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Review Article

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EXTRACORPOREAL CARDIOPULMONARY RESUSCITATION

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ABSTRACT

Extracorporeal cardiopulmonary resuscitation (ECPR) is the application of mechanical circulatory support by means of veno-arterial extracorporeal membrane oxygenation (VA-ECMO) to a patient during cardiac arrest. The VA-ECMO provides a more effective cardiopulmonary support than conventional cardiopulmonary resuscitation with 6-month survival of up to 30%. Besides, there is long term neurological benefit of ECPR over conventional counterparts. However, randomized controlled trials comparing ECPR and conventional CPR are difficult to carry out. Current recommendations on ECPR are largely based on expert opinion. Moreover, there are other technical and ethical issues that remain unanswered. Yet, there is increasing trend of ECPR performed both in Hong Kong and worldwide. This review will discuss the evidence of ECPR, as well as the technical, practical and ethical issues that are related to ECPR.

KEYWORDS: Extracorporeal cardiopulmonary resuscitation, extracorporeal life support, adult,

INTRODUCTION

Extracorporeal cardiopulmonary resuscitation (ECPR) is the application of mechanical circulatory support by means of veno-arterial extracorporeal membrane oxygenation (VA-ECMO) to a patient during refractory cardiac arrest. Refractory cardiac arrest refers to the situation when conventional CPR has failed to provide a return of spontaneous circulation, or when repetitive cardiac arrests occur without a sustained ROSC.[1] It usually applies to failure to regain spontaneous circulation in the setting when ECPR is contemplated, and it is usually about 15 minutes of conventional resuscitation. A study showed that the probability of good functional outcome was down to around 2% only, after 15 min of conventional resuscitation.[2] Compared with automatic mechanical compression which offered up to 27% of cardiac output in an animal study,[3] ECPR can provide 3 to 4 liters per minute blood flow as cardiopulmonary support while the potentially reversible causes are treated. Fig.1 illustrates how the VA circuit supports heart-lung function on top of patient's native one. In VA-ECMO, blood is drained from the venous system to pass through the oxygenator of the ECMO, and then pumped back to the arterial system. Once the VA-ECMO is established, the resuscitation team can stop conventional chest compression. Currently, ECPR is done on highly selected group of patients who developed refractory cardiac arrest, but whose long-term outcomes are believed to be good.

This new resuscitation modality has revolutionized the practice of resuscitation. The hospital survival of in-hospital cardiac arrest and out-of-hospital cardiac arrest were reported to be 15% and 9.6% respectively.[6,7] While the survival of those with refractory cardiac arrest would be expected to be even lower, it was shown that the use of ECPR boosted the hospital survival to nearly 30%.[6] For those who survived after ECPR, majority of patients has favorable neurological outcome.[7] As ECPR has been recognized by the American Heart Association in 2015 as an alternative to conventional CPR for patients with reversible etiology of cardiac arrest,[8] the number of ECPR performed has been markedly increasing worldwide [Fig.2]. This article will review the practical aspects, current evidence, and the ethical challenge related to ECPR.

Practical aspect of ECPR

2.1 Eligibility

Prognostication at the time of contemplating ECPR initiation is often difficult with lack of time and information. Patients' relatives are often not immediately present for collateral history taking or informed consent. It was suggested that the decision of initiation should preferably be started at 10 minutes of conventional resuscitation and completed by 15 minutes to allow the setup of ECPR within the limited time frame.[9] Witnessed cardiac arrest, bystander CPR, shockable rhythm, presumed cardiac origin of arrest were commonly cited inclusion criteria for ECPR initiation. Patients with advanced age, do-not-resuscitate order, terminal illnesses, malignancies, hypothermia, or poor activities-of-daily-living status were generally excluded.[10,11] However, no single parameter has been shown to be reliable enough to draw a concrete conclusion on the eligibility of a patient.

The use of risk scores such as the Survival After Veno-Arterial ECMO score (SAVE score) has been suggested for patient selection. The SAVE score has previously been validated in patients with refractory cardiogenic shock on VA-ECMO, with a lower score representing poorer prognosis.[12] Disappointingly, study by Richardson showed that the SAVE score poorly discriminated survivors from non-survivors in patients receiving ECPR, and a higher score was ironically found in the non-survivors.[6] Therefore, the application of the SAVE score outside the original setting is hardly the right choice to decide the fate of a cardiac arrest patient.

To complicate the issue, these conventional survival predictors could potentially be modified by ECPR itself, although data are lacking to prove the direct impact.[1] For example, improved perfusion to the myocardium after ECPR might allow successful defibrillation by eliminating myocardial hypoxemia, which might result in non-shockable rhythm otherwise. The extracorporeal circuit could also permit rapid control of temperature and so hypothermic cardiac arrest in no time.[13]

As a result, so far, there are no universally accepted ECPR initiation criteria or validated risk scores in the selection of ECPR candidates. Different ECMO centers often adopt their own criteria. In our center, case-by-case decisions of ECPR initiation are made jointly by ECMO specialists. Issues to consider would include patients' premorbid condition, cause of cardiac arrest being cardiac origin, expected reasonable neurological prognosis given the duration and quality of resuscitation, and the center's manpower and resource availability.

Organizational settings and personnel

The ECPR service should be an extension from the existing ECMO program. In contrast to the setup of venovenous ECMO for respiratory failure, initiation of ECPR is an emergency. Dedicated planning is required to prepare for the manpower, ECMO circuit, equipment, location, and imaging facilities. A resuscitation team experienced in ECMO management should be standby on a 24-7 basis. The decision to start ECPR should be made as soon as possible. The availability of pre-primed circuit may shorten the time to initiate the ECMO flow and in-vitro study confirmed the safety of pre-primed circuit with crystalloids for 2 to 4 weeks without increase risk of infection.[14,15] The best location to perform ECPR is still under investigation. It depends on the original setting where the patient develops cardiac arrest, the ease and safety of transport and the availability of a dedicated location to perform the cannulation. Jaski et al. showed that ECPR performed in the catheterization laboratory was associated with significantly better long-term survival than in other hospital locations.[13] The improved long-term outcome was postulated to be related to the availability of resuscitation equipment, catheters and guidewires, ultrasound and fluoroscopic guidance and assistants experienced in endovascular intervention. The addition of fluoroscopic guidance on top of ultrasound guidance was shown to decrease cannulation complication incidence (adjusted odds ratio 0.14, p-value = 0.024).[16] On the other hand, the better outcomes of ECPR initiated in the catheterization laboratory might just reflect the more predominant underlying cardiac etiology.

As soon as a patient is stabilized on ECMO, the underlying cause of cardiac arrest should be sought and treated accordingly, such as coronary revascularization, valvular heart surgery, or pulmonary embolectomy. A close collaboration with cardiologists and cardiothoracic surgeons is mandatory to the successful ECPR service. If bridge to recovery is unlikely or slow, timely referral should be made to a transplantation center for consideration of other mechanical circulatory supports or heart transplant.

ECPR should be performed by well-trained ECMO specialists who are experienced in ECMO cannulation and management. Barbaro studied the data from ELSO registry and revealed an inverse relationship between case volume and mortality. Compared with centers which perform less than 6 cases of ECMO a year, centers with more than 30 cases have a lower mortality (adjusted odds ratio 0.61, 95% confidence interval 0.46 to 0.80).[17] In the position paper of ECMO organization, the ECMO Network and ELSO set the threshold of case load of 30 adult ECMO cases per year, but centers were also reminded not to perform ECMO just to increase the case volume.[18]

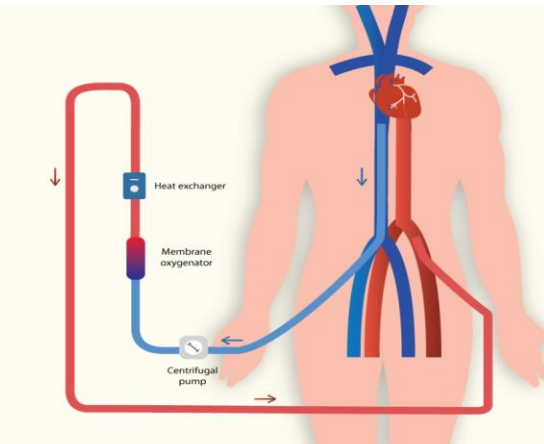

Fig. 1: Diagram of a VA ECMO circuit shows that blood is drawn from the femoral vein, passing through an oxygenator and pumped back to the femoral artery. On top of his native heart-lung, the patient has extra heart lung function supported by the VA ECMO.

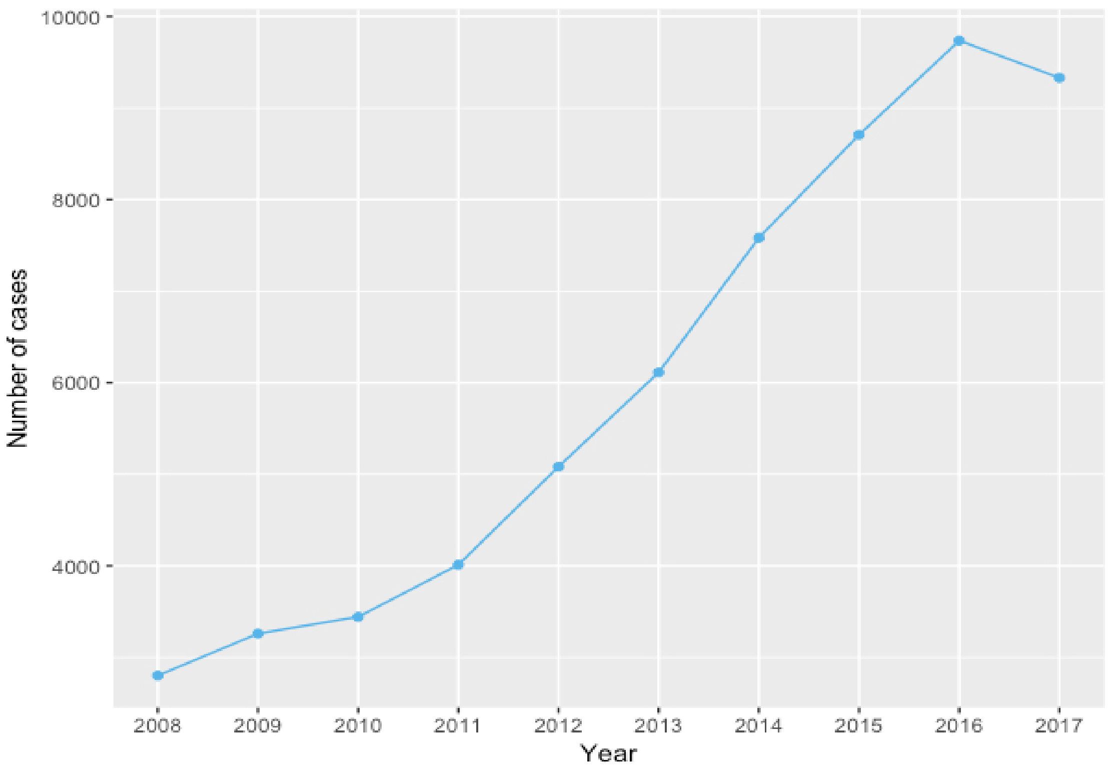

Figure 2: Annual ECPR cases reported to ELSO registry.

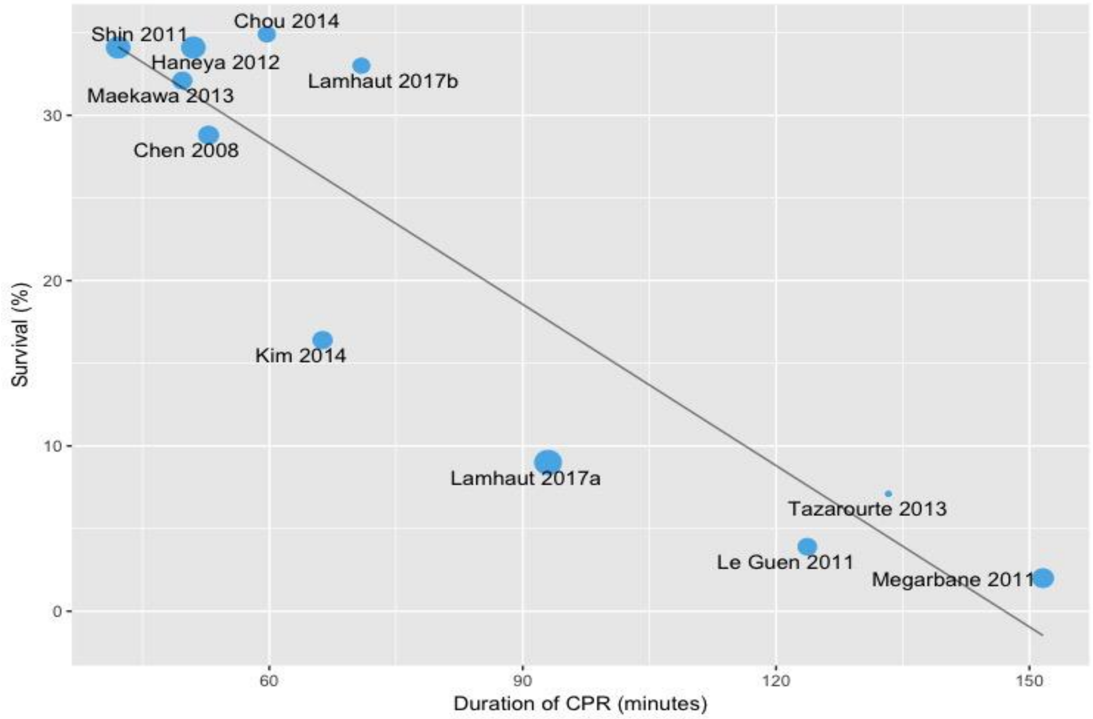

Figure 3: Relationship between duration of CPR and survival in reported literature. Sample size of the studies were represented by the size of the point. Lamhaut 2017 was a two-phase study in 2011-2014 (a) and 2015 (b).

Cannulation

There is no single best cannulation strategy in ECPR and the current practice is adopted from experience in venoarterial and venovenous ECMO. Cannulation can be performed by open, percutaneous or mixed approach. An open approach allows direct visualization of the anatomy. It requires surgical expertise, and has been used in pre-hospital settings.[19] However, bleeding remains a significant concern because of the anticoagulation use during the ECMO run. Percutaneous approach refers to the Seldinger technique using a guidewire. It is often more challenging compared with the cannulations in venoarterial and venovenous ECMO. The absence of arterial pulsation and color differentiation between arterial and venous blood in a patient under cardiac arrest creates difficulty to confirm correct arterial or venous puncture. Ongoing chest compression may interfere with needle puncture and acquisition of echocardiography images to confirm the guidewire position. The use of fluoroscopy, therefore, has been advocated in ECPR. It not only confirms the position of the guidewire, but also allows a real time visualization of the direction and location of the ECMO catheters during cannulation. The combination of ultrasound and fluoroscopic guidance was shown to decrease the risk of vascular complications.[16] The mixed approach ('semi-Seldinger') describes an incision in the groin with needle insertion distal to that incision. It also allows the direct visualization of the needle puncture and the subsequent cannulation. To date, no single cannulation technique is shown to be superior to the others. Operators are advised to adopt a method according to their experience, patients' risk stratification (for example cannulation in morbidly obese patients) and the availability of the imaging facilities.

Peripheral cannulation is the most common practice unless in post-cardiotomy patients. Common practice includes single femoral cannulation, bi-femoral cannulation or less commonly venous drainage from the internal jugular vein with return to the femoral artery. There is no concrete evidence recommending the optimal cannulation sites and the decision is frequently made according to the experience and the number of the operators available. Although bi-femoral approach may be more time-saving when manpower allows, one must pay attention to avoid venovenous or artiero-arterial cannulation. The risk might be minimized, but not eliminated, with the single femoral approach.[1] In situation where vascular access is limited, internal jugular vein can be considered for the venous drainage, but it may interfere with the chest compression. The central approach at the right atrium or the aorta is generally reserved for the postoperative cardiac patients by reopening the sternum. The cardiopulmonary support by central cannulation is more physiological than the peripheral VA-ECMO configuration because the antegrade flow would not increase the afterload as in the retrograde flow in the peripheral counterpart. There is risk of life-threatening bleeding and mediastinitis.[20] Therefore, conversion to peripheral VA-ECMO should be considered if a patient does not improve favorably in a few days.

ECMO flow

The regulation of ECMO flow remains controversial. Theoretically, a lower ECMO flow is required in the state of hypothermic cardiac arrest. The need to target an ECMO flow for restoration of systemic perfusion should be balanced against the risk of left ventricular distension, endoventricular stasis and pulmonary edema,[21,22] Until strong evidence should come up, we would agree that pump flow should be set to values allowing for a rapid lactate clearance, restoration of urine output and resolution of metabolic acidosis, which prevent propagation of the substrates for cardiac arrest.[23]

Complications

ECPR is a highly invasive therapy with notable risks of complications. According to the data from ELSO registry,[6] bleeding was reported to be one of the most common complications in ECPR patients, occurring in more than half of the patients. The bleeding sources ranged from cannulation sites, pulmonary hemorrhage, gastrointestinal bleed, to catastrophic intracranial bleeding. One in five of the patients developed neurological complications, including brain death and cerebrovascular accident. Nosocomial infection was diagnosed in more than 20% of patients. The incidence of limb ischemia was about 6%.

Post ECPR management

The aim of ECPR is to support a patient's cardiopulmonary function and allow time for clinicians to treat the underlying cause of arrest. This concept which seems universally true still invites a lot of discussion, mainly due to concern of bleeding complications. For example, the risk of bleeding is multiplied with the use of double antiplatelet agents after percutaneous cardiac intervention, on top of the anticoagulation used during ECMO, and the intrinsic deranged coagulation system in the critically ill.[24-26] Similarly, the decision to administer thrombolytic agent in a patient with massive pulmonary embolism soon after resuscitated by ECPR necessitates careful consideration.

Although the ELSO guideline recommends the use of hypothermia during CPR and for 48-72 hours after ECMO cannulation.[27] the recommendation is mainly extrapolated from evidence in therapeutic hypothermia or targeted temperature management in out-of-hospital cardiac arrest survivors for neuroprotection. Few observational studies suggested improved neurological outcome with the application of therapeutic hypothermia in patients supported with ECPR,[28,29] However, therapeutic hypothermia is not without risk. The complications include hemodynamic disturbance and arrhythmia, bleeding, infection, and coagulopathy.[30] As a result, therapeutic hypothermia in ECPR is not an universal practice.

Evidence supporting ECPR versus conventional CPR

Studies evaluating the use of ECPR were largely observational. Table 1 summarizes the key findings of these studies. Hospital survival ranged from 2% to 34.1% while the majority of survivors had favorable neurological outcome. The reasons for the significant difference in the survival outcome across the studies were likely multifactorial. Firstly, a shorter duration of cardiopulmonary resuscitation before ECMO initiation was shown to be associated with improved survival.[31] This inverse relationship remained consistent across studies (Fig. 3). Secondly, stringent patient selection to those with cardiac arrest due to cardiac causes would be important. Studies who reported a lower proportion of cardiac causes of arrest had poorer survival,[32,33] Thirdly, the case volume of an ECMO center should be taken into consideration, but it would be difficult to compare the number of cases performed in the individual centers shown in the literature. Lastly, the location of cardiac arrest might indirectly influence the outcome. The results comparing survival in in-hospital cardiac arrest and out-of-hospital cardiac arrest were conflicting. Although patients with in-hospital cardiac arrest often had a shorter duration of CPR prior to ECMO initiation, and this was linked to improved survival,[32,7] the etiologies for cardiac arrest were often more heterogeneous and less reversible.[10] To address the issue of the heterogeneous results of these studies on ECPR, an ongoing randomized open-label trial (INCEPTION, NCT03101787) evaluating the early initiation of ECPR in out-of-hospital cardiac arrest may help to answer the questions.

ECPR poses new ethical problems

As discussed before, the eligibility criteria for ECPR are not uniformly agreed. The same problem, we believe, exists in every center providing ECPR service: the inability to provide ECPR equally to all patients who may benefit from it. Potentially a very large number of suitable candidates exist, but resources are limited. ECPR is now recommended by international resuscitation societies, and gaining more public awareness, however, ECPR might not be initiated in a patient who could potentially benefit from it. The tremendous manpower allocated to the ECPR service, on the other hand, invariably will jeopardize other acute medical service to a certain extent.

Although pre-priming circuit allows prompt ECMO initiation when needed, if there is no suitable candidate after the safety period elapses, especially in low-volume centers, the circuit would be discarded. Valuable medical resources will be wasted.

Full informed consent or even surrogates' agreement is often not possible at the time of ECPR initiation. However, the potential complications of ECPR can be life threatening or resulting in long term poor functional outcomes. The maleficence can outweigh the beneficence, at least for some of the cases.

There are situations where the patients make a favorable neurological recovery without improvement of cardiac function and deemed not fit for cardiac transplantation. Withdrawal of support in this case is now a very difficult scenario since the patient can participate in decision making. In case these patents opt for continued VA-ECMO support, their autonomy would need to be balanced against resource allocations.[34]

Even when a patient or his surrogates agree that the VA-ECMO is a bridge to no exit, and agree to withdrawal, palliative care to this last journey is not to be forgotten, even though the time from withdrawal to death is usually less than 60 minutes.[35] It is particularly important to ensure patients comfort with adequate symptom medications prior to discontinuing ECMO, because of the probable rapid circulatory collapse.

Death certification in patients on VA-ECMO support is challenging. Irreversible neurologic injury after initiation of ECPR can pose ethical dilemmas, especially in countries that do not recognize brain death. The VA-ECMO can theoretically support the heart-lung function continuously, and the patient would not develop cardiac death unless with VA-ECMO withdrawal. For brainstem death clinical test, the apnea test requires fine titration of the sweep gas and the fractional oxygenation, in order to allow the rise of plasma carbon dioxide level while the patient remains stable by adequate oxygenation.[36] Radiological confirmatory test might be helpful if any doubt arises.

Further dilemma includes when to prognosticate neurologically after ECPR and potential increased sources for organ donation. With the flourishing development in ECPR, future studies will offer the answers to these questions very soon.

CONCLUSION

To date, there is insufficient evidence to support the routine application of ECPR in patients with refractory cardiac arrest. A lot of practical and ethical dilemmas are yet to be solved. On managing refractory cardiac arrest in young patients with good premorbid function, presumed cardiac origin, and those with short periods of high quality CPR, ECPR should be considered. ECPR is not a single procedure but part of the whole chain of resuscitation. Team work and good organizational planning is the key to success of the ECPR service.

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Declaration

The authors have no conflict of interest to disclose. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Author contributions
The authors contributed as follows: study concept, acquisition of data, interpretation of data - KMF and SYA; drafting of the manuscript – SYA; and critical revision of the manuscript – KMF, GWYN and AKHL.

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