

# Rapid Deployment ECMO

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## Opinion statement

In the last two decades, technological advances in equipment and improvements in both safety and patient survival have led to extracorporeal membrane oxygenation (ECMO) being increasingly used for a wide range of conditions causing cardiorespiratory failure. Earlier recognition of the deteriorating patient and use of ECMO to reverse multiorgan failure and prevent sudden cardiac arrest is associated with improved outcomes. As mortality and long-term disability remain high after cardiac arrest in children, ECMO CPR (ECP) has been utilized to reverse the sudden loss of cardiac output after unanticipated cardiorespiratory events. To ensure not only survival but also the absence of major morbidity after ECP, future research should focus on preventative resuscitation, further investigating the natural history of the underlying conditions and minimizing the complications of ECMO.

## Introduction

In pediatric critical care, low cardiac output state (LCOS) and cardiogenic shock, sepsis, and acute respiratory distress syndrome (ARDS) are all conditions that can lead to multiorgan dysfunction and subsequent cardiorespiratory arrest, with substantial morbidity and mortality [1, 2].

Extracorporeal membrane oxygenation (ECMO) siphons venous blood out of the patient, oxygenates it, clears carbon dioxide, and then pumps it back in. It can provide complete cardiorespiratory support and re-establish end-organ perfusion and oxygen delivery. In

the early days of ECMO, this support was considered experimental with very strict indications and length of support. The last 15 years have been rich in technological advances, experience sharing through single center reports, and thorough analyses of the registry of the Extracorporeal Life Support Organization (ELSO), together with improvement in patient and circuit management. Despite a lack of extensive grade I evidence, ECMO has become a standard of care in pediatrics to support respiratory and/or cardiac function when conventional medical treatment is failing. Venovenous

ECMO (VV-ECMO) supports lung function by oxygenating venous blood, reduces or obviates the risk of ventilator-induced lung injury, corrects respiratory acidosis by removing carbon dioxide, and indirectly improves cardiac function through reducing intra-thoracic pressure, reducing pulmonary vascular resistance and oxygenating coronary arterial blood. Venoarterial ECMO (VA-ECMO) provides full cardiac and respiratory support ensuring adequate perfusion pressure and oxygen delivery to organs and allowing additional cardiac rest and recovery [3, 4]. A cardiac arrest represents the most extreme form of cardiopulmonary failure and carries high morbidity and mortality [5, 6•].

Extracorporeal cardiopulmonary resuscitation (ECPR) is the use of ECMO during cardiac arrest. Several levels of intervention are required to establish ECMO support during cardiac arrest. This review will outline the indications for pediatric ECPR, the necessary components of an ECPR program, and the outcomes in selected patient populations.

#### **In-hospital versus out-of-hospital arrest**

In children, morbidity and mortality after cardiac arrest remain high, with better survival rates in in-hospital cardiac arrest (IHCA) versus out-of-hospital cardiac arrest (OHCA). In the past three decades, rates of survival to hospital discharge for pediatric IHCA have progressively improved from 9 % in the 1980s [7] to 35 % in the 2000s [6•]. In the 2013 report from the American Heart Association, ECPR was used in 10.5 % of the patients with a reported acute resuscitation survival rate of 34.3 % (RR, 1.22) but lower longer term survival [6•]. In the same year, a study of pediatric OHCA demonstrated survival rates of 5.4 % [8]. In the large 2013 multicenter observational prospective study [5], greater mortality after IHCA was seen in patients with malignancy and those requiring inotropic support. Other risk factors for poor outcomes included the location of cardiac arrest (with emergency departments being worse than intensive care units), epinephrine doses, bicarbonate administration, and volume expansion. The non-ROSC (return of spontaneous circulation) and death rate increased as duration of CPR increased; CPR more than 10 min was a risk factor for mortality [5]. Similar findings were shown in another study, where longer duration of CPR before ECMO was associated with worse survival and neurological outcome [9•]. However, this is not a consistent observation [10, 11] and suggests that the quality of CPR rather than its duration before

ECMO support may be more important. In a subgroup analysis of a larger study, survival after ECPR for more than 35 min was 33.3 %, compared to 12.5 % if CPR was for more than 35 min without the use of ECMO, with lower survival in the general (surgical and medical) patient group compared to the cardiac patients; neurological outcome did not differ between the two groups [12].

Other factors associated with worse outcomes include higher lactate and lower pH levels before ECPR [10, 13, 14]. Renal dysfunction pre- or post-ECPR as well as the need for renal replacement therapy (RRT) during ECMO have been linked to poor outcome [15–18]. These additional factors stem from more prolonged periods of inadequate end-organ perfusion and poor oxygen delivery—perhaps in patients in refractory shock, which culminates in cardiac arrest, for example. In addition to prompt, high-quality CPR, earlier deployment of ECMO or more aggressive conventional care might lead to better outcomes.

The bleaker outcomes from OHCA may be explained by these factors, as the likelihood of prompt, effective CPR is reduced. Witnessed arrest, older age, and shockable rhythm at presentation have been associated with better long-term survival [8]; no survival was reported for CPR more than 31 min in emergency department (ED) and more than three doses of epinephrine [19]. Some adult centers have started offering ECPR for OHCA patients, but data on this practice in pediatrics are very limited [20•, 21–23]. A metaanalysis in 2011 of OHCA and ECMO revealed that ECPR provided higher survival rates (26.7 %) compared to conventional CPR [24••]. In a large prospective multicenter study in Japan (SAVE-J study), neurological outcomes after OHCA at 1 and 6 month was better for the ECPR group rather than conventional CPR (12.3 vs. 1.5 % and 11.2 vs. 2.6 %, respectively) [25]. It is difficult to generalize the Japanese experience to the rest of the world and even harder to extrapolate it to a pediatric population. A large number of patients had witnessed arrests (90.7 %) and received bystander CPR (71.8 %). In the SAVE-J study, patients in ventricular tachycardia or fibrillation were selected, who have better survival rates when compared to patients presenting with nonshockable rhythms (70.8 vs. 36.8 %) [24••, 25]. However, the cause of pediatric OHCA is rarely primary cardiac, but rather respiratory with secondary hypoxia, with consequently higher risks of hypoxic brain injury during CPR and worse long-term outcomes. We do not recommend ECPR for pediatric OHCA except in cases of witnessed arrest with immediate, good quality CPR and evidence of adequate end-organ perfusion (e.g.,

low lactate on arrival and equal and reactive pupils) or with intermittent ROSC. ECPR could also be considered in nonasphyxial accidental hypothermia (<28 °C); ECPR can facilitate rapid rewarming up to 33 °C with subsequent slow rewarming to normothermia. Adverse prognostic factors in this setting include pH<6.5, hypercarbia, and hyperkalemia on arrival [26•, 27–29].

### Technology

Rapid deployment of ECMO is now possible because of recent technological advances in circuit design. The ideal circuit has small priming volumes, is quick to prime or can be preprimed, and has minimal sites of stasis and turbulence. All of these factors reduce both the risk of clot formation and the inflammatory response due to contact of blood with a nonbiological surface [30–32]. They facilitate rapid priming and utilization of ECMO, with reduced complications and improved outcomes [9•]. One area of controversy in ECMO concerns what constitutes the best type of pump head [33, 34]: Roller pumps are large, dependent on gravity to function properly, and are not particularly portable. Tubing rupture is a rare but substantial complication. On the other hand, centrifugal pumps are much smaller but can lead to hemolysis and complications related to the negative pressure they generate [31, 35•, 36, 37]. Many high volume centers will keep preprimed circuits for up to 30 days; this allows a stand-by ECMO machine at any time without an apparent increase in the risk of infection [38, 39•] (Fig. 1).

### ECLS programs and rapid response teams

Pediatric cardiac arrest is clearly a very stressful situation for clinicians and families, perhaps even more so when the decision is made to use ECMO. In 1998, a report of the Boston experience demonstrated that a rapid response team could achieve cannulation and initiate ECMO within 15 min from the call-out, with improved survival to 64 % [40]. Several subsequent reports from different centers around the world have followed a similar model, in which a rapid response team (RaRT) is alerted in the setting of cardiac arrest or emergent cannulation [40, 41, 42•, 43••, 44•]. The members of the RaRT have predefined roles and generally train with medical simulation to improve performance [45]. Different institutions have different members as part of their RaRT (i.e., general surgeons, cardiac surgeons, ECMO nurses, respiratory technologists, intensivists, and perfusionists), but there is still variation in the immediate availability of team members, whether staff



**Fig. 1.** **a** ECMO circuits pre-primed, sterile, and ready to use. These can be kept on stand-by for at least 30 days. **b** An ECPR simulation in progress. Larger ECLS programs often use simulation to maintain skills, team work, and in-house credentialing. (Courtesy of Amy Johansen, Royal Children's Hospital, Melbourne, Australia).

are in-house or on-call from home. A study of ECPR found a reduction in neurological complications after implementation of a RaRT but with no difference in mortality [42•]. In another small, single center study, the survival to hospital discharge after ECPR was high (57 %) in the absence of a RaRT [46]. Team composition varies but should include a person able to cannulate, a person dedicated to the ECMO circuit and pump and a person capable of helping as needed; the rest of the resuscitation team can then focus on the patient. It is important to establish an ECLS program with clear direction, protocols, continuous education, and quality

assurance [3, 47••]. Although higher center volume has been associated with better survival, it is unlikely that center volume is the sole determinant of the quality of a program [48, 49•].

### Cannulation

The type of cannulation strategy is determined by many factors, but is almost always VA, and the goal is partial support with cannulae that are easy to insert, rather than the largest available size. A very important factor is whether or not the event is in patients after cardiac surgery, where usually a clear hospital policy is in place. The cardiac surgeon will use either a central or peripheral approach. For patients who have acquired cardiac disease or cardiac arrest due to sepsis or drug overdose peripheral VA cannulation will usually be performed.

In patients following cardiac surgery, sternotomy and central cannulation are the fastest means of initiating ECMO. This allows the largest cannulae to be inserted and facilitates the highest blood flows. Limitations of central cannulation for ECPR include the need to interrupt chest compressions and the subsequent risk of bleeding and infection. Peripheral cannulation generally remains the best modality for noncardiac surgical patients, with jugular vein and carotid artery cannulae for children <15 kg and femoral artery and vein cannulae for children above 15 kg [50, 51]. However, in a recent review of the ELSO registry, carotid artery cannulation was associated with a higher risk of neurological complications and longer duration of mechanical support when compared to central or femoral cannulation [52••]. The risks of femoral cannulation include more frequent pulmonary and gastrointestinal bleeding, limb ischemia, and differential cyanosis, where deoxygenated blood is ejected out of the systemic ventricle into the coronary and cerebral arteries, while blood from the ECMO circuit perfuses only the descending aorta. Specific cannulation strategies have been considered in the setting of:

- Pulmonary hypertension (neck cannulation in order to minimize cerebral desaturation) [51]
- Fulminant sepsis (central cannulation to allow very large venous and arterial cannula and hence very high blood flow rates of 150+ ml kg<sup>-1</sup> min<sup>-1</sup>) [53, 54••]
- Single ventricle anatomy with cavopulmonary anastomoses (bicaval or central cannulation, or takedown of the cavopulmonary anastomoses) [51, 55, 56•].

Cannulation strategies may change throughout an ECMO run, based on recovery of cardiac or pulmonary function and evolution of the disease, such as conversion from VA- to VV-ECMO (in ECPR for fulminant bacterial pneumonia, cardiac recovery can occur within 3–5 days, but pulmonary recovery may be substantially slower over 2 weeks), short term centrifugal VAD, or long-term bridge to transplantation.

### Patient selection

The criteria used to select patients for ECPR vary between institutions. Some centers will deploy mechanical support only in children who suffer cardiac arrest in the operating theater, cardiac catheterization laboratory, or in the ICU. Others will offer it to children who suffer out-of-hospital cardiac arrest or in the emergency department or general wards. Ideally, in intensive care units with large ECLS programs, a decision about candidacy for ECPR should be made in every patient, as well as a plan for the type of support, cannula size, and site. This is especially important in chronically ill patients whose long-term outcome might be poor and the risk of complications too high.

In an ELSO registry review of all reported cases between 1992 and 2005, 73 % of children who received ECPR were cardiac patients, 8 % had sepsis, and 6 % had respiratory failure and 2 % accidental injury [14]. The majority of cardiac patients requiring ECPR were newborns (83 %). Prematurity and weight <3 kg were associated with worse outcomes after ECPR, presumably because of the high risk of neurological sequelae related to brain immaturity [57•]. In one case series, survival after ECPR in cardiac patients <3 kg was only 25 % compared to 35 % in the group who was semi-selectively cannulated [58]. In a recent, single-center review of cardiac patients receiving ECPR [59], survival rates varied based on the underlying disease, with patients supported for cardiomyopathy/myocarditis having 89 % survival rate compared to 47 % of the postcardiotomy group. Patients with myocarditis may develop cardiac arrest because of worsening disease or sudden arrhythmias, and this is commonly precipitated by medical intervention. For example, in a case series of 20 fulminant myocarditis patients, 7 children required CPR, 5 of whom were cannulated onto ECMO; in 6 out of 7 cases, cardiac arrest followed medical intervention (2 during intubation, 2 during amiodarone administration, and 2 during cardioversion) [60]. Having an ECMO team on stand-by during high risk procedures is important in this patient group.



ECPR in children with single ventricle physiology has been associated with higher mortality when compared to biventricular physiology (69 vs. 39 %) [59]. In one series, postcardiotomy ECPR in single ventricle physiology reported 1-year survival rates of 50 % [61]. In another series, children with single ventricle physiology who were cannulated for shunt obstruction had much better outcomes compared to those cannulated for poor ventricular function (81 vs. 29 % survival) [62]. There are fewer data on survival rates for ECPR in Glenn and Fontan circulations. In an early review, only two out of five patients with Fontan circulation requiring ECPR survived and one out of three for Glenn physiology [55]. In an ELSO database review, 68 patients with Fontan circulation who received mechanical support had a cardiac arrest, and only 17 survived (25 %) [63]. In a recent retrospective study, survival rates were significantly higher after correction of residual lesions (35 patients out of 119); therefore, mechanical support may improve outcomes by providing cardiovascular support as a bridge to further surgery [64•]. In an ELSO database review of all patients with Glenn anastomosis supported with ECMO, survival rate to hospital discharge (41 %) was not dissimilar than overall ECMO survival for cardiac patients, but with a higher incidence of neurological complications (23 %) [56•]. This is not surprising considering the physiological implications of a cavopulmonary anastomosis in a patient undergoing conventional CPR: High cerebral venous pressures, hypoxia, and inadequate forward flow because of high intrathoracic pressures during active compressions combine to increase the risk of venous stroke, hypoxic-ischemic events, and cerebral hemorrhage. Interestingly, despite the absence of neurological injury in children with Glenn circulation receiving ECPR (9/103), only four survived to hospital discharge. This might suggest that survival is correlated to the natural history of the disease and that even in the setting of adequate support and absence of complications, ultimately the key point for good outcome remains the reversibility of the underlying trigger for cardiorespiratory failure. In this series of children with Glenn anastomosis, factors associated with mortality were need for inotropes before ECMO, longer ECMO runs, combined cardiopulmonary indications, and renal failure while on ECMO [56•].

Considerable debate still occurs on the role of ECPR in the setting of nonprimary cardiac diagnoses—in septic shock, for example. Data from our center report an overall survival rate of 55 % in patients receiving CPR during cannulation [53]. Improved outcomes may be achieved through central cannulation [54••]. While

good survival after ECPR for sepsis can be achieved, much worse outcomes have been described for medical patients on mechanical support. In a case series by Morris et al. [65], survival after ECPR differed between patients with a cardiac diagnosis (44 %) and those with a noncardiac diagnosis (9.5 %). It can be difficult to decide emergently whether the patient is a good ECPR candidate in the setting of an arrest. Cardiac arrest is usually sudden and unanticipated, in which case ECPR can be used as a bridge to buy time to investigate and correct the etiology and allow the parents to try and come to terms with their child's critical illness.

Interestingly, while many ECPR studies focus on populations with cardiac disease, primary respiratory disease remains the most common cause for cardiac arrest in the pediatric population. The early use of ECMO in severe respiratory failure improves patient outcome by limiting lung injury and also allowing less fluid administration to patients as a result of the negative circulatory effects of mechanical ventilation.

Additional indications for ECPR other than cardiac disease include poisoning [66, 67], blunt chest trauma [68, 69], electrolyte disturbances [70], hypothermia [26•, 27, 71], and anaphylaxis [72]. Extrapolating clear guidelines on the basis of these brief reports is difficult, and candidacy for ECPR must be established on a case-by-case basis.

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### Hypothermia and ECPR

The use of therapeutic hypothermia (TH) for neuroprotection following ECPR is controversial. Some centers have used it routinely since the 1990s [11, 41] while others have not [10, 59]. A recent review concluded that TH may be of benefit in adolescents who remain comatose after resuscitation from witnessed, out-of-hospital, ventricular fibrillation cardiac arrest, and could be considered for children who remain comatose after resuscitation from cardiac arrest [73]. The outcome data for TH (32–34 °C) following cardiac arrest are difficult to interpret because of the large number of underlying conditions which precipitate cardiac arrest, variably slow times to achieve the target temperature, and variations in the speed and timing of rewarming. ECPR can bypass some of these obstacles by facilitating rapid cooling and maintenance of hypothermia, as well as permitting a more controlled rate of rewarming, when compared to standard measures. In one small retrospective series, survival rates at discharge for children with asphyxial IHCA and OHCA were higher in the hypothermia group [74]. Nonetheless, the evidence for TH in children

remains limited [75]. In 2013, one study randomised newborns needing ECMO to normothermia or TH; the results of the study showed no difference in outcome at 2 years, with slightly higher risk for adverse events in the TH group [76••]. However, there is no evidence that these results are applicable to older children. Although there are some encouraging data from animal studies showing improved survival and outcome with TH [77, 78], a recent large randomised trial in adults showed no difference in outcome for OHCA patients [79]. In another randomised trial, there was no difference in survival or neurological outcome after rapid cooling prehospital admission [80]. While in the first trial cooling was delayed and rewarming was very rapid, in the second, there was no comment regarding rewarming practices. While TH may be controversial, avoiding hyperthermia with controlled temperature management is generally regarded as a standard of care [81]. The major problem with most studies is the lack of ability and understanding on the correct use of hypothermia; patient temperature needs to be  $<33$  °C within 4 h, TH should continue for 48–72 h, and rewarming should be very gradual and physiologically based [82].

#### Rapid deployment versus early deployment

There is no doubt that the training for and an introduction of a rapid deployment system for ECMO will decrease times to institute ECPR and potentially improve survival [45]. Hence, if rapid deployment ECMO can reduce the period of minimal or no cardiac output and end-organ damage, then early mechanical support might improve outcomes. As ECMO becomes safer, more familiar, and easier to manage, it may be considered earlier in the management strategy of critically ill children. In a review of all complications in the neonatal group supported with ECMO, the presence of a cardiac arrest pre-ECMO was associated with worse outcome [83•, 84, 85]. In the presence of progressive respiratory failure and hypoxia leading to cardiac arrest (e.g., ARDS, asthma, meconium aspiration, congenital diaphragmatic hernia), early venovenous support could improve outcomes, with low risk of complications and good overall survival. Moreover, there is some evidence that venovenous ECMO might also be useful in selected cardiac patients. Further analysis is needed to better define the correct indications for this group of patients [86]. In postcardiotomy patients, progressive cardiac dysfunction with raising lactate, falling mixed venous saturation, and escalating inotropes should trigger early

discussion and consideration of mechanical support. Exact figures that should trigger the initiation of ECMO (e.g., oxygenation index,  $\text{PaO}_2/\text{FiO}_2$  ratio,  $\text{SvO}_2$ , lactate, inotrope scores) have not been established, and the decision to initiate ECMO preemptively relies on clinical experience and the quality of the local ECLS program. For patients with borderline cardiac output and high inotropic scores, cardiac surgeons and intensivists should always discuss initiating mechanical support in the operating theatre. In fact, improved outcomes have been described for children cannulated onto ECMO in the operating room compared to support later in the postoperative period [84, 85, 87].

#### Outcome

The ELSO registry is a very useful source of information, but the standard outcome measure is survival to hospital discharge. This has several limitations, including that late deaths and long-term neurological morbidity are not captured, and it is hard to control for the enormous global variability in technology, clinical management strategies, anticoagulation, patient selection, cannulation strategies, and follow-up. A very comprehensive review of the literature examining ECMO-related outcomes in cardiac patients and children requiring ECPR was published in 2012 [88••]. Data from the ELSO registry from 1989 until January 2014 show survival after ECPR in 40 % (388/980) of neonates and 41 % in the pediatric group (840/2071) [89]. Noncardiac indications, kidney injury on ECMO and need for RRT, lower pH on ECMO, and development of neurologic complications negatively impact survival. The duration of CPR relates to mortality in only two studies [41, 90]. In a recent study, neurologic complications occurred in 20 % and were associated with higher mortality, especially in the group receiving ECPR (OR, 1.7) [83•]. In another study, both short- and long-term survivals after ECPR in cardiac patients were very high (75 and 70 %, respectively), possibly related to a reduction in complications (less bleeding, acidosis, and renal failure), higher blood flows, and less delay in decannulation. Encouragingly, 89 % were normal or had mild disability at follow-up (1.9 years) [91].

Fewer data are available on functional outcomes and late mortality. In a review of the ECPR literature from 2000 to 2011, overall functional outcomes were good, with normal or mild dysfunction in 79 % of children surviving ECPR [88••]. One limitation of this report may be publication bias, where only high volume centers with excellent outcomes publish their results. Another report, in which 49 % of the survival group received ECPR,

assessed the quality of life after ECMO. Physical summary scores were lower than the general American population and similar to those of children with congenital heart disease, while the psychosocial ones were similar to the general population [92]. It remains debatable if the lower physical scores reflect underlying cardiac disease history or are related to mechanical support. Regardless, good quality of life can be achieved following ECPR. However, late mortality does occur, even in patients who have seemingly recovered from their initial illness. A large

series from the UK found that late mortality (beyond 90 days following ECMO) was 6.2 %, with a survival rate at 5 years varying between 32 % for the cardiac population and 88 % for meconium aspiration [93•]. Long-term follow-up and more widespread research are needed to better understand what factors contribute to the future of patients we currently support with ECMO, or if there is a group of patients where very close follow-up and prevention of deterioration might reduce late mortality, especially in the cardiac population.

## Conclusions

The availability of ECMO for children in cardiac arrest is becoming a standard of care for tertiary paediatric intensive care units in high-income countries. Reduction of end-organ failure and its impact on outcome can be achieved by good CPR and prompt consideration of mechanical support. Patient selection, cannulation strategy, mode of support, circuit management, and avoidance of complications are key factors for successful outcomes. Overall survival and long-term neurological outcomes are influenced by the natural history of the primary disease, the timeliness of ECMO initiation, and the risks of iatrogenic complications. Prompt identification of the deteriorating patient, early reversal of shock and organ failure, and rapid deployment of ECMO without ECPR should be the focus to improve survival and quality of life.

## Compliance with Ethics Guidelines

### Conflict of Interest

Roberto Chiletto, Warwick Butt, and Graeme MaClaren declare that they have no conflicts of interest.

### Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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