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Extracorporeal membrane oxygenation for cardiac arrest: what, when, why, and how

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Abstract

Introduction—Extracorporeal membrane oxygenation (ECMO) facilitated resuscitation was first described in the 1960s, but only recently garnered increased attention with large observational studies and randomized trials evaluating its use.

Areas Covered—In this comprehensive review of extracorporeal cardiopulmonary resuscitation (ECPR), we report the history of resuscitative ECMO, terminology, circuit configuration and cannulation considerations, complications, selection criteria, implementation and management, and important considerations for the provider. We review the relevant guidelines, different approaches to cannulation, postresuscitation management, and expected outcomes, including neurologic, cardiac and hospital survival. Finally, we advocate for the participation in national/international Registries in order to facilitate continuous quality improvement and support scientific discovery in this evolving area.

Expert Opinion—ECPR is the most disruptive technology in cardiac arrest resuscitation since high-quality CPR itself. ECPR has demonstrated that it can provide up to 30% increased odds of survival for refractory cardiac arrest, in tightly restricted systems and for select patients. It is also clear, though, from recent trials that ECPR will not confer this high survival when implemented in less tightly protocoled settings and within lower volume environments. Over the next 10 years, ECPR research will explore the optimal initiation thresholds, best practices for implementation, and postresuscitation care.

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Study design: MB, CO, JT; Data acquisition and analysis: MB, CO; Drafting the manuscript: MB, CO, JT; JT revised the article for important intellectual content, and approved the final manuscript for publication.

Keywords

Extracorporeal cardiopulmonary resuscitation; Extracorporeal membrane oxygenation; Extracorporeal life support; Cardiac arrest; Resuscitation

1.0 INTRODUCTION

Extracorporeal cardiopulmonary resuscitation (ECPR) is the provision of temporary extracorporeal support to the failing heart and lungs in the setting of cardiac arrest when conventional high-quality CPR fails to achieve sustained return of spontaneous circulation (ROSC).[1,2] In defining ECPR, the Extracorporeal Life Support Organization (ELSO) incorporates the International Liaison Committee on Resuscitation (ILCOR) definition of sustained ROSC (i.e., spontaneous circulation for 20 consecutive minutes following cardiac arrest).[3] ECPR is a potentially life-saving therapy when applied to the appropriate patient population within specific systems of care.[4] Non-randomized and observational studies have repeatedly shown an association between ECPR and improved survival (compared to conventional CPR) for cardiac arrest in select patient populations for both in-hospital cardiac arrest (IHCA) and out-of-hospital cardiac arrest (OHCA) populations.[5,6] Select randomized trials, though not all, [7] have subsequently demonstrated a mortality benefit with ECPR for specific OHCA scenarios/populations.[8,9] This benefit for select patients has been subsequently confirmed in individual patient data pooled analysis [10].

This comprehensive review discusses the multifaceted dimensions of ECPR, spanning its historical evolution, underlying physiologic principles, patient selection criteria, procedural nuances, clinical outcomes, and the broader implications for modern resuscitative paradigms. By synthesizing current evidence and shedding light on unresolved questions, this exploration aims to elucidate ECPR's role as heart-lung support while outlining avenues for future research and refinement in its application.

1.1 Brief history

The foundation of ECPR can be traced back to the development of cardiopulmonary bypass (CPB) machines in the 1950s.[11] These devices were initially designed for open-heart surgery, allowing blood circulation and oxygenation while the heart was opened and/or stopped. Over the following decades, CPB technology underwent significant improvements, enhancing its safety and applicability, thus providing a platform for rapidly initiating and sustaining extracorporeal life support.[12] This paved the way for the adaptation and simplification of CPB to extracorporeal membrane oxygenation (ECMO) within the context of intensive care unit for patients with refractory cardiopulmonary failure.[13] Around this time, the first descriptions of using CPB to resuscitate patients with cardiac arrest were published, leading to the birth of ECPR.[14,15]

In the late 20th and early 21st centuries, ECPR underwent substantial refinement. Advances in miniaturization, centrifugal pump technology, and membrane oxygenator design made ECMO systems more portable and user-friendly. This evolution, combined with the H1N1

viral pandemic in 2009,[16] supported rapid growth in adult ECMO,[17] preparing the way for expanded use in the emergency department settings.[5,18]

The following review sections are divided into *What, When, Why, and How* in an attempt to address the current state of the art regarding ECPR. We review the foundational component parts of ECPR and the ECMO circuit, current data guiding the use of ECPR, guidelines and trial results, and systems considerations for using this complex therapy.

2.0 WHAT: ECMO NOMENCLATURE, CIRCUIT, CANNULATION AND COMPLICATIONS

2.1 Terminology

ECMO support terminology was defined in 2018 in the Maastricht Treaty.[19] ECMO circuits (whether in the context of ECPR or in the context of non-cardiac arrest ECMO) were subsequently defined in 2019.[20] Simplistically, all circuits involve a drainage cannula, a pump, an oxygenator, and a return cannula. While drainage and return cannulas can be duplicated or even combined, they are most commonly single. The drainage cannula extracts blood from any of a number of venous sites (e.g., internal jugular or femoral vein); the return cannula returns blood either back to the venous system (i.e., veno-venous [VV] for respiratory support) or back to the arterial system (i.e., veno-arterial [VA] for cardiorespiratory support).[21,22] The configurations can get complicated; nomenclature describes the physical configurations and can imply the specific organ supported.[23] Unlike CPB, modern adult ECMO circuits lack a blood reservoir which extracts venous circulating volume and has physiologic implications beyond the scope of this review.[21,22]

2.2 Approach

Functionally, the distinction between ECPR and ECMO is that the former is the rapid deployment of VA ECMO during chest compressions.[2,24] Cannulation strategies are subdivided into peripheral versus central. Peripheral cannulation in adults involves the femoral, axillary, or neck vessels. Central cannulation involves the great vessels of the chest, commonly through a sternotomy or thoracotomy. In the resuscitative setting, ECPR/ECMO is generally performed using peripheral cannulation via either a percutaneous or vascular cut-down at the femoral vessels.[24–27] This approach and location has the advantage of being possible during simultaneous chest compressions.[24–27] Central cannulation is most often performed in post-operative sternotomy patients. Central ECPR cannulation is performed more commonly in patients after sternotomy/thoracotomy in whom the chest can be rapidly re-opened in the operating room or ICU.

Cannulation can be performed with a Seldinger/modified-Seldinger technique or using a cutdown. Given the urgency of cannulation, grafting is almost never done during ECPR in adults. The cannulae vary in size and are chosen to balance the ease of placement of smaller canulae and reduced risk of limb complications with the competing desire to achieve sufficient flow, which during cardiac arrest provides the entirety of cardiopulmonary support. Venous drainage cannulas typically range from 19–25Fr, with arterial return cannulas from 15–23Fr; these are ultimately chosen/informed by patient anatomy.[24] The

size of the cannula can affect the level of flow which will directly translate to level of circulatory support with the venous drainage catheter size functionally having the largest impact on flow rates in this clinical context.[24]

2.3 Circuitry and function

The VA-ECMO circuit set up consists of cannulae, tubing, a pump and an oxygenator or "membrane lung".[22] Adult circuits have become more simple in the most recent two decades, with fewer access points, which is felt to minimize the opportunity for thrombosis and complications. Branch points, excess tubing, pressure monitors, and access sites creates an opportunity for thrombus or air entrainment.

In comparison to the original bubble oxygenators, modern membrane oxygenators utilize a polymethylpentene (PMP) membrane to separate the patient's blood from the administered sweep gas (oxygen, oxygen/air mixture).[21,22] Blood flows on one side of the membrane, while the sweep gas flows counter current on the other side, diffusing oxygen into the blood, and allowing carbon dioxide to diffuse out. Membrane oxygenators offer several advantages, including efficient gas exchange, minimal hemolysis, and reduced risk of clot formation.

Advancements from early roller pumps are evidenced by the international trend in transitioning from roller pumps to centrifugal pumps (e.g., Centrimag®, Cardiohelp®, Revolution®), especially among adults and pediatric populations.[28] Centrifugal pumps use a spinning rotor to apply suction, pulling blood in, and subsequently propelling it outward with positive pressure. While early ECMO centrifugal pumps were fraught with heat generation, sheer stress and hemolysis, newer, more efficient designs utilize low friction pivot bearings and reduced friction magnetic levitation designs, reducing hemolysis.[29]

3.0 COMPLICATIONS

As ECPR is a time-sensitive and emergent procedure, many complications occur secondary to the procedure itself—which is influenced by proceduralist competency, patient comorbidities, the duration of no and low flow ischemia, and postresuscitation management.

3.1 Left ventricular distension

Relevant to ECMO cannula configuration, there are a series of key issues with the femoral vein-femoral artery ("fem-fem") configuration that need to be monitored. Namely despite venous drainage, there is still blood that enters the pulmonary circulation and subsequently the left ventricle, bypassing the circuit.[21,22] Additionally, ECMO return flow is directed retrograde up the aorta. Classically, blood filling the LV and the retrograde ECMO flow increase left ventricular (LV) afterload. Whether due to intrinsically poor function or temporally depressed function attributable to under filling, insufficient LV ejection can lead to distension. This is particularly relevant when the native cardiac output is very low, and the ECMO flow is high, potentially causing LV stasis. This can lead to clot formation, and subsequent embolization or death. Alternatively, the combination of incomplete ejection/distension and retrograde flow can lead to pulmonary edema, hemorrhage, coronary ischemia and worsening hypoxemia.[21,22]

Initial clinical management of LV distension can be achieved by rapidly and temporarily decreasing ECMO flow rates and/or adding inotropes. Decreasing ECMO flow enables LV filling (via the pulmonary circulation), which, together with adding inotropes, increases contractility. Patients may ultimately require more durable solutions, including volume modulation, or mechanical decompression/venting with intra-aortic balloon pumps (IABP), percutaneous ventricular assist devices (e.g., Impella®) or atrial septostomy.

3.2 Differential oxygenation

Unique to femoral VA ECMO, differential oxygenation occurs when there is cardiac recovery but poor lung function. The upper half of the body can be perfused with native oxygen-poor blood (via native LV contractility ejecting hypoxemic blood circulating through poorly functioning lungs), while the lower half of the body receives predominantly oxygen-rich blood from the femoral return ECMO cannula. The mixing point of these two blood sources varies based on various factors, largely the native cardiac output. Early during ECPR management, if the native cardiac function is poor, the mixing point will be proximal in the aortic root. This is acceptable, as freshly oxygenated, decarboxylated blood flowing retrograde in aorta from the ECMO return cannula will predominantly perfuse the cerebral vasculature. As cardiac function improves, this mixing point will progress distally at some point preferentially perfusing the head vessels with hypoxemic blood circulating from the poorly functioning lungs. Because of the underlying lung dysfunction, there may be a cephalad-caudal discrepancy in tissue oxygenation, resulting in poor cerebral and upper body perfusion with well-perfused lower extremities. This condition has previously been called Harlequin or North South syndrome;[22] differential oxygenation is the preferred term.

3.3 Limb ischemia

Limb ischemia during femoral VA ECMO is a prevalent and potentially devastating problem.[30] This can be seen on the side ipsilateral to the arterial return cannula, attributable to the large and potential occlusive properties of the cannula, especially during states of under-resuscitation, vasopressor use, peripheral vascular disease or patient/cannula mismatch. During the post-resuscitation period with active fluid administration and changing vasopressor needs, the adequacy of arterial flow past the return cannula can dynamically change, leading to rapid, and delayed recognition of ischemia. At the least, clinicians should judiciously and continuously monitor for signs of limb ischemia. Alternatively, centers are increasingly adopting a strategy of placing an additional return catheter (often 5–9F in size) into the artery ipsilateral and distal to the return cannula. Recent data in ECPR suggest a benefit to proactive placement of these distal perfusion catheters (DPC).[31] ELSO guidelines recommend DPC placement within 4 hours of cannulation,[2] but DPC placement should not delay other time critical interventions addressing arrest etiology (e.g. coronary angiography or pulmonary thrombectomy). Further, recent studies have identified novel approaches using a bidirectional return cannula to avoid limb ischemia during femoral cannulation,[32] however, the utility of this remains to be seen.

3.4 Hemorrhage

Amongst the most common complications during ECMO (whether for cardiac or pulmonary support) is hemorrhage. Cannulation during active chest compressions increases the probability of inadvertent vascular trauma. Recent analyses of the ELSO Registry data have described the increasing use of critical care ultrasound across time with an increased proportion of patients cannulated with ultrasound-guided percutaneous cannulation.[33] As coagulation is a complex process influenced by multiple exogenous forces during ECMO (*e.g.* mechanical forces of the pump, the artificial membranes of the circuit, and the pores of the membrane lung), combined with the need for administration of systemic anticoagulation, hemorrhage is a prevalent and difficult complication during ECMO support.[34] Given the functional difficulty with standardizing clotting assays across laboratories, there is a relative paucity of research in this important area. Limited publications have demonstrated the prevalence and risk factors for bleeding,[35,36] but these are reflective of the available data, and only begin to scratch the surface of the complexity of anti-coagulation during ECMO.[37,38] While the majority of centers across the world manage patients on unfractionated heparin, increasing series have been published on the use of alternative anticoagulants, notably bivalirudin.[39] Bivalirudin has been associated with favorable outcomes in meta-analysis,[40,41] and multiple randomized trials are in currently underway (NCT05959252, NCT03707418, NCT03965208).

4.0 WHEN: GUIDELINES AND THE PRACTICE OF ECPR

While ECMO technology and even reports of ECPR have been available since the 1960s, the evidence supporting the use of ECPR had been limited until 2008.[5] Only recently have there been randomized controlled trials evaluating outcomes in ECPR compared to conventional CPR,[7,9,42] with prior studies relying on case-control studies or historical data to evaluate outcomes.[2,7] Due to these historical gaps in knowledge, there remains variability in the use and implementation of ECPR.[43] Herein, we highlight the published ECPR Guideline, including recent consensus statements, with a discussion of specific population considerations (i.e., in-hospital cardiac arrest [IHCA] and out-of-hospital cardiac arrest [OHCA]).

4.1 Selection criteria

The Extracorporeal Life Support Organization (ELSO) recently published the adult ECPR Guideline statement.[2] The best data we have on optimal patient selection for ECPR comes from observational studies analyzing patient and arrest predictors of survival,[44–46] and the Prague OHCA ECPR RCT,[9] which included both shockable and non-shockable initial rhythms, enabling a functional comparison (Table 1). Outcome associated inclusion criteria for ECPR include age, witnessed arrest/bystander CPR, initial cardiac rhythm, baseline comorbidities and duration of low flow (CPR) time prior to ECPR. Younger age, shockable initial rhythms, short duration of CPR prior to ECPR, lack of comorbidities, and witnessed arrests have all been associated with improved survival.[44–52] ELSO proposes age less than 70, no flow less than 5 minutes or low flow less than 60 minutes, but ultimately does not provide strong recommendations regarding inclusion criteria.[43] A recent ECPR expert

consensus recommendation from predominantly emergency medicine physicians advised largely similar criteria.[53]

4.2 Cannulation approach

Beyond inclusion criteria, there is recognized variability in the cannulation approach and location. For approach, the ECPR(2) statement advised Emergency Department-based cannulation with ultrasound-guided modified Seldinger, which is a generally accepted approach. [25]. In contrast, two of the recent RCTs performed cannulation assisted by fluoroscopy.[9,42] Further, an operative approach with graft placement has been described for cardiac arrest patients who achieve ROSC.[54]

4.3 Cannulation location

Cannulation location likewise varies, including pre-hospital,[55,56] emergency department, [57] operating room,[54] and catheterization laboratory settings[9,42]. While no studies have directly assessed the best approach to cannulation, multiple approaches have been described, including percutaneous access[25] and modified cut-down.[58] Studies have assessed the comparative outcomes associated with percutaneous cannulation, especially compared to standard open surgical approaches, and have generally found improved survival and neurological outcomes.[25,33,59] While this has not been proven in randomized trials, the findings, if true, may be attributable to the quicker approach of percutaneous approaches vs open when taking into consideration the known association of improved outcomes with faster cannulation.[45]

4.4 Technical considerations

The technical approach to cannulation varies depending on the location of cannulation (coronary catheterization laboratory, prehospital, emergency department, or operating room) and according to the skillset of the provider and their resources. Unique to ECPR, in preparation for cannulation, the femoral areas are prepared with antiseptic while continuing with conventional CPR. To facilitate this process, it is generally recommended to utilize mechanical CPR devices to reduce fatigue, minimize personnel, avoid contamination, and maintain hemodynamic consistency,[2,53] though this is not supported by data. It is generally agreed that cannulation itself should be performed by the most experienced operator due to technical complexity, however it can be effectively performed by providers from multiple specialties.[2,7,9,42,53,55] Finally, there is a paucity of data on the optimal size of the cannulae themselves[60] and the laterality of approach,[61] but recent data suggest a bilateral femoral approach is associated with reduced limb ischemia complications.[62]

4.5 Post-resuscitation management

Data are more limited on the variability in ECMO care during the post-resuscitation management period.[63] For adult ECPR, one study demonstrated significant variability in on-ECMO hemodynamics and post-resuscitation care, including percutaneous coronary interventions and DPC placement.[31] There was also significant variability for mechanical

ventilation management during ECPR care.[64] Much of this variability in the previous studies was associated with differential survival, suggesting a need for prospective trials.

This variability in inclusion/exclusion criteria, procedural approach and hospital protocols is evident in practice patterns across the US. A recent systematic review of ECPR protocols across multiple institutions revealed significant variability. Firstly, the majority of patients undergoing ECPR had arrested from a cardiac etiology. Out of 1,723 ECPR candidates across 24 studies, 80% arrested from a cardiac etiology with acute coronary syndrome making up the vast majority of these cases, followed by arrhythmia. Non-cardiac etiologies for only amounted to roughly 13% of cases, which included intoxication, hypothermia, pulmonary embolism and post-surgical causes. There was no clear consensus on definition of refractory cardiac arrest, age, initial rhythm or acceptable time of cardiopulmonary resuscitation (low flow time).[43]

4.6 Uncertainty and bridge to decision

Moreover, ECPR is a unique intervention that requires a multidisciplinary approach, is uniquely time sensitive and necessitates a large investment of resources.[65] The 2021 ELSO Adult ECPR Guideline acknowledges the time constraints of fully evaluating a patient for ECPR, and that it may ultimately be incomplete.[2] Ultimately, it recommends ECPR be utilized for patients with a reversible etiology, but that local institutions develop consensus agreements regarding inclusion criteria that allows for appropriate use resources while capturing patients with improved expected survival. Furthermore, the ELSO Guideline recognizes that ECPR may be required as a bridge to obtain further information.

4.7 Cannulation timing

Timing of cannulation for ECPR is also debated, with variability attributable to institutional variation in the ideal duration of CPR prior to initiation of ECPR, and to the functional difficulties in cannulating a patient undergoing chest compressions. ELSO recommends starting the cannulation process within 20 minutes of a refractory cardiac arrest, as beyond that timepoint survival is exceedingly low for normothermic cardiac arrest. Interestingly, data from Bartos *et al* demonstrate nearly 100% survival when ECPR is initiated within 30 minutes of refractory arrest;[46] while these results certainly are influenced by patient selection and programmatic experience/excellence, they demand we consider the unquestionable low efficacy of CPR at achieving ROSC during refractory arrest,[66,67] and the poor perfusion of ongoing CPR.[68] ECPR survival likelihood further diminishes significantly if not placed on ECMO support within 60 minutes, with some studies showing survival drops after 45 minutes of low flow time.[2,69]

5.0 WHY: LANDMARK STUDIES AND THE RANDOMIZED CONTROLLED TRIALS

To date, there are no randomized clinical trials evaluating the role of ECPR in IHCA, with the data from retrospective or prospective cohort studies. The majority are relatively small single center series or observational analyses. However despite these limitations, studies

have demonstrated both feasibility and potential improved outcomes when using ECPR for IHCA.

5.1 Modern Landmark Studies

The evidence supporting extracorporeal cardiopulmonary resuscitation has grown extensively over the past two decades, despite the technology being established since the 1960s.

One of the initial benchmark papers by Chen *et al.* retrospectively reviewed 135 patients who received ECPR for IHCA.[70] Patients qualified for ECPR if they required greater than 10 minutes of CPR, and excluded if had trauma with uncontrolled bleeding, terminal malignancy, severe CNS pathology or age greater than 75 (later adjusted to 80 due to institutional guidelines). Of 135 patients reviewed, 46 survived to hospital discharge with an average CPR duration of 55.8 minutes. Additionally, their review indicated that conventional CPR of a shorter duration—mean of 35.3 minutes—had a substantially lower survival at 9.5%. The vast majority of patients had arrested due to a cardiopulmonary etiology (*i.e.,* ACS, cardiomyopathy, acute myocarditis), or pulmonary emboli; only 4 patients required ECPR due to unspecified non-cardiopulmonary etiologies. At the time of publication, this was one of the larger published case series for adult ECPR, influentially demonstrating that ECPR was a modality that could extend resuscitation, and potentially improve survivability with acceptable neurologic outcomes.[70]

This study was followed by prospective observational series of IHCA from the same group, wherein they performed a propensity matched analysis comparing extracorporeal cardiopulmonary resuscitation to conventional cardiopulmonary resuscitation.[5] Fifty nine patients were enrolled in the ECPR group if that had received >10 minutes of CPR, and were matched to 113 patients who had received conventional CPR groups. Matching was done on known prognostic factors. In the matched analysis, the ECPR group had markedly higher rates of ROSC and survival to hospital discharge compared to conventional CPR. ECPR was associated with significantly decreased hazard of death at 1 year (HR 0.53 (CI 0.33–0.83 p=0.006) compared to conventional CPR. They additionally demonstrated that shockable initial rhythms were associated with improved survival, whereas CPR duration was negatively associated with hospital survival.

These data was further supported by a follow up study by Shin et al in 2012, who performed a retrospective cohort propensity analysis of 406 in hospital cardiac arrest patients from 2003 to 2009.[71] Patients were included who underwent more than 10 minutes of CPR and were between 20 to 80 years of age. Exclusion criteria included unwitnessed, traumatic or septic arrest, severe neurologic injury, hemorrhage, irreversible multi-organ failure, terminal malignancy or a do not resuscitate order. Patients were propensity matched for comparison. Among the included patients, the arrest etiology was attributed to a cardiovascular cause in the majority, which included acute coronary syndrome, heart failure or pulmonary embolism. CPR duration was similar in both cohorts, and PEA was the predominant initial rhythm. At one year, survival was 25.8% in the unmatched ECPR cohort vs 9.1% among conventional CPR patients. In the propensity score-matched analysis, 21.6% of ECPR patients survived to 1 year, compared to 8.3% in the conventional cohort. Moreover,

there was a clear distinction in functional status between conventional CPR and ECPR patients. However, 18.5% of ECPR patients who received between 35 – 53 minutes of CPR survived to 2 years with minimal neurologic impairment, and 4.5% of ECPR patients who received longer resuscitation survived with similar neurologic function. While observational in design, this was one of the first studies to demonstrate long term survival from ECPR for IHCA.

After these studies, three observational series were published close together demonstrating feasibility of high volume ECPR and survival easily exceeding that of cardiac arrest treated by conventional measures. The first, the SAVE J study, was a prospective observational study from Japan conducted among 46 hospitals which enrolled 454 patients. It compared conventional CPR to ECPR, and in the per protocol analysis, demonstrated 12.4% survival in the ECPR group at 6 months compared to 3.1% in the conventional CPR group (P=0.002).[72] The second, an observational series (not a comparative trial) known as the CHEER trial, was a single center prospective study from Australia including both IHCA and OCHA.[73] It included 26 ECPR patients (15 IHCA, 11 OHCA), of whom 14 patients (54%) survived to hospital discharge with full neurologic function (CPC 1). Thirdly, Yannopoulos *et al.* published a case series of OHCA patients treated with ECPR as part of a comprehensive program to identify and treat refractory arrest from AMI.[74] Among 62 patients transported to the center, 55 were placed on ECMO, and 45% of these patients survived to hospital discharge.

These three series demonstrated the feasibility of high-volume high survival ECPR for both in- and out-of-hospital cardiac arrest. While the earlier initial studies were primarily focused on IHCA, which has a substantially better prognosis compared to aggregated outcomes of out-of-hospital cardiac arrest (OHCA),[75] the more recent studies demonstrated equal or better survival with select patients with OHCA. The initially observed improved survival advantage for IHCA may be related to the proximity of resources; the providers capable of initiating ECPR, or to differences in the probability of witnessed arrest and duration of no-flow times.[76] Later studies such as the Minnesota series examining ECPR within high volume experienced systems and limited to shockable rhythms have had markedly higher survival, even for OHCA.[6]

5.2 The Randomized Controlled Trials

ARREST Trial—It is only recently that randomized controlled trials of ECPR have been published. (Table 1). The first, a single center, open label, randomized clinical trial evaluating safety and efficacy of ECPR—the ARREST trial—randomized adult patients with refractory ventricular fibrillation (VF) OHCA to ECPR vs standard advanced cardiac life support (ACLS).[42] From August 2019 to June 2020, 36 patients were screened for inclusions, with 30 ultimately enrolled and randomly assigned 1:1 standard ACLS or ECMO facilitated resuscitation.

Patients qualified for enrollment if they were 18–75 years old with OHCA and refractory ventricular fibrillation, defined as 3 unsuccessful defibrillations. Patients had to have utilized an automated CPR device and have an estimated transfer time <30 minutes.[42] Patients with trauma, burns, drowning, coagulopathic disorders, terminal cancers, inability to tolerate

catheterization, known pregnancy or valid do not resuscitate orders. All patients were rapidly transported to the emergency department.

The primary outcome was survival to hospital discharge; secondary endpoints included survival and functional status at 3 and 6 months, and incidence of adverse events. The study was stopped prematurely by the data safety and monitoring board at 30 enrolled patients for superiority of the ECPR arm. One patient had withdrawn consent, leaving 29 patients for analysis; 6 patients (43%) in the ECPR arm survived to hospital discharge vs 1 patient in the conventional CPR arm. At 6 months, ECPR was associated with significantly improved survival (HR 0.16, 95% CI 0.06–0.41; $p<0.0001$). Six patients ultimately survived to 6 months, with an average CPC score of 1.

The ARREST trial demonstrated that within this high volume ECPR center with limited providers, ECPR improves survival for adult patients with refractory VF arrest. Extrapolating these results, it is generally accepted that ECPR is an intervention that has the potential to increase survivability for patients with VF OHCA within high volume/experienced systems.[4] However, recognizing that this trial was conducted by interventional cardiologists, within a fluoroscopic capable coronary catheterization laboratory at a high-volume tertiary care enter, with an integrated community emergency response system, care coordination, facilitated prompt transport and ECPR activation, the subsequent ECPR RCTs provide important perspective on the ability to implement ECPR within different systems.

5.3 EROCA Trial

The subsequently published EROCA trial evaluated the feasibility of expediting transport to an ECMO capable center for patients with OHCA.[57] Similar to the ARREST trial, the investigators restructured prehospital emergency medical services to expedite ECPR cases. Whereas in the ARREST trial, patients in both arms were expeditiously transported to the hospital prior to their care diverging in either arm, the EROCA trial randomized patients to expedited transport for ECPR vs standard pre-hospital ACLS. Inclusion and exclusion criteria were similar to the ARREST trial, selecting for witnessed non-traumatic arrests or initial shockable rhythm. The primary endpoints were feasibility, defined as the proportion of patients with qualifying OHCA arriving to emergency department (ED) within 30 minutes, and ECPR eligible patients cannulated within 30 minutes of arrival.

Out of 151 patients who met initial screening criteria, only 15 were randomized and the trial was terminated early due to low recruitment. The trial revealed unexpected delays in expected emergency medical system (EMS) arrival, evaluation and transport times. While scene to ED transport times were 5.7 minutes faster than predicted, there were unexpected delays in EMS leaving the scene. Duration to ECPR flow for eligible patients was 66.2 minutes, greater than the goal of 60 minutes. Of the 5 cannulated patients, all died prior to hospital admission or shortly thereafter due to anoxic brain injury or multi-organ failure.

While the EROCA trial was limited by lower than desired enrollment, the trial importantly highlights the significant structural barriers to ramping or implementing an ECPR program for OHCA. Beyond the difficulty in estimating accurate transport times, the trial demonstrates the potential variability in EMS evaluation and treatment. This further

compounds the difficulty in identifying potential ECPR candidates and transporting them to ECPR capable centers within an allotted time frame.[77] The EROCA trial highlighted key issues with ramping or instituting an OHCA ECPR program, demonstrating the need for tight integration with prehospital EMS protocols.

5.4 Prague OHCA RCT

The Prague OHCA trial by Belohlavek *et al.* attempted to expand on the integration of ECPR with EMS in order to expedite evaluation and use of ECPR for OHCA with a presumed cardiac etiology.[9] The trial was conducted in Prague, Czech Republic and focused on patients age 18–65 who had a witnessed OHCA, but included non-shockable in addition to shockable initial rhythms. The trial prioritized early intra-arrest transport to an ECMO center for evaluation and treatment. Out of 4345 OHCA patients assessed, 264 were randomized to either standard of care–consisting of advanced cardiac life support in the field–or an invasive strategy involving immediate transfer to an ECMO center with resuscitation ongoing. The primary outcome was 180-day survival with favorable neurologic status (Cerebral Performance Category [CPC] score of 1 to 2), assessed by a treatment arm blinded neurologist. After 7 years of enrollment the primary outcome was achieved in 39/124 patients in the invasive strategy, compared to 29/132 patients in the standard of care (OR 1.63 [95% CI 0.93–2.85]). Though a secondary outcome, the authors observed that 30-day survival with CPC score of 1–2 was significantly higher in the invasive strategy arm (OR 1.99 [95% CI 1.11 to 3.57]). Cardiac recovery trended higher with the invasive strategy as compared to the standard of care arm, it did not meet statistical significance (OR 1.49 [95% CI 0.91 to 2.47]). The trial was stopped for failing to meet the prespecified effect size difference.

While the primary outcome did not meet predefined criteria for statistical significance, there are a series of key caveats regarding the nuance of trial design (Table 1). Firstly, there was higher than expected survival in the standard of care arm at 22%, with the investigators expecting 10% survival rate in the standard arm which increased during the trial. This was attributed to the overall effect of the enhanced protocolization of care as part of the trial. Secondly, crossover from conventional (intention to treat) to ECPR (per protocol) occurred in 10 patients, of whom 4/10 patients survived to 180 days, improving the survival in the standard arm, despite receiving ECPR per protocol. This pragmatic allowance ensured ethical care to all enrolled patients when the providers felt it appropriate to treat with ECPR for the refractory arrest, and thus reflects real world ambiguity in clinical care, this certainly contributed to the failure to achieve the desired effect size. Finally, due to the design wherein patients were randomized in the field, a subset of patients in both arms achieved ROSC before reaching the hospital and being allocated to ECPR treatment.

Rob *et al.* published a secondary analysis of the trial attempting to adjust for these issues (Table 2).[78] In the secondary analysis, investigators pooled the 256 patients three separate groups: patients who achieved prehospital ROSC, patients with prolonged ACLS who did not receive ECPR, and patients who received ECPR. Notably, patients without prehospital ROSC had significantly less initial shockable rhythms. Overall survival at 180 days was 1.2% in patients without prehospital ROSC, 23.9% in patients without prehospital ROSC

treated with ECPR and 61.5% in patients with prehospital ROSC. Cox proportional hazard analysis demonstrated ECPR was associated with a lower risk of death at 180 days; the strongest predictive factor was prehospital ROSC status.

5.5 INCEPTION RCT

The most recent RCT evaluating ECPR, the INCEPTION trial was published in January 2023 by Suverein *et al.*[7] Designed as a multicenter, unblinded randomized controlled trial in the Netherlands, enrolling patients at 10 cardiosurgical centers from 2017 to 2021 with integration with the Dutch EMS system. The trial was temporarily halted during the first coronavirus outbreak in 2020 but subsequently resumed. Notably the trial did not have a mandated protocol but allowed for local and hospital ECPR protocols to be used.

Adult patients between 18 to 70 with a witnessed refractory OHCA and an initial shockable rhythm were eligible for inclusion, with similar exclusion criteria from prior trials including expected arrival time. The primary outcome was survival with a favorable neurologic outcome (i.e., Cerebral Performance Category score of 1 or 2) at 30 days. Only 5 out of the 10 trial sets kept a screening log with 113 patients selected for randomization, and another 47 from sites without a screening log. Of 160 patients randomized, 26 were excluded after randomization in the ED, with 70 assigned to ECPR and 64 assigned to conventional CPR.

Ultimately no significant difference in survival with a favorable neurologic outcome was detected at 30 days (OR 1.4 [95% CI, 0.5–3.5; P=0.52]), and no significant difference in secondary outcomes of 6-month favorable neurologic survival. The trial evaluated ECPR in a real-world capacity by allowing for local EMS and hospital protocols and enlisting a range of medical centers. However, the lack of a mandated protocol and the inclusion of ECPR centers with variable experience led to outcomes such a 6% cannulation failure rate. When compared to the other RCTs of ECPR, the INCEPTION trial's range of medical centers showed longer median times low flow time (Table 1). Further, similar to the Prague trial, randomization occurred prior to allocation to each treatment arm, and so in the INCEPTION trial, only a portion of the patients randomized to ECPR actually were placed on ECMO due to attainment of ROSC prior. These factors together added real world complexity. The final outcomes reflect this pragmatic implementation, rather than idealized ECPR systems.

5.6 Interpretation of the RCTs

In best case scenarios, data from the ARREST, Prague OHCA and INCEPTION trials show improved survival in selected populations and single systems of care, but not when pragmatically implemented within a lower volume system (Table 2). The utility of ECPR for OHCA and variables predicting survival in this population are complicated by the systems of care providing ECMO, the lack of robust prediction tools and the complexity of ECPR ethics. While ECPR is not beneficial for every patient, the decreased likelihood of sustained ROSC as low-flow resuscitation time progresses in conventional CPR creates a scenario where ECPR use has to be considered within the complex ethical framework.[79] Multiple observational series of survival from increasing durations of CPR during refractory arrest demonstrate that when conventional CPR cannot attain sustained ROSC after 20 minutes, the choice to continue without ECMO support is tantamount to choosing futility.[66,67] In

contrast, wanton use of ECPR in the patient with little hope for neurologically intact is not ideal and likely causes harm and waste. Temporary heart-lung support and organ perfusion without hope for neurologically intact survival may create time for a family to say goodbye yet is costly and complex.[80]

6.0 HOW: ECPR IMPLEMENTATION

One common theme throughout all the ECPR RCTs is that ECPR is more than an ECMO circuit, and is a complex, multidisciplinary intervention that requires a systems-based approach. A top-down reorganization and integration of prehospital emergency medical services with tertiary care ECPR centers is needed to ensure success.

One of the key aspects of the ECPR resuscitation strategy for OHCA is the limited time available to implement the intervention. To optimize prognosis, the no-flow (i.e., downtime to conventional CPR) and low-flow (i.e., conventional CPR to ECMO flow) times of cardiac arrest should be cumulatively less than 60 minutes before ECMO flow is initiated,[2,53] with the best survival seen with shorter durations of time.[46] This rapidity requires rapid mobilization of EMS and physician personnel, plus equipment, to identify optimal patients using minimal information, and then perform an invasive and technically challenging intervention while resuscitation efforts are ongoing.

6.1 Starting ECPR and ECMO Programs

When considering initiation of an ECPR program, we and others advocate that it be an outgrowth of an existing high performing, high volume ECMO program.[2,53,65] While we recognize that the prevalence of refractory cardiac arrest will not always align with the prevalence of these high volume programs, limiting new ECPR programs within the context of existing ECMO programs ensures the ability to provide the high quality care that is required starting immediately after cannulation.[81] The inherent mismatch between the disease and the availability of ECPR can be addressed through a variety of ways, including pre-hospital ECPR programs such as are seen in Paris and London, or through collaborative efforts whereby an experienced hospital partners with surrounding hospitals to provide ECPR.[56]

6.2 Physician decision making

The process of decision making for ECPR candidacy is one that is fraught with emotionality for the providers involved.[80] Many physicians feel strongly about utilizing ECPR when available, especially for patients who are young or otherwise healthy. Given this tendency to utilize the tool of ECPR when available, we advocate for protocolization, with regular internal review. This facilitates internal quality assurance, locally acceptable outcomes, and comparison to national standards. International groups such as the Extracorporeal Life Support Organization (www.elso.org) provide guidelines, quality benchmarking and outcomes comparison for ECMO programs, including ECPR.

6.3 Prognostic Scores

A limited number of prognostic scores have been developed and validated for ECPR, including the RESCUE-IHCA score for IHCA patients,[45] and the TiPS65 score for OHCA.[44] These scores integrate available variables, such as known patient and arrest characteristics, and sometimes laboratory markers, in order to generate a predicted probability of survival from the moment of cannulation. These scores can be utilized by centers to evaluate their observed to expected outcomes, or to counsel families and staff on expected survival.

6.4 Idealized patients for ECPR

While the relative benefit of ECPR varies within distinct populations and systems, it is generally recognized that ECPR has the potential to benefit young patients with refractory cardiac arrest (especially >20 minutes), who have received immediate high-quality CPR, and who had an initial shockable arrest rhythm.[4] ECPR may benefit patients without any one or more of these strict criteria, but the relative benefit is probably less and is also less clear from the trials. For instance, the lower survival in the Prague OHCA trial compared to the ARREST trial may be attributable in part to the inclusion of non-shockable initial rhythms. Indeed, an individual pooled patient data analysis demonstrated this.[10] Further, patients who have initial non-shockable rhythms could have an etiology of a massive pulmonary embolism, which is generally well treated with ECPR[82], whereas respiratory failure eventually leading to cardiac arrest is a less ideal use of ECPR as there may already be substantial neurological injury by the time the arrest is recognized.[4] Shockable initial rhythms are strongly associated with acute coronary ischemia for cardiac arrest patients,[83] and refractory arrest even more so.[74] Indeed, data demonstrate that ECPR is less utilized for non-shockable cardiac arrests[84] and is associated with worse outcomes.[1]

6.5 Expected outcomes

Survival after ECPR is influenced by patient and etiology factors, arrest factors, cannulation factors, and post-resusctiation management. Published series of ECPR have reported survival ranging from ~13% to ~45%.[42,72] ELSO Registry data have consistently reported a survival of 30% among all comers for adult ECPR.[17,85] Of note, among survivors, most remain neurologically intact.[45] This may reflect early withdrawal of life support in patients with anticipated or observed neurologic injury.[86] Families often experience distress during the post-arrest period;[80] as the decision to withdrawal life support is often irreversible, patients with ECPR often have short duration ECMO runs of 5 days or fewer, which is partially influenced by active withdrawal of care in addition to rapid cardiac recovery. It should be noted though that rapid return of cardiac function is common for ECPR,[87,88] and that some patients who are neurologically normal by hospital discharge nonetheless take up to 22 days to “wake up.”[89]

7.0 CONCLUSION

The application of ECMO as a resuscitative measure for patients with cardiac arrest is not new, but has recently expanded within the adult population, with numerous observational studies, and three recent randomized trials. ECPR has the potential to impart a significant

increase in the probability of survival for select patients with refractory cardiac arrest when performed within optimized and practiced systems of care, though it may not benefit patients outside of these parameters at this time. Guidelines and prognostic scores exist to help clinicians in their decision making around the development, implementation and clinical practice of ECPR.

8.0 EXPERT OPINION

Survival from sudden cardiac arrest has remained relatively unchanged for 10 years, with the previously most recent improvements seen with widespread availability of automated external defibrillators and CPR education.[90–92]. While high-quality CPR remains at the core of cardiac arrest initial resuscitation and recent European Resuscitation Council and American Heart Association guidelines[93–95] provide a weak recommendation for ECPR, new trials on ECPR in the past years show the possible improvements on the horizon.

While a sizable proportion of the non-survivors are not rescuable even with current technology in an idealized setting—primarily due to protracted unrecognized down time and ischemia, non-repairable sudden aortic rupture, or bystander ignorance of CPR—the remainder are rescuable, yet die nonetheless. The cause of their deaths can be broadly attributed to insufficient perfusion with ACLS and inability to timely diagnose and then reverse the cause of arrest. It is this patient population in whom ECPR may be of benefit at this time. ECMO can provide full cardiopulmonary support, enabling cessation of chest compressions—which are themselves simultaneously injurious—and thereby confer days to weeks of stable hemodynamics, during which time any number of diagnostic studies and therapeutic interventions can be performed. Ample data have demonstrated the high prevalence of CPR-induced injuries in sudden cardiac arrest patients,[96,97] and in ECPR patients.[98] Further, we have already discussed the high prevalence of coronary artery disease in VF arrests,[74] which warrants expedited angiography and percutaneous coronary interventions.[93] Commonly, next steps following ECPR are coronary catheterization, angiography, pulmonary angiography or CT head angiography.[7,9] These diagnostics and interventions are facilitated, if not made plausible, by ECMO. The benefit of ECPR thus is both due to the direct perfusion benefit, and indirectly from being able to perform diagnostics and interventions.

Over the coming decade, the frontier of ECPR includes the following issues:

- **a.** Defining the optimal duration of CPR prior to initiating ECPR (which fundamentally means balancing the risk of ECPR-induced complications with the waning probability of spontaneous ROSC).
- **b.** Defining optimal implementation—both provider competency and training (*i.e.* should the technique be restricted to particular specialties, or to providers with a minimum annual cannulation volume) and systems requirements (*i.e.* what, if any, geographic restrictions should be in place?). Some may argue that rural settings may benefit the most, whereas others argue that the low volume precludes competency. If a retrieval/pre-hospital cannulation approach is utilized,

what response time needed, and who should be cannulating? Is this financially sustainable?

c. What is the role of adjuvant therapies and post-resuscitation management? Many of the early observational studies and the ARREST and Prague OHCA trials utilized temperature management,[9,42,65,73] which despite its mixed results in recent non-ECMO trials, may provide a different risk/benefit profile on ECMO.[99] Additional workup following ECPR initiation include imaging of coronary, pulmonary or cerebral arteries. While the majority of sudden cardiac arrest with VT/VF stem from coronary occlusion, a fraction of patients have other causes to their arrest. Further, what are optimal blood pressure, ECMO flow and ventilatory targets across patient types? Avoidance of hyperoxia is generally accepted, and increasing data suggest rapid changes in carbon dioxide may be profoundly detrimental. The ability to provide hemodynamic support independent of vasopressors, and blood gas modulation independent of the ventilator enable an entirely new level of post-resuscitation control compared to non-ECMO patients. These management strategies warrant prospective trials.

d. What is the optimal timing of initiation of ECPR? Should EMS services transport earlier, and at what point in the resuscitation [2,58,100,101]?

e. What is the optimal location for ECPR cannulation (hospital vs pre-hospital and ED vs catheterization laboratory)?

f. Should patients with ECPR who die be considered for organ donation? If so, should ECPR inclusion criteria be expanded, understanding that it will increase the number of survivors, and also (even more so) the number of patients who might become organ donors. Should organs from ECPR patients, and their associated outcomes, be considered different even than donation after cardiac death (DCD) organs?

As we continue to utilize and study ECPR, prospective high quality data collection is vital. Guidelines recommend, at a minimum, participation in a standardized, formalized and national/international quality-assured process such the ELSO Registry. These authors recommend further participation in data collection of sufficient quality to support research, which can mirror or build from quality data. These quality and research data enable continuous quality improvement at the center level and scientific discovery internationally to improve patient relevant outcomes and cost efficiency for this invasive and transformative therapy.

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Declaration of interest

J Tonna is the Chair of the Registry Committee of the Extracorporeal Life Support Organization (ELSO). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial

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102*. Low CJW, Ramanathan K, Ling RR, et al. Extracorporeal cardiopulmonary resuscitation versus conventional cardiopulmonary resuscitation in adults with cardiac arrest: a comparative meta-analysis and trial sequential analysis. Lancet Respir Med. 2023 May 22.# Meta-analysis including all three RCTs for ECPR in OHCA

Article Highlights

- While not a new technology, ECMO facilitated resuscitation has recently grown with large case series, new programs, and multiple randomized trials.
- Extracorporeal cardiopulmonary resuscitation (ECPR) can be performed by multiple providers and within multiple settings, including the emergency department, intensive care unit, and pre-hospital environments.
- The hemodynamic support provided by ECMO facilitates diagnostic studies and interventions to reverse the cause of cardiac arrest, that are otherwise difficult or impossible during conventional resuscitations.
- Ideal patients for ECPR are young and healthy with initial shockable rhythms and immediate high-quality CPR, who can be cannulated within 60 minutes. Many patients outside these strict characteristics may benefit from ECPR, though the expected survival may be less.
- ECPR programs are best developed from existing high volume ECMO programs. Expected survival will reflect patient selection and subsequent care. Survival in the international Extracorporeal Life Support Organization (ELSO) Registry is 30%.
- Participation in a standardized, multi-center quality reporting and/or data collection platform will facilitate outcome tracking, continuous quality improvement, and scientific advancement.

Table 1.

Summary of Randomized Controlled Trials for ECPR (Results and Comments)*

	Rhythm, n (%)	Intention-to-Treat Population & Age, y	Time Intervals, min	Primary Outcome	Comments
ARREST[42]	Refractory VF or pulseless VT	ECMO-facilitated resuscitation (n=15) vs. Standard ACLS treatment (n=15) mean age (SD): 59 (10) vs. 58 (11)[1]	Time from 911 call to VA ECMO: mean time (SD): 59 (28)[1]	Survival to hospital discharge: (6 [43%, 21.3–67.7] vs. 1 [7%, 1.6–30.2])[3]	Stopped prematurely at 30 patients by Data Safety and Monitoring Board (DSMB) for ECPR superiority At 6 months, ECPR was associated with significantly improved survival: (HR 0.16, 95% CI 0.06–0.41; p<0.0001) Randomization in-hospital
Prague OHCA[9]	VF (72 [58%] vs. 84 [65%]) Asystole (31 [25%] vs. 24 [18%]) PEA (21 [17%] vs. 24 [18%])	Invasive strategy (n=124) vs. Standard strategy (n=132) median age (IQR): 59 (48–66) vs. 57 (47–65)[2]	Time to ECMO: median time (IQR): 61 (55 to 73) vs. 62 (51 to 73)[2]	Survival with CPC 1 or 2 at 180 days: (31.5% [39/124] vs. 22% [29/132]) (odds ratio, 1.63 [95% CI, 0.93 to 2.85]; absolute difference, 9.5% [95% CI, −1.3% to 20.1%]; P = .09)	Stopped per DSMB for futility to achieve the prespecified effect size of 20% Secondary outcome of 30-day survival with CPC 1–2 was significantly higher in invasive strategy arm: (38 [30.6%] vs. 24 [18.2%]) (OR 1.99 [95% CI 1.11 to 3.57]) Higher than expected survival in standard of care arm (22%) Crossover from standard of care arm to ECPR arm occurred in 11 patients; 9 patients from invasive strategy crossed over to standard care Randomization prehospital on-scene
INCEPTION[7]	VF Pulseless VT Shockable rhythm detected by AED	ECPR (n=70) vs. Conventional (n=64) mean age (SD): 54 (12) vs. 57 (10)[1]	Start of arrest to ECMO flow start: median time (IQR): 74 (63 to 87)[2]	Survival with CPC 1 or 2 at 30 days: (20% [14/70] vs. 16% [10/62]) (OR 1.4 [95% CI, 0.5–3.5; P=0.52])	Halted during the first coronavirus outbreak in 2020 “Postresuscitation care…delivered according to current guidelines and institutional protocols” Randomization prehospital 13 patients assigned to ECPR did not receive ECPR because of sustained ROSC before ED

*Results presented by invasive or ECPR group vs. standard advanced cardiac life support (ACLS)

[1]mean (SD)

[2]median (IQR)

[3]n (%), CrI=credible interval

CPC=Cerebral Performance Category 1 or 2

VF=ventricular fibrillation, VT=ventricular tachycardia, PEA=pulseless electrical activity, AED=automated external defibrillator

Table 2.

Summary of Key Secondary Analyses for ECPR (Results and Comments)*

	Aim	Type	Methods	Findings	Comments
Rob et al. Crit Care 2022[78]	Secondary analysis of Prague OHCA examining whether ECPR is associated with improved outcomes	Secondary analysis of Prague OHCA	256 patients from Prague OHCA were individually clustered according to treatment received (per protocol) and spontaneous ROSC, and then analyzed for primary outcome of all-cause 180-day survival using Kaplan-Meier estimates and Cox proportional hazard model Pooled into three groups: 1) Patients with prehospital ROSC (and thus not ECPR candidates) 2) Patients with prolonged ACLS, no prehospital ROSC, and no ECPR 3) Patients who received ECPR after arrival to hospital	Patients without prehospital ROSC had significantly less initial shockable rhythms Overall survival at 180 days: 1) 61.5% in patients with prehospital ROSC 2) 1.2% in patients without prehospital ROSC 3) 23.9% in patients without prehospital ROSC treated with ECPR	Multivariate Cox regression analysis showed ECPR (HR 0.21, CI 0.14–0.31, p<0.001) and prehospital ROSC (HR 0.10, CI 0.06–0.16, p<0.001) were significantly associated with 180-day survival
Belohlavek et al. EClinicalMedicine 2023[10]	To combine patients from the ARREST and Prague OHCA ECPR RCTs [9,42] to identify optimal patient characteristics for ECPR, and treatment approach.	Individual patient data pooled analysis of ARREST and Prague OHCA	Corresponding authors of RCTs provided anonymized individual patient data, coding, and definition of variables	Modified intention to treat analysis (pooled) for 180-day neurologically intact survival: Pooled analysis across both trials; invasive (n=139) vs. standard (n=147), 45 (32.4%) vs. 29 (19.7%) Among shockable presenting rhythms: invasive (n=87) vs. standard (n=99), mean (SD): 41 (47.1%) vs. 28 (28.3%) Among patients with CPR >/= 45 min: invasive (n=97) vs. standard (n=83), mean (SD): 23 (23.7%) vs. 6 (7.2%)	Differences between ARREST[42] and Prague OHCA[9] trials 1) Randomization location (ARREST: upon hospital arrival, Prague OHCA: prehospital setting) 2) Standard arm local protocols (ARREST: intra-arrest transport for patients without ROSC during initial resuscitation, Prague-OHCA: primarily on-scene treatment)
Low et al. Lancet Respir Med 2023[102]	Meta-analysis of OHCA and IHCA RCTs and propensity matched studies to investigate whether ECPR improves outcomes in people with cardiac arrest	Systematic review and meta-analysis	Between Jan 1, 2000, and April 1, 2023, RCT or propensity-score matched studies on effects of ECPR in adults with cardiac arrest identified via keywords “extracorporeal membrane oxygenation”, “cardiac arrest”, and “cardiopulmonary resuscitation”, without language restrictions	ECPR reduced mortality in studies reporting on IHCA: (OR 0.42, 95% CI 0.25–0·70; p=0·0009) No mortality difference in studies reporting on OHCA: (OR 0.76, 95% CI 0.54–1.07; p=0.12)	Increasing center volumes (i.e., the number of ECPR runs done per year in each center) was associated with reductions in odds of mortality Variables such as varying robustness of responses of EMS before hospital admission and stay-and-play or scoop-and-run approaches via EMS could confound outcomes in

	Aim	Type	Methods	Findings	Comments
					patients with OHCA, resulting in different findings across different settings

ROSC=return of spontaneous circulation, ACLS=advanced cardiac life support