

Role of extracorporeal cardiopulmonary resuscitation in adults

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Extracorporeal cardiopulmonary resuscitation (ECPR) has been performed with increasing frequency worldwide to improve the low survival rate of conventional cardiopulmonary resuscitation (CCPR). Several studies have shown that among patients who experience in-hospital cardiac arrest, better survival outcomes and neurological outcomes can be expected after ECPR than after CCPR. However, studies have not clearly shown a short-term survival benefit of ECPR for patients who experience out-of-hospital cardiac arrest. Favorable outcomes are associated with a shorter low-flow time, an initial shockable rhythm, lower serum lactate levels, higher blood pH, and a lower Sequential Organ Failure Assessment score. Indications for ECPR include young age, witnessed arrest with bystander cardiopulmonary resuscitation, an initial shockable rhythm, correctable causes such as a cardiac etiology, and no return of spontaneous circulation within 10–20 minutes of CCPR. ECPR is a complex intervention that requires a highly trained team, specialized equipment, and multidisciplinary support within a healthcare system, and it has the risk of several life-threatening complications. Therefore, physicians should carefully select patients for ECPR who can gain the most benefit, instead of applying ECPR indiscriminately.

Key Words: advanced cardiac life support; extracorporeal membrane oxygenation; cardiopulmonary resuscitation; out-of-hospital cardiac arrest

INTRODUCTION

Despite numerous studies and detailed guidelines, survival after cardiopulmonary resuscitation for sudden cardiac arrest remains low. Reported survival rates range from 15% to 17% for in-hospital cardiac arrest (IHCA) and from 8% to 10% for out-of-hospital cardiac arrest (OHCA) [1-3]. It is possible that more robust end-organ support is the key to improving survival rather than chest compressions and endotracheal ventilation. Extracorporeal life support (ECLS) is a life support system that provides artificial extracorporeal blood oxygenation and circulatory support. Venoarterial ECLS uses the principles of cardiopulmonary bypass, implementing a blood pump and artificial lung to replace natural cardiopulmonary function. It was first proposed for cardiac resuscitation in the early 1960s [4]. After subsequent progression in ECLS technology, now it is deployed rapidly for patients in cardiac arrest.

Concept and Definition of Extracorporeal Cardiopulmonary Resuscitation

The goal of extracorporeal cardiopulmonary resuscitation (ECPR) is to support end-organ

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perfusion while potentially reversible conditions are addressed. It is defined as initiation of ECLS during cardiopulmonary resuscitation after conventional measures have failed or after repetitive arrest events have occurred without return of spontaneous circulation (ROSC) for >20 minutes [5]. The general concept is to replace conventional cardiopulmonary resuscitation (CCPR) with ECLS. However, ECPR is a much more complex intervention and requires a highly trained team, specialized equipment, multidisciplinary support, and setup time ranging between 5 and 30 minutes (Figure 1).

It is difficult to determine ROSC once ECPR has been initiated. In CCPR, patient vital signs are regularly monitored to determine ROSC. In contrast, the ECLS system is not routinely stopped during ECPR to check: this is why the textbook definition cited above specifies “repetitive arrest without ROSC for > 20 minutes.” Based on this definition, ECLS initiated immediately after ROSC can be considered ECPR. Because sustained ROSC is important in defining successful resuscitation, direct comparison of ECPR and CCPR is difficult and confusing to both researchers and clinicians. Understanding the differences between these two methods is crucial to properly interpret ECPR studies.

Since 1989, the Extracorporeal Life Support Organization (ELSO) has collected ECLS usage and outcome data. According to the ELSO registry, the incidence of ECPR use increased more than 10-fold between 2003 and 2014, from 35 to over 400 per year (Figure 2) [6,7], and the overall survival to hospital discharge was 29% in adults [8]. The Advanced Cardiac Life Support (ACLS) Guidelines state that ECPR may be considered for selected patients as rescue therapy when CCPR efforts are failing in settings in which it can be expeditiously implemented and supported by skilled providers (class 2b; level of evidence, C-LD) [9,10]. However, there is insufficient evidence to recommend its routine use in patients with cardiac arrest. This review focuses on the current evidence for ECPR indications and the benefit of ECPR over CCPR.

KEY MESSAGES

- For in-hospital cardiac arrest, extracorporeal cardiopulmonary resuscitation (ECPR) provides better survival and neurological outcomes than conventional cardiopulmonary resuscitation (CCPR).
- For out-of-hospital cardiac arrest, ECPR provides better medium-term survival outcomes and overall neurological outcomes than CCPR.
- A short low-flow time and an initial shockable rhythm are associated with better outcomes of ECPR.

CURRENT EVIDENCE

ECPR versus CCPR

To date, there have been no large prospective randomized controlled trials (RCTs) comparing ECPR and CCPR. However,

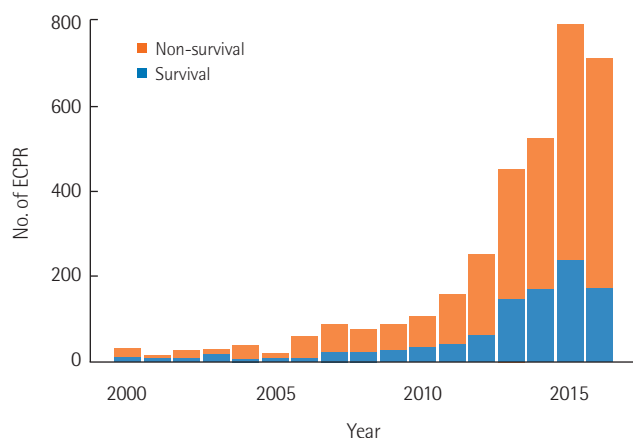


Figure 2. Annual extracorporeal cardiopulmonary resuscitation (ECPR) episodes 2000-2016 [6]. According to Extracorporeal Life Support Organization registry, the number of ECPR has increased worldwide, and so has the survival rate. The recent reported survival to discharge was 23% to 31%.

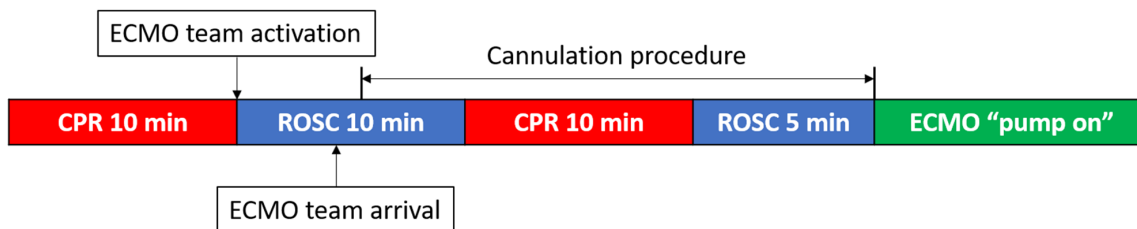


Figure 1. A typical example of in-hospital extracorporeal cardiopulmonary resuscitation (ECPR). There was two recovery of spontaneous circulation (ROSC) during whole CPR process. Extracorporeal circulation was successfully established after 35 minutes of resuscitation which includes 20 minutes of convectional resuscitation and 15 minutes of ROSC. ECPR is defined, despite pump-on during ROSC, if ROSC duration is less than 20 minutes. Because resuscitation is complex and various, like this example, there can be debates on this definition of ECPR. ECMO: extracorporeal membrane oxygenation.

numerous ECPR studies have resulted in several notable findings (Table 1).

Overall Survival to Discharge

A subgroup meta-analysis of 4 propensity score-matched studies that compared overall survival to discharge between ECPR and CCPR by Kim et al. [11] showed no significant difference; however, there was a nonsignificant trend toward benefit of ECPR for overall survival to discharge (risk ratio [RR], 1.86; 95% confidence interval [CI], 0.99 to 3.50; $P=0.05$). In another meta-analysis of 17 studies by Twohig et al. [12], subgroup analysis of nine propensity score-matched studies found a significant benefit of ECPR over CCPR for overall survival at discharge or 30 days (odds ratio [OR], 0.40; 95% CI, 0.27 to 0.60; $P<0.001$). However, there was moderate heterogeneity ($P=0.01$, $I^2=59%$) among the studies. According to these results, the deployment of ECPR tends to improve survival to discharge compared with CCPR. However, the outcomes according to type of cardiac arrest should be analyzed and reviewed carefully due to study heterogeneity. In addition and more importantly, high possibility of cardiac origin and reversibility was the indication

for ECPR in most of the studies. Furthermore, these studies had two major limitations that should be considered in their interpretation. First, no study disclosed how cardiac cause and reversibility was suspected in the ECPR groups. Second, the control groups (CCPR) were generally unselected, as CCPR is not selectively performed. This selection bias between ECPR and CCPR patients cannot be adjusted for by regression analysis or propensity score matching.

Outcome in IHCA

Chen et al. [13] reported an observation study comprised of 172 witnessed IHCA that found a short-term and long-term survival benefit for ECPR over CCPR. Additionally, neurological outcomes tended to be better at discharge for ECPR patients (30.4% vs. 15.2%, $P=0.09$). In 2011, another retrospective single center study investigated 120 IHCA patients and showed that ECPR was associated with a survival benefit over CCPR in patients who received CPR for more than 10 minutes, especially in patients with a cardiac origin [14]. The study also showed better neurological outcome in patients who received ECPR.

Table 1. Previously reported survival and neurological outcome comparisons of ECPR and CCPR

Study	Type of arrest	outcome	ECPR vs. CCPR	P-value
Chen et al. (2008) [13]	IHCA	Survival rate to discharge	HR, 0.51; 95% CI, 0.35–0.74	<0.001
		Survival at 30 days	HR, 0.47; 95% CI, 0.28–0.77	0.003
		Survival at 1 year	HR, 0.53; 95% CI, 0.33–0.83	0.006
		CPC score 1–2 at discharge	30.4% vs. 15.2%	0.09
		CPC score 1–2 at 1 year	19.5% vs. 10.8%	0.27
Shin et al. (2011) [14]	IHCA	Survival to discharge	31.7% vs. 10.0%	0.013
		Cardiac origin	35.5% vs. 8.8%	0.004
		Survival at 6 months	26.7% vs. 8.3%	0.019
		Cardiac origin	28.9% vs. 8.9%	0.035
		CPC score 1–2 at discharge	23.3% vs. 5.0% (adjusted OR, 0.17; 95% CI, 0.04–0.68)	0.012
		Cardiac origin	26.7% vs. 8.8% (adjusted OR, 0.19; 95% CI, 0.04–0.82)	0.026
		CPC score 1–2 at 6 months	23.3% vs. 5.0% (HR, 0.48; 95% CI, 0.29–0.77)	0.003
Maekawa et al. (2013) [15]	OHCA	Survival to discharge	37.5% vs. 12.5%	0.093
		Survival at 3 months	37.5% vs. 8.3%	0.036
		CPC score 1–20 at 3 months	29.2% vs. 8.3%	0.14
Kim et al. (2014) [16]	OHCA	Survival at 24 hours	57.5% vs. 30.8%	0.010
		Survival to discharge	17.3% vs. 21.2%	0.804
		Survival at 3 months	15.4% vs. 7.7%	0.358
		CPC score 1–2 at 3 months	15.4% vs. 1.9%	0.031

ECPR: extracorporeal cardiopulmonary resuscitation; CCPR: conventional cardiopulmonary resuscitation; IHCA: in-hospital cardiac arrest; HR, hazard ratio; CI, confidence interval; CPC: cerebral performance category; OR, odds ratio.

According to a meta-analysis of three retrospective propensity score-matched studies comparing ECPR and CCPR in IHCA, ECPR was associated with better survival at discharge (RR, 2.37; 95% CI, 1.35 to 4.15; P=0.003) and at 3–6 months (RR, 2.54; 95% CI, 1.38 to 4.66; P=0.003) (Figure 3) [11]. Moreover, the study reported better neurological outcome (cerebral performance category [CPC] score 1–2) at discharge in the ECPR group (RR, 2.72; 95% CI, 1.21 to 6.13; P=0.02). Although no high-quality evidence is currently available, the studies so far have shown better survival and neurological outcomes in IHCA patients who receive ECPR.

Outcome in OHCA

According to a post hoc analysis of a prospective observational cohort reported in Japan [15], 3-month survival of OHCA patients was higher in the matched ECPR group than the matched CCPR group (37.5% vs. 8.3%, P=0.036; stratified log-rank P=0.018). However, the study did not find a significant difference in survival rate at discharge or neurological outcome between ECPR and CCPR.

In contrast, a multivariate retrospective analysis of a prospective cohort that included 499 patients showed that ECPR should be considered in order to achieve a good neurological outcome in OHCA patients who required prolonged CPR, especially ≥21 minutes [16]. However, there was no significant difference in survival to discharge or 3-month survival between ECPR and CCPR.

Kim et al. [11] conducted a meta-analysis comparing ECPR and CCPR in OHCA that included the above two observational studies. Although the analysis showed no significant difference in survival at discharge (RR, 1.45; 95% CI, 0.41 to 5.16; P=0.56), ECPR was associated with significantly better survival at 3–6 months (RR, 2.74; 95% CI, 1.13 to 6.67; P=0.03) and better neurological outcome at 3 months (RR, 4.64; 95% CI, 1.41 to 15.25; P=0.01) (Figure 3) [11]. Unlike IHCA, there is a lack of evidence to support a benefit in survival at discharge for ECPR over CCPR in patients with OHCA. On the other hand, studies have shown that the use of ECPR in OHCA improves both medium-term survival (3–6 months) and neurological outcome. We believe that the ECPR patients in OHCA were less selected than those in IHCA because of lack of information and lack of time to investigate in the emergency room.

Prognostic Factors in ECPR

Prognostic factors for ECPR largely overlap with those for CCPR. Among 133 patients who received ECPR in a retrospective study, low-flow time (duration of CCPR until perfusion of ECPR started) strongly correlated with survival (P<0.001) and was an independent predictor of mortality [17]. Similarly, another retrospective analysis of 111 ECPR patients showed that survival to discharge was associated with shorter CPR duration (P=0.022) and younger age (P=0.003) [18].

Neurologic outcome of ECPR according to the initial cardiac arrest heart rhythm has been evaluated in several studies [16,

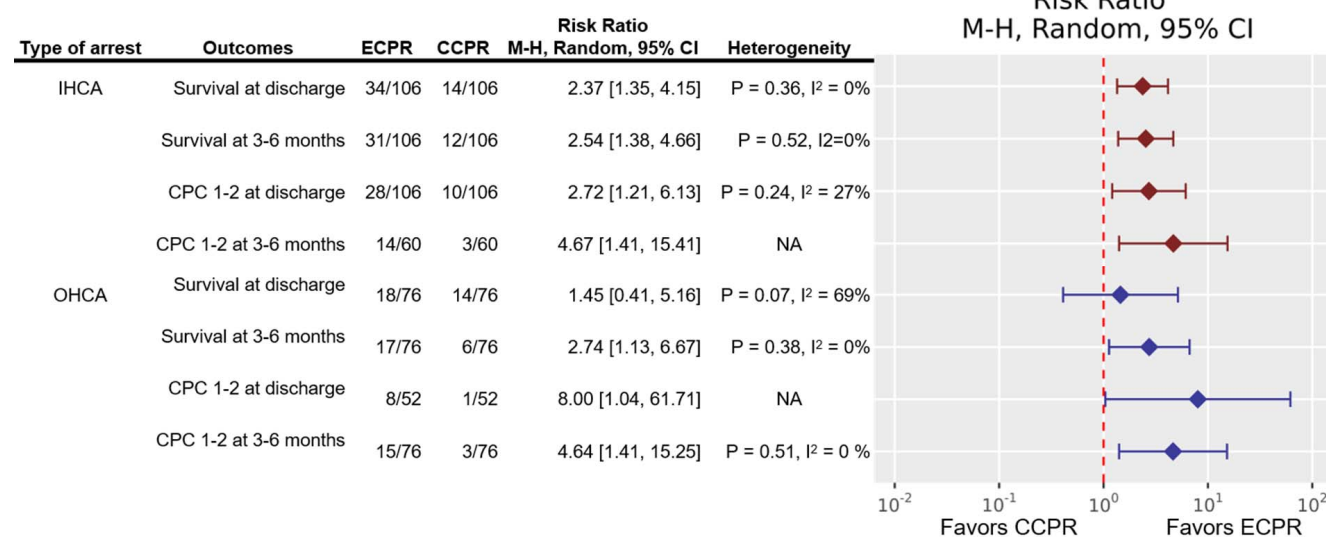


Figure 3. Results reported by the meta-analysis by Kim et al. [11]. Risk ratios and 95% confidence intervals (CIs) were plotted in logarithmic scale. All outcomes, except for survival at discharge in out-of-hospital cardiac arrest (OHCA), favor extracorporeal cardiopulmonary resuscitation (ECPR), although there was a little in-study heterogeneity (red: IHCA, blue: OHCA). CCPR: conventional cardiopulmonary resuscitation; IHCA: in-hospital cardiac arrest; CPC: cerebral performance category; NA: not applicable.

19]. A retrospective observational study of 294 adult patients who underwent ECPR for IHCA found that poor neurological outcome (CPC score 3–5) was associated with the following initial heart rhythms: asystole, 88.1%; pulseless electrical activity (PEA), 66.3%; and shockable rhythm, 50.6% ($P < 0.001$). In addition, a significant association was found between low-flow time and neurologic outcome in patients with initial PEA ($P = 0.005$) and/or shockable rhythm ($P = 0.006$) [19]. Another retrospective analysis based on a prospective cohort of 499 adults who experienced OHCA showed that neurologic outcome in patients who received ECPR correlated with age ($P = 0.014$), witnessed arrest without initial asystole ($P = 0.015$), mean arterial pressure > 60 mm Hg within 2 hours after ECPR ($P = 0.021$), left ventricular ejection fraction after ECPR implantation ($P = 0.009$), therapeutic hypothermia ($P = 0.025$), and complications during ECPR ($P = 0.047$) [16]. In a retrospective observational study of 95 adult patients who underwent ECPR during hospitalization, Ryu et al. [20] proposed a new risk prediction model for neurologic outcome (C-statistic, 0.867; 95% CI, 0.823 to 0.912, $P = 0.917$) using age, initial Sequential Organ Failure Assessment (SOFA) score, first monitored arrest rhythm, duration of low-flow time, initial pulse pressure, initial mean arterial pressure, and serum glucose level as independent variables [20].

According to a meta-analysis of 856 patients who underwent ECPR following IHCA pooled from 11 studies, survival correlated with initial shockable rhythm (OR, 1.65; 95% CI, 1.05 to 2.61; $P = 0.03$), shorter low-flow time (pooled mean dif-

ference [PMD], -17.15 minutes; 95% CI, -20.90 to -13.40 minutes; $P < 0.001$), lower lactate level both immediately before ECPR start (PMD, -4.12 mmol/L; 95% CI, -6.0 to -2.24 mmol/L; $P < 0.001$) and on intensive care unit (ICU) admission (PMD, -4.13 mmol/L; 95% CI, -6.38 to -1.88 mmol/L; $P < 0.001$), lower SOFA score (PMD, -1.71 ; 95% CI, -2.93 to -0.50 ; $P = 0.006$), and lower creatinine level within 24 hours after ICU admission (PMD, -0.37 mg/dL; 95% CI, -0.54 to -0.19 mg/dL; $P < 0.001$) [21]. However, the study did not find a significant association between survival and age, sex, or cardiac vs. non-cardiac etiology.

Similarly, a meta-analysis of 15 primary studies that included a total of 841 patients who underwent ECPR for OHCA showed that favorable outcome, defined as survival with CPC score 1–2 at 30 days or at discharge, was significantly associated with low-flow duration ($P = 0.04$), initial shockable rhythm (OR, 2.20; 95% CI, 1.30 to 3.72; $P = 0.003$), arterial pH ($P = 0.01$), and serum lactate level ($P < 0.001$); age, sex, and receiving bystander CPR had no association with favorable outcome [22].

INDICATIONS AND CONTRAINDICATIONS

We believe that ECPR should only be used in highly selected patients with a cardiac origin of arrest. Furthermore, indications and contraindications may vary according to hospital, experience level of the cardiac arrest team, and readiness of ECLS deployment. To date, there has been a lack of RCTs of ECPR and there are no prospectively validated criteria for EC-

Table 2. ECPR criteria

Favorable criteria	Unfavorable criteria
Witnessed collapse & bystander CPR (no-flow time < 5 minutes)	
Age < 75 years	Age ≥ 75 years
Initially shockable rhythm	
No sustained ROSC within 15 minutes of ACLS (short low-flow time < 60 minutes)	Prolonged CPR > 20 minutes in the case of asystole (exceptions: accidental hypothermia, intoxication, near-drowning, and suspected pulmonary embolism) or ≥ 120 minutes in the case of persistent VF/VT
Presumed correctable causes, especially cardiac etiology	Cardiac arrest due to a clearly uncorrectable cause or trauma
High-quality CPR (ETCO ₂ ≥ 10 mm Hg)	Low-quality CPR (ETCO ₂ < 10 mm Hg)
	Clinical signs of severe irreversible brain damage or poor neurological prognosis
	Presence of a terminal illness, malignancy, or comorbidity with reduced life expectancy
	Patient refusal
	No informed consent from the family
	Low pH (< 6.8) or high lactate level (≥ 20 mmol/L)

ECPR: extracorporeal cardiopulmonary resuscitation; CPR: cardiopulmonary resuscitation; ROSC: return of spontaneous circulation; ACLS: Advanced Cardiac Life Support; VF: ventricular fibrillation; VT: ventricular tachycardia; ETCO₂: end-tidal expiratory pressure of carbon dioxide.

PR indications or patient selection. However, favorable outcome can be expected with ECPR when employed for cardiac arrest under several conditions (Table 2) [23,24]. In the real world, ECPR is commonly performed and quite useful in the cardiac surgical ICU, medical cardiac ICU, and cardiac catheterization laboratory. ECPR is also generally indicated in patients who experience cardiac arrest before or after cardiac surgery or intervention. When a cardiac diagnosis appears to be irreversible, cardiac replacement therapy, such as heart transplantation or artificial heart, should be considered.

Patients who experience witnessed collapse and receive immediate bystander CPR are the ideal target for ECPR. The no-flow time, defined as the duration of cardiac arrest before CPR, is considered to be the main variable that determines neurological prognosis. Although the effect of bystander CPR failed to show statistical significance in a meta-analysis (OR, 2.81; 95% CI, 0.95 to 8.32, $P=0.06$) [22], there was substantial interstudy heterogeneity and lack of robustness.

Since advanced age in OHCA has been associated with low probability of survival [25], many institutions only implement ECPR in cardiac arrest patients under 75 years of age [13,14,17]. However, other previous studies have shown that age itself does not have a negative effect on survival after ECPR [15,22]. Thus, advanced age alone should not be considered an absolute contraindication to ECPR. Shockable initial heart rhythm, which includes ventricular fibrillation (VF) and pulseless ventricular tachycardia (VT), is considered a favorable prognostic factor for ECPR [16,19,21,22]. A retrospective study of 232 adult patients in OHCA with an initial rhythm of VF or VT found that early ECPR with angiography in the cardiac catheterization laboratory was associated with better neurological outcome at discharge compared with CCPR (42.0% vs. 15.3%; OR, 4.0; 95% CI, 2.08 to 7.7; $P<0.001$) [26].

As mentioned in the previous section, duration of low-flow time is strongly associated with survival and neurologic outcome in ECPR, especially in patients with initial PEA or shockable rhythm. However, evidence for the appropriate timing of transition from CCPR to ECPR is lacking. According to Ko et al., among patients with IHCA and initial PEA, the best discriminative low-flow time for favorable neurologic outcome was 22 minutes; the corresponding time for those with a shockable rhythm was 46 minutes [19]. A retrospective propensity score-matched study of 156 patients with refractory OHCA evaluated the time of transition to ECPR and showed that mean low-flow time was shorter by 20 minutes when ECPR was initiated after 20 minutes of CCPR compared with ECPR initiation after 30 minutes of CCPR; survival was also better with ECPR initia-

tion after 20 minutes of CCPR (29% vs. 8%, $P<0.001$) [27].

Arterial or venous pH and serum lactate are important prognostic factors for ECPR [21,22]. However, there is no well-validated cutoff value for either pH or serum lactate. A high lactate level suggests that a long period of anoxic metabolism has occurred. However, considering that obtaining a level in the peri-arrest period is difficult, its usefulness for selecting patients for ECPR is questionable.

The contraindications for ECPR are few and similar to those for ECLS. They include patients with poor physical activity level, such as those confined to bed; severe permanent neurologic injury; noncardiopulmonary cause of arrest, such as severe sepsis; prolonged CCPR without ROSC; inadequate ACLS, such as failed advanced airway or ineffective chest compression due to severe hypovolemia or unfavorable chest wall anatomy (for example, aortic rupture or severe pectus excavatum); pre-existing severe multiple organ failure; and so on. However, no single one can be considered an absolute contraindication for ECPR; the physician in charge of a patient's care should discuss resuscitation with leaders of the CPR and ECLS teams if the situation arises.

AREA OF UNCERTAINTY AND FUTURE PERSPECTIVES

Although both ECPR and ELCS are used for patients in cardiac arrest, they are completely different in nature. ECPR is a process that includes CCPR, patient selection, insertion procedure, complication management, post resuscitation care, cause investigation, and cause correction. Much remains to be learned regarding the ECPR process, including indications and proper patient selection.

Controversy over the short-term survival benefit of ECPR over CCPR in patients with OHCA remains [11,15,16]; the reason why ECPR seemed not effective is considered due to prolonged low-flow time in OHCA, which is one of the most important prognostic factors for ECPR. Two French studies attempted to reduce low-flow time by performing pre-hospital ECPR on site in selected patients as part of the emergency medical system protocol; early ECPR was initiated after 20 minutes of ACLS [27,28]. These trials found that shorter low-flow time improved survival. On the other hand, some centers transport patients in OHCA with refractory VF or VT early to the cardiac catheterization laboratory for percutaneous coronary intervention while performing mechanical CPR until ECPR is started [26]. This strategy improved functionally favorable survival when compared with historical ACLS.

Although there is currently no high-quality evidence for ECPR, several RCTs are currently underway. The INCEPTION (NCT03101787) and ARREST (NCT03880565) trials are RCTs designed to evaluate the effect of early ECPR initiation in refractory OHCA [29]. The Prague OHCA (NCT01511666) study is a multicenter prospective randomized clinical study investigating the effect of prehospital intra-arrest hypothermia, mechanical chest compression, ECPR, and early invasive investigation and treatment in all patients with OHCA of presumed cardiac origin.

ECPR is a complex intervention that requires a highly trained team, specialized equipment, and multidisciplinary support within a healthcare system. Disastrous complications such as vessel rupture, bleeding, and thromboembolism may occur [5], hence, rigorous training programs should be established. ECPR should only be performed in those patients who might receive benefit. Its indiscreet application could lead to the survival of patients with poor neurological outcome, which may result in considerable patient suffering and family member distress. Therefore, efforts to improve outcome after ECPR should include all individuals involved in the entire process of ECLS care. Future research should be based on such a multidisciplinary approach.

CONCLUSIONS

ECLS and ECPR are becoming an essential tool in cardiac critical care, cardiac surgery, and cardiac intervention. However, to generalize their use, improved understanding and implementation are required. The studies conducted to date have shown that better survival and neurological outcome can be expected in IHCA patients who receive ECPR compared with CCPR; however, a short-term survival benefit has not yet been shown in OHCA patients.

Prognostic factors associated with better survival and neurological outcome include shorter low-flow time, initial shockable rhythm, lower lactate level, higher pH, and lower SOFA score. Although there are no clearly defined indications, most centers perform ECPR for young patients with an initial shockable rhythm or presumed correctable cause and those with a witnessed collapse and bystander CPR without ROSC within 10–20 minutes of CCPR.

Several recent trials investigating survival after ECPR for OHCA have focused on pre-hospital on-site ECPR and early ECPR with cardiac catheterization. Currently, several RCTs are underway to evaluate the possible benefit of ECPR. However, ECPR is a complex intervention that requires a highly

trained team, specialized equipment, and multidisciplinary support and has the risk of potentially fatal complications. Therefore, ECPR should be reserved for carefully selected patients who have the potential to benefit most.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conceptualization: all authors. Data curation: HK. Writing - original draft: HK. Writing - review & editing: YHC.

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