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Controversies in Extracorporeal Cardiopulmonary Resuscitation

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ABSTRACT

Extracorporeal cardiopulmonary resuscitation (ECPR) is the emergent deployment of VA-ECMO for refractory cardiac arrest. Observational and randomized trial data show that ECPR may improve outcomes compared to conventional CPR (CCPR), but many questions and controversies remain. Patient selection is a critical determinant of ECPR success. Most institutions implement inclusion/exclusion criteria, but risk scores may be more apt to correctly predict which patients are likely to benefit from ECPR. Good outcomes from ECPR occur more often in patients with an initially shockable rhythm, reversible etiology of arrest, evidence of effective CPR, and shorter durations of conventional CPR. Shorter total CPR duration is consistently associated with neurologically favorable survival, but optimal and upper limit timing at which the benefits of ECPR outweigh the risks continue to be delineated. Data are emerging regarding pre-hospital implementation of ECPR as a strategy to reduce low-flow time. Vascular access for ECPR can be challenging, particularly in the pediatric population. In adults, percutaneous cannulation of the femoral vessels under fluoroscopic guidance and performed by a small group of highly skilled operators may increase success rates and reduce complications. Data are limited regarding post-arrest care for the ECPR patient, particularly regarding temperature management and anticoagulation. Compared to other resource-intensive therapies, ECPR is cost-effective by modern standards.

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Introduction

Survival rates following cardiac arrest have stagnated over the last decade [1-5]. Patients with prolonged resuscitation durations remain even less likely to achieve good outcomes [6,7]. Recent observational and trial data have shown that the emergent deployment of veno-arterial (VA) extracorporeal membrane oxygenation (ECMO) during cardiac arrest (i.e., extracorporeal cardiopulmonary resuscitation or ECPR) can impart neurologically favorable survival in some patients who would have otherwise died with conventional CPR alone. In response to these promising data, the use of ECPR is increasing worldwide [8-11].

In this review, we discuss controversies in ECPR. We consider which patients are likely to benefit from ECPR, when the transition from conventional CPR to ECPR should occur, who should cannulate and where. We also review areas of uncertainty in vascular access strategies, post-arrest management, neuro-prognostication, organ donation, pediatric ECPR, cost-effectiveness, and ECPR in the era of COVID-19.

Who may benefit from ECPR?

Careful patient selection is one of the most important and challenging decisions in ECPR. Arguably, eligibility criteria should strictly target patient groups who are the most likely to survive with a favorable neurologic outcome, because ECPR is a scarce and resource-intensive therapy. However, most data are observational as to who may benefit from ECPR over continued conventional CPR (CCPR), and in practice, the decision to cannulate (or not) is often made emergently and with incomplete information. The inclusion and exclusion criteria from 3 recent clinical trials of ECPR are displayed in Table 1.

Table 1: Inclusion/exclusion criteria for randomized trials of ECPR

Trial	Inclusion Criteria	Exclusion Criteria
ARREST Trial [8].	• Adults aged 18-75 • Pulseless ventricular tachycardia/ventricular fibrillation as initial presenting rhythm • Absence of return of spontaneous circulation without return of spontaneous circulation • Body morphology able to accommodate a Lund University Cardiopulmonary Assist System • Estimated transfer time to emergency department <30 minutes	• Valid do not resuscitate advanced directive • Nursing home residents • Blunt, penetrating, or burn-related injury • Drowning • Known overdose • Known pregnancy • Prisoner • Presence of an opt-out study bracelet • Unavailability of cardiac catheterization laboratory at receiving center • Terminal cancer • Known contraindications to emergency coronary angiography • Contrast allergies • Active gastrointestinal or visceral bleeding
Prague OHCA Trial [19].	• Adults aged 18-65 • Witnessed OHCA of presumed cardiac etiology • At least five minutes of advanced cardiac life support without return of spontaneous circulation • Unconsciousness (Glasgow Coma Score <8) • ECPR team available at receiving center	• Unwitnessed cardiac arrest • Presumed noncardiac cause for cardiac arrest • Suspected or confirmed pregnancy • Return of spontaneous circulation within five minutes of initial resuscitation • Conscious patient • Known severe chronic organ dysfunction or other limitations in therapy • Known bleeding diathesis or suspected or confirmed acute or recent intracranial bleeding • Suspected or confirmed acute stroke • Known do not resuscitate order or other circumstances making 180-day survival unlikely • Known prearrest cerebral performance category of >3
EROCA Trial [39].	• Presumed or known age 18-70 years • Out-of-hospital cardiac arrest, presumed non-traumatic cause, and requiring CPR • Initial shockable rhythm or witnessed arrest with pulseless electrical activity or asystole as presenting rhythm • Persistent cardiac arrest after initial manual paramedic cardiac rhythm analysis and shock if indicated • Predicted 911 call to arrival time to ECPR-capable emergency department interval predicted to be within 30 minutes	• Do not resuscitate or do not intubate advanced directive • Pre-existing evidence of opting out of study • Prisoner • Pregnant (obvious or known) • ECPR-capable ED not at the destination hospital as determined by EMS destination protocol • Legally authorized representative aware of the study and refused study participation at the scene

Initial rhythm

As in CCPR, first recorded rhythm remains a critical predictor of outcome following ECPR [12-15]. In a meta-analysis of ECPR for OHCA, patients with an initial rhythm of ventricular fibrillation (VF) or ventricular tachycardia (VT) were significantly more likely to survive to hospital discharge compared to those whose initial rhythm was pulseless electrical activity (PEA) or asystole (OR 2.20; 95% CI, 1.30-3.72, P=0.003) [13]. Patients presenting with shockable rhythms are known to have the highest rate of survival following CCPR compared to patients with non-shockable rhythms, but more than half will die with refractory VF unresponsive to conventional therapies [4,12]. This cohort of patients may specifically benefit from ECPR because they are likely to have a reversible underlying cardiac etiology (e.g., coronary artery disease) [16-18]. The data from the two published randomized trials of ECPR compared to standard resuscitation (i.e., CCPR) suggest a clear survival benefit with ECPR for patients initially presenting with shockable rhythms, i.e., 43% and 49% survival with favorable neurological outcome [8,19]. On the other hand, non-shockable rhythms have been associated with poor outcomes and may be excluded a priori from stringent trial eligibility criteria and some institutional protocols for out-of-hospital cardiac arrest (OHCA) ECPR [8,16,20,21].

For patients with in-hospital cardiac arrest (IHCA) treated with ECPR, initial rhythm is less frequently cited as a criterion for cannulation [14,22]. In a recent large registry study from the American Heart Association Get With The Guidelines database, more than 50% of patients who received ECPR had an initial rhythm of PEA or asystole [23]. Indeed, initial shockable cardiac rhythm may be associated with survival in IHCA ECPR, but the effect is both less consistent and less pronounced than in the OHCA population [14,23,24]. PEA may portend a better prognosis in the IHCA population because most events occur in highly monitored areas and patients receive immediate application of high-quality CPR.

Age

Although age cutoffs are frequently cited in eligibility criteria, age is not consistently associated with survival in either observational or randomized trials of OHCA ECPR [8,13,19]. In a systematic review of published ECPR protocols, age cutoff varied between 65-80 as the upper limit with 70 years being most common [22]. While the median age of cannulated patients is in the late 50s, a recent randomized trial found that patients ≥65 years who received ECPR for OHCA had similar survival rates to younger patients (28.6% versus 32.6%) [9,14,19].

Etiology

ECPR is a bridge therapy, and therefore should be targeted to patients with a reversible reason for cardiac arrest. In OHCA, information may be limited, so efforts must be directed to identification of "potentially" reversible etiologies [13,14]. These may include: acute coronary artery occlusion, pulmonary embolism, profound hypothermia, myocarditis, cardiac injury, cardiomyopathy, congestive heart failure, and drug intoxication [25].

In IHCA, potentially reversible conditions and underlying diagnoses may be more myriad; more information is available for clinicians to make nuanced decisions. Clinicians may also consider IHCA ECPR if a patient is known to have a condition in which CCPR would not be effective and whereby bridging with VA-ECMO may be part of a pre-established plan of care (e.g., pulmonary hypertension and possibility to be listed for lung transplantation) [26]. While cardiac outcomes portend the best prognoses, worse outcomes may occur in patients who have prolonged hypoxia (e.g., respiratory failure) or prolonged low-flow (e.g., septic shock) prior to CPR initiation [14,27,28].

CPR effectiveness

High-quality CPR is the cornerstone of cardiac arrest care, but some patients, despite excellent CPR, will not achieve return of spontaneous circulation (ROSC). For patients being considered for ECPR, a strategy that incorporates an individual's physiologic response to CPR efforts (i.e., CPR effectiveness), may further distinguish patients who would be likely to achieve neurologically favorable survival if offered ECPR from those who would not. Signs of CPR effectiveness include intra-arrest continuous physiologic markers such as coronary perfusion pressure, diastolic blood pressure, and end-tidal carbon dioxide, as well as discrete markers of oxygen delivery namely lactate, pH, and arterial oxygen tension [29-31]. In OHCA ECPR, lower lactate and higher pH on admission are associated with survival and favorable neurologic outcomes, but cut-off points are not known [9,13,24,32]. Similarly, signs of life during resuscitation are significantly associated with good outcomes following ECPR, even among patients with other negative features such as prolonged CPR duration and non-shockable rhythms [32].

Intermittent ROSC, here defined as the transient occurrence of any ROSC and importantly differentiated from sustained ROSC (>20 min without CPR) [27] prior to ECMO flow, is not consistently reported in observational studies of ECPR but may be associated with outcomes [13-15, 23,32]. In a large European registry study, patients who had intermittent ROSC were more likely to survive to hospital discharge (OR 2.3; 95% CI, 1.1-4.7, P=0.03) but were not statistically more likely to have a favorable neurologic outcome (OR 2.1; 95% CI, 0.9-5.0, P=0.08). More study is needed [15].

Bystander CPR

It is well-known that bystander CPR is associated with improved outcomes in OHCA [33-35]. Observational and trial data for ECPR similarly indicate that patients who receive bystander CPR have increased likelihood of short-term survival and neurologically favorable survival [8,13]. Recent randomized controlled trial data has shown that a very high incidence of bystander and telephone assisted CPR is a prerequisite for favorable survival in patients with refractory OHCA, including those who ultimately undergo ECPR [19].

Risk scores

Systematically restricting enrollment to highly selected patient groups may lead to overall higher survival rates, but there will be individual patients who would benefit from ECPR who are deemed non-candidates due to specific unfavorable characteristics. Risk scores may be more apt to accurately predict who may benefit from ECPR than inclusion/exclusion criteria. Tonna and colleagues developed a multivariable model and survival prediction score using a cohort of in-hospital ECPR patients from the Get With The Guidelines registry which was validated against a separate cohort using the Extracorporeal Life Support Organization (ELSO) registry. The prediction score consisted of 6 variables (age, pre-existing renal insufficiency, time of day, illness category, initial rhythm, and duration of CPR) and had good discrimination (AUC: 0.72; 95% CI: 0.68-0.76) and acceptable calibration (Hosmer and Lemeshow goodness of fit P=0.079) [23]. However, risk prediction scores must be deployed with caution. Prognostic tools that prioritize a high specificity (where the determination of futility is held to a high standard) come at the cost of lower specificity. Further, tools developed from a national database may not wield the same discrimination when applied within a particular institution. Ultimately, whether to implement ECPR for an individual patient is a binary decision. Additional work is needed to develop prognostic scores for patients with OHCA to inform ECPR candidacy decisions.

When should ECPR be initiated?

Duration of no and low-flow (i.e., total CPR duration) may be the single most important predictor of good outcomes following ECPR and should be included in patient selection criteria [9,13,14,23,36]. In a retrospective study by Bartos et al. of 160 adults who received protocolized ECPR for OHCA versus 654 who received standard ACLS (i.e., conventional CPR), all patients in the ECPR group with CPR durations < 30 minutes survived with favorable neurologic outcomes. Importantly, patients were not able to be cannulated prior to 20 minutes of CPR due to logistical reasons. In the CCPR group, no patients who required CPR beyond 40 minutes survived with favorable neurologic outcome, whereas in the ECPR group, neurologically favorable survival declined by 2.5% per minute up to 60 minutes of CPR (Figure 1) [9]. Another observational study found that CPR duration was associated with outcomes in patients who received ECPR; those who survived to discharge had significantly shorter total durations of CPR compared to those who died (43.2 ± 19.9 min vs 62.1 ± 27.9 min, P<0.001). The probability of survival following ECPR was 0.5, 0.3, and 0.1 when CPR duration was 30, 60, and 90 min respectively [37].

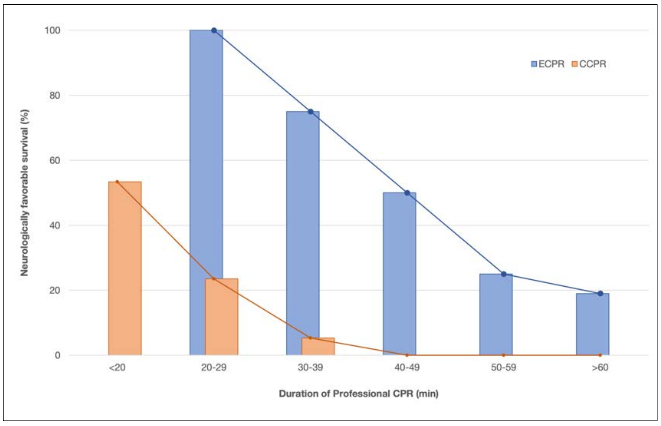

Figure 1: Association of CPR duration with neurologically favorable survival following ECPR versus conventional CPR. Modified from Bartos et al., [9]. Circulation 2020

These observational data have also been confirmed in a randomized population, where ECPR implemented for OHCA after 61-62 minutes of CPR resulted in 22% neurological favorable survival after 180 days [19].

In light of these data, the decision to launch ECPR should be made as soon as possible in order to limit ineffective CPR, but not be too soon as to preclude an opportunity for ROSC with conventional resuscitation. In most cases, there will be a minimum period of CCPR or defibrillation attempts before the decision to initiate ECPR is made. There is variability among institutions as to how a definition of "refractory cardiac arrest" with minimum CCPR duration around 10 minutes and cut-off times ranging from 20 to 120 minutes, and 60 minutes being the most common upper limit [22]. Whether to designate candidacy when the patient is in the hands of EMS using estimated transfer times to the hospital or when the patient has physically arrived at the hospital will also impact this timing.

Numerous studies have found that survival declines rapidly after 10 minutes of CPR [6,7,38]. In patients who do not promptly achieve ROSC, ECPR may be advantageous over continued advanced cardiopulmonary life support and may prolong the duration of CCPR that can lead to a good neurologic outcome [8-10,19]. A prospective, observational study of ECPR versus CCPR during IHCA using propensity score-matching found that patients who received ECPR had longer total durations of CPR but roughly 20% increase in survival rate and favorable neurologic outcome, with better cumulative survival in the ECPR group at 30 days and 1 year (1 year hazard ratio 0.53, 95% CI 0.33-0.83, P=0.006). In another observational study, patients who received ECPR for OHCA, compared to those who received only CCPR, had a relative risk reduction for death or poor neurological function of 29% (95% CI ; P<0.001) if the total resuscitation duration was between 20 and 59 minutes and 19% (95% CI; P<0.001) if the total resuscitation duration was ≥60 minutes [10,18,27,41]. Survival was significantly improved in ECPR patients for all durations of CPR [9]. Trial data comparing ECPR to CCPR are emerging. The "ARREST" trial, which randomized patients with OHCA and refractory VF to either ECPR or continued ACLS upon hospital arrival, showed that cumulative survival was significantly better with ECPR (hazard ratio 0.16, 95% CI 0.06-0.41, log rank test P<0.0001); patients who continued to receive standard ACLS had dismal outcomes [8]. Although the "Prague OHCA study," comparing early intra-arrest transport and ECPR versus continued ACLS, missed its primary endpoint for 180-day favorable neurologic survival with ECPR (31% versus 22%, P=0.09), it did show statistically significant improvement for 6-month survival and 30 days neurological outcome. Further, and in concordance with the ARREST trial, it demonstrated a dramatic >7x higher survival rate for patients requiring CPR for >45 minutes [19]. The randomization time of 25 minutes in the Prague OHCA study may be a potentially rational and realistic discrimination point but the precise inflection point at which the benefits of ECPR outweigh the risks continues to be defined [19].

Once a patient is deemed a candidate for ECPR, even in an in-hospital setting where conditions are optimal, there is a lag time typically >20 minutes between ECPR launch and ECMO flow start. Deploying ECPR is a complex process that requires a well-rehearsed protocol, rapidly deployable equipment, and experienced personnel. Even experienced centers have reported challenges limiting low-flow time, with a wide range of times to initiation of ECMO [18,39,40]. Therefore, a system's launch target should account for all the steps necessary to achieve ECMO flow. Laussen and Guerguerian describe 3 intervals of ECPR that contribute to total resuscitation duration: (1) cardiac arrest to CPR start; (2) CPR start to ECPR launch; and (3) ECPR launch to return of circulation with adequate ECMO flow [26]. A delay in any interval will contribute to a longer duration of ischemia prior to ECMO flow and may portend worse outcomes. Highly organized systems and expert operators are critical to achieving rapid cannulation and minimizing delays to ECMO flow. Community and EMS collaboration to facilitate transfer to ECMO centers is the cornerstone for optimal outcomes in OHCA [8,39,41].

In lieu of transferring patients for cannulation in the hospital, the ECPR team may be deployed to the patient's location in the field. The Sub30 study is an ongoing prospective feasibility study in London, England that aims to test whether it is possible to implement ECPR within 30 minutes of collapse in OHCA by dispatching a mobile team for cannulation in an ECPR-capable vehicle [42]. In Paris, France, the APACAR2 trial is an ongoing randomized comparative study of pre-hospital ECPR at the site of the cardiac arrest versus transfer for initiation of ECPR in-hospital [43]. Pre-hospital ECPR may be a viable strategy to decrease time to ECMO flow, but more data are needed.

Where should cannulation occur, and who should cannulate?
In-hospital cannulation may occur in multiple, pre-determined locations including the emergency department (ED), intensive care unit (ICU), operating room (OR), and cardiac catheterization lab (CCL). The ideal cannulation setting would be proximal to the patient's location in order to minimize transportation of the patient with ongoing CPR, allow for rapid access to ECLS equipment and personnel, facilitate adjunctive interventions if required (e.g., percutaneous coronary intervention), be large enough to accommodate numerous team members and equipment, and occur in a well-rehearsed, familiar environment to reduce chaos [26].

There is a high level of variation in current practice patterns [22]. In the United States, ECPR for refractory OHCA is increasingly initiated in emergency departments whereas in Japan, the most common cannulation location is the cardiac catheterization laboratory [44,45]. VA-ECMO initiation in the CCL may be advantageous. Direct visualization of cannulation using fluoroscopy may minimize cannulation-related complications and allow for percutaneous coronary intervention as needed for acute coronary syndrome, which is the most common underlying reversible cause in refractory VF [18].

Who should cannulate? In a survey of ED-ECPR programs in the US, ECMO cannulae are placed by cardiovascular surgeons in most programs (78%) [44]. Percutaneous cannulation by emergency department physicians and intensivists is increasingly reported in the literature [16,39,44-47]. Whether more or fewer operators should be trained remains an area of controversy. More people trained may lead to reductions in delays, as procedures could start sooner. However, expert high-volume operators may be more likely to achieve cannulation rapidly and with few complications. We demonstrated that cannulation with a core group of interventional cardiologists had no vascular complications and no failed cannulations [8,9,18]. Along these lines, it may be preferable for patients to be transferred to experienced, high-volume ECMO centers, because higher annual case volume is associated with better outcomes compared to low-volume centers [48]. An alternative approach would be the establishment of a mobile ECMO resuscitation program where a team based at a high-volume ECMO center would work in tandem with EMS in a metropolitan area to cannulate patients in an ED closest to the location of the arrest. Cannulated patients would then be transferred to the high volume ECMO-center for ICU level of care. This system was successfully implemented in Minnesota and led to 100% successful cannulations and 43% three-month survival [49]. Regardless of the approach deployed, it is critical to account for a steep learning curve associated with large-bore VA-ECMO cannulae placement in the development of any new ECPR program.

What vascular access strategy is optimal?

Cannulation for VA-ECMO may be accomplished via central cannulation of the right atrium and aorta, peripheral cervical cannulation of the internal jugular vein and common carotid artery, or peripheral femoral cannulation of the common femoral vein and artery. Whichever the strategy, vascular access for VA-ECMO during cardiac arrest must be achieved rapidly. The most recent ELSO consensus does not make a strong recommendation for a particular cannulation strategy, instead leaving the decision to the discretion of the most skilled immediately available provider [27].

Percutaneous cannulation of the femoral artery and vein is the most common approach for ECPR in adult patients with both in- and out-of-hospital cardiac arrest [22]. While cervical cannulation is used frequently in pediatric ECPR, it is not a recommended site for adults [27,28]. Peripheral cannulation allows for increased "hands-on" time on the chest during the cannulation procedure, and this may be additionally facilitated by a mechanical chest compression device such as the LUCAS (Physio-Control Inc./ Jolife AB, Lund, Sweden). A major potential complication with peripheral cannulation is critical distal limb ischemia, which occurs in 17% of peripheral VA-ECMO cannulations due to the relatively large size of the femoral arterial cannula which can limit perfusion to the lower leg [50,51].This incidence is likely higher in the ECPR population where systemic perfusion is likely worse and vascular cannulation must occur rapidly. Following ECMO flow initiation, routine placement of a separate catheter to achieve distal perfusion to the lower extremity (distal perfusion catheter) is successful at preventing leg ischemia [52-54].

Central cannulation has been standard of care for post-surgical cardiac patients with a recent sternotomy [55]. Advantages to central cannulation may include superior hemodynamics with open-chest CPR and potentially higher ECMO flow rates. Challenging this dogma, a high-volume ECMO center reported improved neurologic outcomes at 72 hours with peripheral ECPR cannulation for post-cardiac surgery patients, but there was no survival benefit [56,57]. Additional downsides of central cannulation include increased risks of bleeding and infection [58]. More data are needed to understand which patients may benefit from central versus peripheral cannulations.

Cannulation for ECLS has traditionally been performed via an open surgical approach [59]. The main advantage of a cut-down technique is direct visualization of the vessels, which allows the operator to optimize cannula size and avoid vessel injury [27]. However, surgical cannulation may be time-consuming and requires multiple steps, including soft tissue dissection, vessel exposure and ligature placement, venotomy or arteriotomy, cannula insertion, ligation of the vessel distal to the cannula, and incision closure [47]. Newer data suggest that percutaneous peripheral cannulation may be faster, result in a lower rate of vascular complications, and may improve survival compared to surgical techniques [49,60]. Fluoroscopy in addition to ultrasound further improves percutaneous cannulation success, shortens cannulation times, and reduces complications [8,61,62].

Should mechanical left ventricular (LV) unloading be used routinely?

Current dogma maintains that VA-ECMO with femoral cannulation leads to an increase in afterload generated by retrograde flow through the aorta. This is thought to lead to increased LV end diastolic pressure (LVEDP), decreased native stroke volume, and increased pulmonary edema, ultimately delaying or limiting myocardial recovery [63-65]. To this end, the use of an intra-aortic balloon pump or peripheral ventricular assist device (Impella, Abiomed, Danvers MA) have been used to mechanically "unload" the LV. Available data are based on observational studies including all-comers with cardiogenic shock which introduces significant selection bias. Data suggest a mortality benefit of LV unloading with an increased risk of complications [65-68]. However other studies report neutral results [63]. The issue is controversial since presented data do not account for differences in cardiac contractility, ECMO flow, use of vasopressors or inotropes, and other confounding variables that may interfere with LVEDP and cardiac recovery. Importantly, there is a dearth of invasive hemodynamic data that confirms the hypothesized increased LVEDP or stroke work in patients who receive VA-ECMO therapy without an adjunctive unloading device. Experimental studies have shown benefit in terms of decreasing left ventricle work load by various unloading techniques, including pulmonary artery cannula, Impella device, and septostomy [69,70]. More likely, a tailored approach using LV unloading in those who are determined to derive benefit from it is ideal, albeit understanding which patients may benefit from LV unloading and what strategy to use still deserves further research [71].

What is the optimal post-cardiac arrest strategy for patients resuscitated with ECPR?

Temperature management

Since 2015, the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation (ILCOR) has recommended selecting and maintaining a constant target temperature between 32-36 °C for at least 24 hours for adults who remain unresponsive following in- or out-of-hospital cardiac arrest [25]. This recommendation has come into question following the results of the Targeted Hypothermia versus Targeted Normothermia after Out-of-Hospital Cardiac Arrest (TTM2) randomized superiority trial. In this study of 1,850 patients with OHCA, Dankiewicz and colleagues showed that targeted hypothermia at 33 °C did not lead to a lower incidence of death by 6 months compared to targeted normothermia with fever prevention [72]. Although smaller trials have shown possible benefit with mild and moderate hypothermia two meta-analyses which included the most recent trial data found that there was no survival or neurologic benefit to targeted 32-34 °C compared to actively controlled normothermia [73-76].

Whether any degree or duration of therapeutic hypothermia improves survival and neurologic outcomes in the ECPR sub-population is essentially unknown. Based on expert consensus, the current guidelines from ELSO advise active temperature control to 33-36 °C for 24 hours, followed by gradual rewarming to 37 °C [27]. Patients who undergo VA-ECMO cannulation during cardiac arrest may be more likely to benefit from therapeutic hypothermia. ECPR patients have prolonged low-flow periods and resultant ischemia-reperfusion brain injury that could theoretically benefit from hypothermia-induced reductions in cerebral metabolism, excitotoxicity, and inflammation [77-79]. On the other hand, patients resuscitated with ECPR may be at increased risk of complications from hypothermia, such as coagulopathy and bleeding [80,81]. Dedicated studies are needed to better understand optimal temperature management in the ECPR population. Importantly, all patients enrolled in published randomized trials of ECPR who reached the intensive care unit were subjected to TTM [19].

Anticoagulation

Anticoagulation on VA-ECMO remains an active area of discussion. The use of anticoagulation aims to mitigate thrombotic risk including stroke, arterial emboli, intracardiac thrombi, pump thrombosis, and hemolysis [82,83]. Current anticoagulation practices do not typically parse out ECPR from the general VA-ECMO population, but literature suggests that ECPR patients are at particular risk of bleeding due to traumatic injuries from chest compressions and severe abnormalities in their coagulation cascade [84-87]. A study by Cartwright and colleagues found significant differences in coagulation profiles between ECPR and other ECMO cohorts, with ECPR patients having hypofibrinogenemia and lower indices of clot strength [86]. Another study found that patients with refractory cardiac arrest who underwent VA-ECMO cannulation had a high incidence of coagulation derangements, particularly disseminated intravascular coagulation, even prior to ECMO flow initiation [87]. Cardiac arrest sets off a cascade of inflammatory cytokines that leads to marked coagulo-fibrinolytic derangements, with initially impaired anticoagulant mechanisms and hyperfibrinolysis followed by a fibrinolytic shutdown [88,89]. Therefore, ECPR patients have both bleeding and thromboembolic complications [90]. There are important questions that deserve further study regarding the initial loading dose of heparin as well as anticoagulation intensity and targets during ongoing ECMO management for patients with ECPR.

Neuro-prognostication and organ donation

Hypoxic-ischemic brain injury is the primary cause of morbidity among survivors of cardiac arrest. Neurologic outcomes following ECPR remain poor, with 15% of OHCA and 38% of IHCA survivors achieving favorable neurologic outcomes in meta-analyses of observational data [13,14,91]. Accurate neuro-prognostication is necessary to avoid inappropriate continuation of technologies leading to patients who remain alive but with severe devastating brain injury, as well as premature termination of life-supporting therapies in patients who may otherwise have had a meaningful neurologic recovery. It is reasonable to align neuro-prognostication practices for ECPR with those currently in place for general post-cardiac arrest care. In their most recent update, the AHA recommended a multimodal approach to neuro-prognostication including clinical examination, EEG, somatosensory evoked potentials, blood biomarkers (neuron-specific enolase), CT, and MRI [92]. While individual testing may be performed earlier, global neuro-prognostication should not occur until after adequate time has passed in order to avoid confounding with sedation or transiently poor examination in the early post-injury period [92]. For patients on ECMO, there may be additional delays in neuro-prognostication due to sedation burdens. ECPR patients may require deeper sedation to maintain extracorporeal devices and increased time for clearance due to more profound kidney and liver injury from longer down times. Further delays may occur because of difficulties transporting a patient on ECMO.

Compared to a general CCPR population, the prevalence of brain death is higher in patients resuscitated with ECPR [93,94]. Organ donation may be an added potential benefit of ECPR when survival is not possible [19,91,93]. Eligibility for ECPR should remain driven by the unique patient's likelihood to benefit from this rescue therapy, but ethical dilemmas may arise regarding which patients should or should not be cannulated based on their likelihood of survival versus likelihood to be an organ donor. Importantly, there remains a large gap between organ availability and organ need [96].

Pediatric ECPR

The application of ECPR for children with refractory cardiac arrest has increased significantly during the last 20 years [97,98]. Outcomes in pediatric ECPR are comparably much better than in adult ECPR with pooled survival of 46% and functional neurologic outcome 30% in a recent meta-analysis [99]. Nevertheless, there are many knowledge gaps and areas of discussion related to pediatric ECPR.

The first relates to patient selection. Currently, ECPR is restricted to children who experience cardiac arrest in a hospital setting, as there are insufficient data regarding ECPR for children with OHCA [28]. OHCA in pediatrics typically portends a grave outcome due to severe anoxic brain injury but there may be a subset of patients with favorable features such as shockable rhythm and prompt initiation of bystander CPR who may benefit from ECPR [100-102]. The best outcomes for pediatric ECPR occur in children with a primary cardiac disease [98,99,103]. In those without a primary cardiac disease, reported outcomes are worse; this may be attributable to increased severity of ischemia due to prolonged hypoxemia or hypotension prior to the cardiac arrest event [28].

Little is known about cannulation practices in pediatric ECPR. Vascular access for ECPR may be additionally challenging due to varying underlying patient physiologies, anatomic differences, and a range of patient sizes. Therefore, cannulation requires highly specialized and experienced operators. Neonatal and pediatric cannulation occurs peripherally via the cervical vessels or centrally with cannulation of the right atrium and aorta by pediatric cardiovascular or general surgeons [28,104,105]. A minority will undergo femoral cannulation, because the femoral vessels are proportionally smaller and will not support adequate ECMO flow. Open surgical technique is standard in pediatric ECPR, whereas percutaneous cannulation is not widely practiced in pediatric ECMO in except in a subset of older and heavier patients being cannulated for veno-venous support for respiratory failure [106].

In addition to the above-mentioned points of controversy, future research in pediatric ECPR should explore the influence of CPR quality in central versus peripheral approaches, neuroprotective strategies and relationship to long-term neurodevelopment in survivors, and the impact of ECMO team experience, structure, and activation processes on outcomes.

Is ECPR cost-effective?

ECPR is perceived to be one of the more costly therapies offered in health care systems today. Institutions and individual providers increasingly want to understand the value of a given therapy in comparison to potential alternatives in order to provide efficient, evidence-based care to their patients and communities.

Cost analyses of ECPR have been conducted in the US, Europe, Australia, and Japan [20,107-110]. In a cohort of ECPR for patients with IHCA and OHCA, the calculated cost-utility for ECPR was $56,156 USD per quality-adjusted life-year (QALY) saved [107]. Cost per QALY was less for OHCA compared to IHCA, and less for initially shockable versus non-shockable rhythms [20,110]. Contemporary thresholds of acceptable cost-effectiveness range from $50,000 to up to $150,000 per QALY, placing ECPR comfortably within this range (Figure 2). For context, the cost-utility of ECPR is comparable to that of VV-ECMO ($36,000/

QALY) and dialysis ($72,476/QALY), and more attractive than heart transplant ($94,800/QALY) and destination left ventricular assist devices ($198,184/QALY) [111-115]. Given that there are few mature adult ECPR programs worldwide, it is likely that this cost will decrease as ECPR care is operationalized at more centers. Although pediatric ECPR cost analyses are lacking, with greater survival to discharge and survival with favorable neurologic outcomes ECPR may be even more cost-effective in the pediatric population [99].

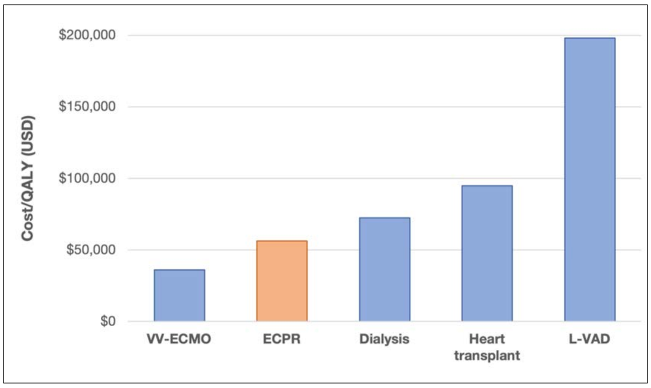

Figure 2: Cost Utility of ECPR and different therapies per quality-adjusted life year (QALY)

Should ECPR be offered during the COVID-19 pandemic?

The COVID-19 pandemic presents new challenges to the safe, timely, and appropriate application of ECPR [116,117]. Throughout the pandemic, institutions have been grappling with overwhelming demands on critical care resources and have been forced to justly and deliberately manage resources. Even under normal circumstances, ECMO is a resource-intensive therapy that requires additional staff, space, and equipment. In the face of escalating levels of surge capacity, should ECMO during cardiac arrest be offered, and if yes, for which patients? Shekar and colleagues, on behalf of ELSO, produced a consensus document regarding ECPR usage in the context of the pandemic [116]. They stated that ECPR may be considered at experienced centers for highly selected non-COVID patients with IHCA. They recommended against: (1) ECPR in less experienced centers; (2) ECPR for OHCA if under significant resource constraints; and (3) emergency conversion from veno-venous to veno-arterial configuration in patients who suffer an arrest during cannulation. Conventional CPR for patients being treated for COVID-19 portends poor outcomes, so ECPR in these patients must also balance a small potential benefit against a high risk of transmission to staff [116-118]. As resource availability varies with the waxing and waning of the pandemic, ECPR selection criteria and processes should be regularly reviewed along with rigorous tracking of inventories, usage, and outcomes.

Conclusion

ECPR is an increasingly used strategy that represents an important advance in the care of patients with cardiac arrest. However, due to the relative novelty of the strategy, several facets of ECPR therapy and programmatic development remain unclear. This has created a plethora of controversies and dilemmas pertaining to the technical and critical care strategies in caring for this complex and critically ill population. In order to address them, a collaborative multidisciplinary effort involving further hypothesis-guided investigations and routine evaluation of patient and system-based outcomes is critical. Above all, ECPR programs should be tailored to the specific clinical context in which they are being deployed.

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