CURRENT OPINION

Extracorporeal cardiopulmonary resuscitation

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Purpose of review

To discuss the role of extracorporeal membrane oxygenation (ECMO) in patients with cardiac arrest.

Recent findings

Return to spontaneous circulation dramatically decreases with the duration of cardiopulmonary resuscitation (CPR). In this context, it has been proposed to implement venoarterial ECMO in order to assist CPR (ECPR) both in inhospital cardiac arrest (IHCA) and in out-of-hospital cardiac arrest (OHCA).

Summary

This review highlights that ECPR is feasible for both IHCA and OHCA. In the recent series, the outcome of ECPR in IHCA is satisfactory, with survival rates good with neurologic outcome reaching the 40–50% range. All series converge in highlighting that time from cardiac arrest to ECMO flow is a critical determinant of outcome, with survival rates of 50% when initiated within 30 min of IHCA, 30% between 30 and 60 min, and 18% after 60 min. Results of ECPR in OHCA are more challenging. Recent series suggest that good outcome can be obtained in 15–20% of the patients, provided that time from arrest to ECMO is shorter than 60 min. Duration of cardiac arrest seems to be more important than location of cardiac arrest. ECPR thus seems to be a valuable option in selected cases.

Keywords

cardiac arrest, extracorporeal life support, neurological outcome, organ donation

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is often used in patients who present cardiogenic shock shortly after surviving cardiac arrest. As the probability of achieving return to spontaneous circulation (ROSC) decreases rapidly when duration of cardiopulmonary resuscitation (CPR) exceeds 10 min and dramatically after 30 min [1,2▪▪,3▪▪], some clinicians questioned whether ECMO could also be used to restore flow in patients not responding to classical resuscitation procedures [4]. On the basis of these results and on pediatric experience in which the use of ECMO as rescue therapy started earlier [5–7], the rates of publication describing resuscitation with the use of ECMO increase exponentially (four in 2011, 13 in 2012, and 11 in 2013). In this article, we will review the evidence associated with ECMO after and during CPR.

EXTRACORPOREAL MEMBRANE OXYGENATION IN CARDIOGENIC SHOCK AFTER CARDIAC ARREST

Venoarterial ECMO has been used successfully for several years in refractory cardiogenic shock. Of note, the survival rate is markedly affected by the underlying condition and, especially, its capacity to recover. Combes *et al.* [8] demonstrated a short-term and long-term survival (11 months of median follow-up time) of 42 and 36%, respectively, in a large series of patients with cardiogenic shock of various origins, including fulminant myocarditis (30%), postcardiotomy (24%), post-myocardial infarction (15%), and shock after heart transplantation (15%). Survivors reported satisfactory mental health and vitality, but persistent physical and social trouble. Similar results were reported recently in another series of 105 patients [9▪▪].

In many of these trials, a significant proportion of the patients had undergone CPR prior to ECMO implantation. A trial focusing on 134 patients with cardiogenic shock of various origins in whom ECMO

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KEY POINTS

- Chances of recovery with good neurologic outcome decrease dramatically over time.
- ECPR is a valuable option in IHCA and should be implemented as soon as cardiac arrest is considered refractory to standard CPR.
- ECPR can be considered for OHCA in selected patients (witnessed cardiac arrest, no flow <5 min) if time from arrest to initiation of ECMO flow can be shorter than 60 min.
- ECPR should be provided for OHCA related to hypothermia or intoxication even if time from arrest to ECMO flow is longer than 60 min.
- Organ donation after cardiac death should be considered in patients with poor neurological recovery.

was inserted shortly after or during CPR reported that 43% of these patients were alive at hospital discharge [10]. Several recent trials suggest that cardiac arrest prior to ECMO implantation is associated with a moderate increase in the risk of death [9■■,11■]. In 105 patients with cardiogenic shock, cardiac arrest occurred prior to ECMO implantation in 24 (23%), but the increased risk of death was not significant [odds ratio, OR 2.00 (0.79–5.05)] [9■■]. However, in another trial of 87 patients with cardiogenic shock, cardiac arrest occurred in 36 (41%) patients before ECMO implantation, and this was associated with an increased risk of death [OR 2.12 (1.27–3.54)] [11■]. Of note, the point estimate of these trials concurs and suggests a two-fold increase in the risk of death when ECMO is inserted in patients with cardiogenic shock with recent history of CPR.

In several of these reports, ECMO implantation occurred while CPR was performed. ECMO implantation during CPR was associated with a marked increase in the risk of death [OR 20.68 (1.09–392.03)] in the trial by Cheng *et al.* [12] and 4.12 (2.17–7.83) in the trial by Beurtheret *et al.* [11■]. ECMO implantations shortly after CPR and during CPR carry different risk of death and should thus be considered separately. ECMO implantation shortly after CPR sounds reasonable, with reported survival rates between 22% [11■] and 50% [9■■].

EXTRACORPOREAL MEMBRANE OXYGENATION DURING HYPOTHERMIC CARDIAC ARREST AND IN TOXICOLOGY

Some indications have been well established for many years, such as hypothermia [13]. Recently, Wanscher *et al.* [14■■] reported a 100% survival rate in a series of seven victims of a Danish Fjord boating accident found in circulatory arrest with dilated pupils and a median temperature of 18.4°C (15.5–20.2°C). In these severely hypothermic patients, the time to ECMO was 226 min (178–241), and only one patient had cognitive impairment. ECMO is now considered as the gold standard for refractory hypothermic cardiac arrest.

Many case reports and series described the use of ECMO for cardiac arrest due to intoxication [15–17], and demonstrated that ECLS resulted in otherwise unexpected survival. These cases are often characterized by recurrent episodes of cardiac arrest (because of ventricular arrhythmias) combined with underlying profound cardiogenic shock. The largest series reporting ECMO-supported CPR (ECPR) in refractory cardiac arrest of toxic origin only included 17 patients and reported a 24% survival rate [18]. These satisfactory results were observed despite the very long delay between initiation of CPR and ECMO initiation (120 ± 60 min). Another series of seven patients reported a 71% survival rate, with also a long time to ECMO initiation (101 ± 55 min) [19]. ECPR is now considered in refractory cardiac arrest of toxic origin.

EXTRACORPOREAL MEMBRANE OXYGENATION FOR INHOSPITAL CARDIAC ARREST

Several recent studies [20,21,22■,23–25] have suggested that ECPR may be effective for patients with refractory inhospital cardiac arrest (IHCA). The main characteristics of the studies reporting outcome of ECPR in series of cases of IHCA are reported in Table 1 [11■,12,23–31,32■■,33,34,35■]. In their landmark study, the largest trial in the field, Chen *et al.* [21] reported a cumulative 30-day survival rate of 34%. They also demonstrated that compared to conventional CPR, ECPR increased the rate of successful defibrillation and extended the duration of resuscitation associated with good neurological outcome. The probability to survive to discharge was 50% when ECMO flow was initiated within 30 min of IHCA, 30% between 30 and 60 min, and 18% after 60 min. Of note in the conventional group, these percentages were 20, 9, and 0%, respectively [21]. Similar survival rates of 34% [22■] and 53% [23] were reported by others. All these studies [12,33,34,36] demonstrated that the longer the time before ECMO initiation, the poorer the outcome. Importantly, 1-year survival with good neurological outcome was very close to hospital discharge in most of these trials [21,36]. Altogether, these studies suggest that ECPR is a valuable option for IHCA and that it should be initiated as soon as possible when cardiac arrest is considered to be

Table 1. Studies including inhospital cardiac arrest patients

First author	Year	*n*	Time to ECMO	Survival
Mair [26]	1996	5	NA	2 (40%)
Willms [27]	1997	68	29 ± 17	17 (25%)
Chen [20]	2003	57	47.6 ± 13.4	18 (31.6%)
Sung [28]	2006	22	48.5 ± 29	9 (41%)
Lin [29]	2010	55	48.7 ± 26.9	13 (23%)
Shin [30]	2011	85	42 ± 25.7	26 (31%)
Liu [31]	2011	11	NA	4 (37%)
Haneya [23]	2012	59	25 (20–50)	25 (42.3%)
Kagawa [32▪▪]	2012	44	NA	25 (57%)
Loforte [33]	2012	16	31 ± 14	2 (12.5%)
Sakamoto [34]	2012	64	25 ± 22	18 (28%)
Beurtheret [11▪]	2012	13	48 ± 53	1 (7%)
Fagnoul [35▪]	2013	10	55 (42–60)	3 (30%)
Cheng [12]	2013	68	NA	16 (24%)
Attanà [24]	2013	22	50 (40–60)	5 (23%)
Guenther [25]	2013	14	NA	4 (29%)

ECMO, extracorporeal membrane oxygenation.

refractory to standard CPR. On the basis of these findings, the American Heart Association guidelines for resuscitation mentioned ECPR as a potential support to be considered in experienced centers where the technique is rapidly available, in patients with short arrest period before CPR initiation, and when the condition leading to the cardiac arrest was reversible or amenable to heart transplantation [37].

EXTRACORPOREAL MEMBRANE OXYGENATION FOR OUT-OF-HOSPITAL CARDIAC ARREST

For out-of-hospital cardiac arrest (OHCA), the data are scarce and conflicting (Table 2) [22▪,23,32▪▪,35▪,38–41,42▪]. Several case reports and small series suggested some benefit, but these were subject to publication bias. The first large study of 51 patients with OHCA showed a very low survival rate, with only two survivors [40]. Recently, some other teams reported more favorable outcomes. In 42 patients with OHCA, Kagawa *et al.* [32▪▪] reported a 30-day survival of 24%, with favorable neurological outcome of 21% in the group of OHCA patients who received intra-arrest percutaneous coronary intervention (PCI). It was confirmed in several studies in a mixed population of IHCA and OHCA [35▪,42▪,43]. One of the explanations for the variability of the results is the duration from cardiac arrest to ECMO initiation [42▪]. Le Guen *et al.* [40] reported a 4% survival with a time

Table 2. Studies including out-of-hospital cardiac arrest patients

First author	Year	*n*	Time to ECMO (min)	Survival
Nagao [38]	2000	36	67 ± 43	9 (25%)
Haneya [23]	2012	26	70 (55–110)	4 (15%)
Kagawa [32▪▪]	2012	42	59 (45–65)[a]	7 (24%)
Nagao [39]	2010	171	66 ± 3	21 (12%)
Le Guen [40]	2011	51	120 (102–149)	2 (4%)
Avalli [41]	2012	18	77 (69–101)	1 (5.5%)
Fagnoul [35▪]	2013	14	66 (56–80)	3 (21%)
Maekawa [22▪]	2013	53	49 (41–59)	17 (32.1%)
Leick [42▪]	2013	28	53 (40–61) nonsurvivors, 44 (31–45) survivors	11 (39%)

ECMO, extracorporeal membrane oxygenation.
[a]ECMO time was reported for 39 of the 42 patients in a previous report of the same group [36]. Series dealing exclusively with intoxication and severe hypothermia cases were not included.

to ECMO of 120 (102–149) min, whereas studies with more favorable outcomes reported shorter time to ECMO [40 min (25–51)] in the trial by Kagawa *et al.* [32■■] and systematic implementation of intra-arrest PCI. The difference in outcome between IHCA and OHCA results more from the duration of cardiac arrest than from the location of cardiac arrest itself (Tables 1–3) [11■,12,22■,23–31,32■■,33,34,35■,38–41,42■,43–57].

In order to further reduce the time to ECMO flow, can ECPR be performed in the prehospital field? Lebreton *et al.* [58] first reported the feasibility of on-field ECMO implantation in an adult patient presenting cardiac arrest during a half marathon. Lamhaut *et al.* [59] reported the first series of successful prehospital ECMO implantation for ECPR in seven patients. The results were mitigated, with one patient who survived to hospital discharge. Three patients had confirmed brain death and organ donation was carried out after family consent in two of these. Surprisingly, time to ECMO (57 ± 21 min) was quite long, and obviously longer than the interval observed in scoop and run strategies [32■■]. One may thus question whether it would not be more judicious to rapidly transport the patient to ECMO centers (scoop and run strategy) rather than provide ECMO on the prehospital scene.

WHEN SHOULD CARDIAC ARREST BE CONSIDERED AS REFRACTORY TO STANDARD CARDIOPULMONARY RESUSCITATION AND EXTRACORPOREAL CARDIOPULMONARY RESUSCITATION INITIATED?

When can cardiac arrest be considered as refractory to standard CPR? In a large database of 64 339 patients with IHCA, half of the patients achieving ROSC did it within 10 min of the onset of cardiac arrest, one-fourth during the subsequent 10 min, and very few patients experienced ROSC after more than 30 min of CPR [2■■]. In OHCA, ROSC occurred within 16.1 min of CPR in 89.7% of the patients with good functional outcome [3■■]. After 15 min, the probability of good functional recovery among all attempted CPR fell to less than 2%. Hence, cardiac arrest can be considered refractory to standard CPR after 15 min. At Erasme University Hospital, we evaluate the patient with cardiac arrest as a potential candidate for ECPR at 10 min of CPR, which results in initiation of ECMO within 30 and 60 min, depending on the location of cardiac arrest.

WHAT CAN BE DONE TO IMPROVE THE OUTCOME OF THESE PATIENTS?

All series mentioned that selection of candidates for ECPR seems to be crucial, especially in the setting of

Table 3. Studies including patients with mixed location of cardiac arrest

First author	Year	*n*	Time to ECMO (min)	Survival
Hartz [44]	1990	29	NA	1/29 (3.4%)
Kurose [45]	1995	9	82 ± 30	6/9 (67%)
Martin [46]	1998	10	32 ± 13	0/10 (0%)
Younger [47]	1999	25	32 ± 27	13/25 (52%)
Schwarz [48]	2003	21	NA	3/21(14%)
Masseti [49]	2005	40	105 ± 44	8/40 (20%)
Jaski [50]	2010	127	NA	29/127 (23%)
Megarbane [51]	2011	66	155 (120–180)	1/66 (1.5%)
Maj [52]	2012	15	NA	3/15 (20%)
Wu [53]	2012	28	65 (25–90)	9/28 (32%)
Haneya [23]	2012	85	40 (20–70)	29 (34%)
Kagawa [32■■]	2012	86	49 (30–68)	25 (29%)
Belle [54]	2012	24	NA	1/24 (4%)
Schopka [55]	2013	103	NA	29/103 (28%)
Fagnoul [35■]	2013	24	58 (45–70)	6/24 (25%)
Mendiratta [56]	2013	99	NA	22/99 (22%)
Park [57]	2013	45	24 ± 30	7/45 (15.5%)
Mojoli [43]	2013	23	93 (74–107)	8/23 (35.7%)

ECMO, extracorporeal membrane oxygenation.

OHCA: witnessed cardiac arrest, with a no-flow period less than 5 min, whenever possible bystander CPR or a very rapid response team, a prehospital care policy prompt to alert a specialized hospital with an ECMO team, and rapid transport after initiation of CPR (scoop and run strategy). In addition, good-quality CPR should be provided up to initiation of ECMO flow. In our center, we use mechanical CPR not only in order to maintain quality of the CPR during the entire process (which includes transportation) despite duration of CPR that is often comprised between 30 and 60 min, but also in order to spare human resources for other important purposes and to facilitate ECMO implantation.

Given the high incidence of acute coronary syndrome in cardiac arrest patients and the improvement of outcome with postresuscitation PCI, Kagawa *et al.* [32■■] investigated the effectiveness of intra-arrest PCI associated to extracorporeal CPR. They reported a higher survival rate in the intra-arrest PCI groups compared with delayed PCI (30-day survival 36 vs. 12%).

Brain protection and prevention of the post-resuscitation syndrome are the next frontier. In order to enhance the brain protection and limit the generation of reactive oxygen species and the ischemia–reperfusion syndrome, Fagnoul *et al.* [35■] associated hypothermia and prevention of hyperoxia as part of the management of ECPR patients. These two strategies were implemented already during implantation of ECMO, and ECMO flow was initiated with a relatively low oxygen fraction in ECMO gas with blood cooled at 32–33°C.

Further studies are definitively needed in this domain. ECPR is a unique setting in which interventions aiming at preventing ischemia–reperfusion injury can be applied before and at the time of restoration of flow. This opens the door to the implementation of many promising pharmaceutical interventions.

EXTRACORPOREAL CARDIOPULMONARY RESUSCITATION AND ORGAN DONATION

Up to one-third of nonsurvivors after ECPR die from postanoxic brain damage, but only a minority will present brain death. In centers with a program of nonheart beating organ donation, these patients may be selected for organ donation [35■]. Regarding this, a major ethical concern of this strategy was the determination of death after cardiac death. In many patients, absence of recovery of cardiac activity and poor neurologic state were used to define death after cardiac death and suitability for organ donation.

By the way, organ donation also challenges the definition of 'good outcome' in ECPR. Some reports evaluated not only the survival of patients, but also the increase of organ donations. Megarbane *et al.* [51] reported only one survivor, but six patients with confirmed brain death and three organ donations. Fagnoul *et al.* [35■] described the increases of organ donation as an important endpoint for an ECPR program and reported a composite endpoint of 40%, including survival and organ donation.

CONCLUSION

ECPR is feasible and valuable for refractory cardiac arrest. The outcome of ECPR in IHCA reaches 40–50% good neurological outcome and is better than for OHCA, which is close to 15–30% good neurological outcome. This difference is probably related to the duration of cardiac arrest, which seems to be more important than the location of cardiac arrest. ECPR may be considered in patients with refractory cardiac arrest that was witnessed and with a no-flow period of less than 5 min. When used, all efforts should be made to minimize the time from cardiac arrest to ECMO flow, as the latter is a critical determinant of outcome. Organ donation should be considered in patients with poor neurological outcome, but experiencing full recovery of organ function.

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Conflicts of interest

D.F. and D.De B. have no conflicts of interest related to the current work. A.C. has received consulting fees from Maquet.

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