived if ECMO had not been administered. In a single institute study reported by Huang³³ in 2012, there was no significant difference between the survival rate associated with

ECPR administered for cardiac reasons (47%) and that associated with ECPR administered for non-cardiac reasons (44%). Survival rates improved to 55% from 2006 to 2009, which may have been due to shorter ECPR duration.³³ Longer duration of CPR, higher levels of serum lactate prior to ECPR, and renal failure after ECPR were indicators for poor prognosis. ECPR not only increased the chance of survival for pediatric patients, but also resulted in good neurological outcomes in survivors (84%) as evaluated by pediatric cerebral performance categories (PCPC). Joffe reviewed pediatric ECPR from 2000 to April 2011 and found a 49% cumulative survival rate after ECPR in children with a 79% good neurological outcome as assessed by PCPC.³⁴

In 2008, our institute reported on adult ECPR,³⁵ and found that under a mean CPR duration of 55.7 min, successful weaning rates reached 58.5%, and survival rates to discharge were 34.1%. Eighty-nine percent of patients who survived to discharge had an acceptable neurological status. The survival probability was 0.5, 0.3, and 0.1 when the duration of CPR was 30, 60, and 90 min, respectively, indicating that the CPR duration can be extended in hospitals with appropriate ECMO equipment and staff. Our institute also reported an observational study and propensity analysis comparing ECPR and conventional CPR in adults with IHCA in the same year.³⁶ In this study, ECPR had a higher survival rate to discharge and a better one-year survival rate, and after propensity scores were matched, the difference in survival to discharge and 30-day survival rate still favored ECPR with statistical significance. A similar result was also reported by Shin et al in their single-institutional cohort.³⁷

For patients with OHCA, Avalli³⁸ reported the survival rate for patient received ECPR was 5%, and this rate was not as good as IHCA patients in our study. However, Maekawa et al. reported in their study, which used a propensity analysis, that the survival rates were significantly higher in an ECPR group compared to a conventional CPR group (29.2% to 8.3%, $p = 0.018$) for out-of-hospital cardiac patients who received CPR of greater than 20 min.³⁹ The key reason for this positive result may have been due to good CPR quality delivered by a field rescue team, which included three paramedics in all cases and a physician in 60% of the cases.

Sometimes when the ECMO team arrived, conventional CPR had already revived the patient. Lin⁴⁰ an-

alyzed the survival rates of patients whose hearts had been returned to spontaneous beating after ECPR and patients for whom spontaneous circulation had been restored after conventional CPR. The analysis showed no difference in survival rates between two groups (hazard ratio 0.856 with $p = 0.634$). ECMO installation in patients who recovered spontaneous circulation after conventional CPR did not significantly increase survival rates.

Although there was no randomized controlled trial to compare conventional CPR and ECPR, ECPR is now suggested by the American Heart Association for adult patients when the time without blood flow is brief and the condition leading to the cardiac arrest is reversible, or amenable to heart transplantation or revascularization (Class IIb), and for pediatric patients with single ventricle anatomy who have undergone stage I procedure, with Fontan physiology, and with pulmonary hypertension (Class IIa).^{41,42}

Hypothermia has been addressed in the guidelines to improve neurological outcomes and survival rates after cardiac arrest;⁴³ this treatment was not considered in our previous clinical studies. In a recent report by Fagnoul,⁴⁴ survival rates were 25% in a cohort of 14 OHCA and 10 IHCA ECPR patients. In that study, hypothermia to 32.3° Celsius was used during ECMO support. The application of hypothermia during ECPR and during post-cardiac arrest and the monitoring of brain oxygenation need further investigation.

SEPTIC SHOCK

ECMO was once considered a contraindication for patients with septic shock because of the possibility of bacterial incubation on the ECMO circuit and the possibility of triggering inflammatory responses, which is already very common in patients with septic shock.^{45,46} The physiologic responses to septic shock differ according to the age of the patient. In neonates, the response consists of pulmonary hypertension with right heart failure in the majority, and left ventricular dysfunction with low cardiac output may occur in infants and younger children.⁴⁷ This differs from vasodilation with increased cardiac output that occurs in older children and adults. Thus, there may be different indications for ECMO patients with septic shock depending on their age.

The neonate ECMO registry of ELSO was reviewed in 1995.⁴⁸ Patients were divided into two groups: group 1 with sepsis as the primary diagnosis, and group 2 without sepsis. There was a 77% survival rate for group 1, and an 84% survival rate for group 2, but these results were not statistically significant. Group 1 showed higher rates of complication, including seizure, cerebral infarct or hemorrhage, hypernatremia, hyperbilirubinemia, and dobutamine usage.

The author concluded that ECMO should not be withheld from neonates solely on the basis of sepsis, but efforts should be made to decrease complications.

In 2007, MacLaren reported on pediatric patients treated with venoarterial ECMO for refractory septic shock.⁴⁷ Forty-five patients, with median ages and weights of 2.5 (0.4-9) years and 12 (6-32) kg, respectively, were treated and 47% of them survived to discharge. Atrio-aortic cannulation through median sternotomy was associated with improved survival (73%), possibly attributed to the increased flow provided by central cannulation. ECMO usage is included in the international guidelines for management of severe sepsis and septic shock as a Grade 2C recommendation.⁴⁹ ECMO is recommended for refractory septic shock when conventional treatment fails.

The results are different for the adult population. In a study undertaken in our institution in 2013, Huang reported on 52 patients treated with venoarterial ECMO for refractory septic shock. Only 15% of these patients survived to hospital discharge. Twenty-one percent of patients had cardiac suppression with a left ventricular ejection fraction lower than 50%, and that all patients over 60 years of age did not survive.⁵⁰ However, for patients with depressed cardiac function with left ventricular ejection fraction (LVEF) 16% (10-30%) due to septic shock, 71% of 14 patients treated with venoarterial ECMO survived to discharge. After a median follow-up period of 13 months, the LVEF was fully recovered.⁵¹ ECMO may not be useful for treating sepsis, but it appears to be helpful in the treatment of organ dysfunction caused by sepsis.

CONCLUSIONS

Not many of the studies presented in this review

Table 1. Recommendation on the appropriateness of ECMO usage in different situations: 1. The indication of ECMO for respiratory distress was dependent on patient age. It is appropriate to use ECMO for neonates who developed respiratory distress, but for children and adults, ECMO is indicated only if other treatment modalities failed to improve patient's condition. 2. ECMO is indicated for ECPR if ECMO is available. 3. For postcardiotomy shock, it is appropriate to install ECMO to support the patient. In this group of patients, the cardiac pathology could have been fixed during cardiac surgery, and ECMO would be helpful to support the patient during the recovery phase. 4. Due to different pathophysiological responses to sepsis, it is appropriate to support neonates and children with septic shock. But usage for adult patients with septic shock should be limited to those with cardiac suppression

	Respiratory distress	ECPR	Postcardiotomy shock	Sepsis
Neonate	Appropriate	Appropriate	Appropriate	Appropriate
Child	Last effort	Appropriate	Appropriate	Appropriate
Adult	Last effort	Appropriate	Appropriate	Acute heart failure due to sepsis

ECPR, extracorporeal cardiopulmonary resuscitation.

were randomized. It is difficult to conduct a randomized trial in these groups of patients due to ethical issues. Though medical science and technology have advanced rapidly, there are still conditions when only an extracorporeal life support system can support the failing oxygenation and/or circulation. There is one fundamental concept we should keep in mind: no matter what disease or what age group we are dealing with, it is the deficiency of oxygenation and/or circulation that makes ECMO of use as a treatment option. New VAD designs may improve outcomes in the future, but ECMO will still be the preferred treatment option as long as it remains economical.

At the end of the day, organ failure and disease may recover on their own with modern medicine treatments available; however, ECMO is often essential to buy the time needed for recovery. ECMO does not treat the disease as such but allows treatment to begin promptly after installation (Table 1).

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