NARRATIVE REVIEW

ECPR (Extra Corporeal Cardio Pulmonary Resuscitation): Challenges and Future in India

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ABSTRACT

Extra Corporeal Cardiopulmonary Resuscitation is an growing modality in refractory cardiac arrest by which adequate circulation and oxygen delivery is restored and helps to improve the overall outcomes overcoming the limitations of conventional CPR. Evidence from international studies points to improved survival and neurological outcomes in selected patients specifically in in-hospital cardiac arrests,; But its benefit in out-of-hospital settings remains variable and highly dependent on many other factors and not without limitations. ECPR is a time-sensitive, resource-intensive intervention requiring a well-coordinated multidisciplinary team and robust infrastructure.In India, the adoption of ECPR is still in its developing stage with limited data, absence of regional guidelines, and significant challenges and barriers. Despite these limitations, increasing ECMO experience, especially post-pandemic, gives us an opportunity to expand ECPR programs in tertiary centers. Establishing national registries and improving public health measures such as CPR training may ultimately determine the broader impact of ECPR in India.

Keywords: Extracorporeal cardiopulmonary resuscitation; Veno-arterial ECMO; Refractory cardiac arrest; Neurological outcomes

Introduction

High-quality conventional cardiopulmonary resuscitation (CCPR) provides only 20–30% of normal cardiac output. Prolonged CCPR causes inadequate tissue perfusion and oxygen debt until return of spontaneous circulation. Use of veno-arterial extracorporeal membrane oxygenation (VA-ECMO) during CCPR is termed extracorporeal cardiopulmonary resuscitation (ECPR), which restores normal cardiac output and perfusion, terminating the low-flow state; this transition is called return of extracorporeal circulation (ROEC).

Cardiac arrest is the endpoint of many conditions. Survival after out-of-hospital cardiac arrest (OHCA) is 29.7%, with 8.8% survival to discharge.(1) Survival is time-dependent: immediate return of spontaneous circulation (ROSC) has ~60% survival, whereas ROSC after 40 minutes has <10%. In in-hospital cardiac arrest (IHCA), ROSC occurs in 48. 5% with 25% survival to discharge.(1)

In India, there are no randomized or observational ECPR studies apart from case reports. ECMO began in 2001 for cardiac cases, expanded progressively after 2008, and increased markedly during the COVID pandemic. A 2017 study from 18 centers (295 cases) reported 57.6% survival.(2)

ECPR is an extremely time-dependent, resource-intensive intervention requiring coordinated team-work among emergency physicians, intensivists/anaesthesiologists, cardiac surgeons, nurses, perfusionists, and cardiologists.

HISTORY & TRENDS

The first published report on ECPR was by Kennedy et al in 1966 in which 8 patients were resuscitated with the technique.(3) There were 7 survivors with one patient being neurologically intact at discharge. The authors underlined the importance of having expert teams of specialists, the perfusionist ability to establish assisted circulation early and the need for a primed, sterile circuits which is always available.

The Extracorporeal Life Support Organization (ELSO) showed the growing interest in ECMO from <100 cases in 2009 to > 1500 cases in 2019. In propensity matched analysis, they showed improved survival outcome with ECMO which has been further supported by recent randomized controlled trials. The increase in ECMO with the 2009 H1N1 pandemic and the Covid era further improved the belief and expertise in ECMO.

Physiology and Technical considerations.

Cardiac arrest can be considered in different phases:

a) No flow phase: this is the time between a cardiac arrest and the initiation of CPR.
b) Low flow phase: this is the time interval between CPR start and the start of the ECPR. During this phase the generated CO is just 20-30% of the actual CO.
c) Return of extracorporeal circulation (ROEC). This is the time at which ECPR is initiated. ROEC is associated with complete circulatory support and tissue oxygen delivery. CPR should be discontinued only when then ECMO flows are above 3L/min and chest compressions can be abandoned even when there are no significant myocardial contractions.

Normally VA-ECMO is used during CPR. It involves removal of blood from a large vein, passage through a membrane lung for CO removal and oxygenation, and a centrifugal pump generating pressure to return blood via a large arterial cannula to the body. Cannulation site varies with the condition. In post–cardiac surgical patients, reopening the chest allows establishment of central ECMO, with venous drainage cannula in the right atrium and arterial return to the aorta. In non-cardiac surgical cardiac arrest, peripheral percutaneous cannulation via the femoral vein and artery is preferred due to shorter time and lower bleeding and infection rates. Arterial cannulae are usually 15–19 Fr and venous cannulae 21–27 Fr; the arterial tip lies in the common iliac artery and the venous tip in the superior vena cava.

The large arterial cannula may occupy most of the arterial lumen, leading to limb ischemia. Ultrasound-guided distal arterial cannulation is now practiced to reduce this complication, with a distal perfusion cannula supplied from a side port of the arterial inflow cannula. The inflow blood should deliver oxygenated blood to the brain and coronary arteries.

Modifications of ACLS during Cannulation.

The team leader should oversee ECMO cannulation and ensure proper conventional CPR (CCPR).(4) ECPR is only an adjunct to high-quality CPR and not a replacement. Extreme caution is required during defibrillation, especially after guidewire insertion, due to risk of electrocution to personnel; further shocks may be deferred until cannulation is complete, with rhythm checks as advised by the team leader. Achieving ROSC is useful as it provides more time for cannulation. ETCO and tissue oxygen saturation (near-infrared spectroscopy, NIRS) may help identify return of spontaneous rhythm. Adrenaline should be given as per protocol, but withheld when ECMO flow is imminent due to risk of severe hypertension. Interruptions in chest compressions should be minimal and may be stopped once ECMO flow exceeds 3 L/min. Patients are more responsive to defibrillation after ECMO flow is established and coronary oxygenation improves.

Purpose of ECPR.
The purpose of placing a patient on ECPR is:
a) Bridge to recovery: ECPR borrows time for identification of and correction of factors that are amenable to treatment. This may be important in patients with severe arrhythmias, acute coronary syndromes and cardiogenic shock where treatable causes are managed before weaning from ECMO

b) Bridge to organ transplantation: If patients cannot be weaned from ECMO, alternative end points like heart transplantation, use of left ventricular assist device can be considered

c) Bridge to decision: This includes patients where during ECPR neurological injury is severe and decisions have to be made whether to terminate ECMO or shift to palliative care, consider organ donation for other patients as most organs are well perfused and maintained on ECPR. (5)
Understanding outcome in ECPR.

Understanding outcome in ECPR

Survival alone is not an adequate endpoint in ECPR; survival with good neurological outcome is primary, assessed by Cerebral Performance Category (CPC 1–2) or modified Rankin Score (mRS 0–3). Long-term functional outcomes and quality of life are also important, as recommended by the International Liaison Committee on Resuscitation.(6)

The benefits of ECPR over CCPR must be weighed against its risks and high resource use. Although overall survival with good neurological outcome after cardiac arrest is low, even small improvements are valuable. However, it remains important to consider whether investing in public education for bystander CPR may yield greater overall benefit.

Outcomes after IHCA.

There are no major RCTs that looked at IHCA with or without ECPR. In a large study of 135 patients with IHCA and no ROSC within 10 minutes, who were managed with ECPR, the overall successful weaning was 58% with survival to discharge rate of 34.1%. (7) 89% of the survivors had good neurological outcome. Logistic regression analysis showed that survival chances were 50%, 30% and 10% when the CPR duration was 30, 60 or 90 minutes respectively.

The same authors in an attempt to compare potential benefits of ECPR over CCPR did a propensity-based analysis of patients who underwent CCPR lasting more than 10 minutes(8) Overall survival to discharge was 23.1% in the ECPR group and 10.6% in the CCPR group. Among the 46 propensity matched pairs, survival to discharge was significantly better in the ECPR group (HR 0.51, p=<0.0001), which continued for one year. However, a higher portion of patients in the ECPR group underwent percutaneous coronary intervention that could have contributed to a bias.

The RESCUE-IHCA study looked at 1075 patients who underwent ECPR and generated a mortality prediction score. (9) Age, time of the day, initial rhythm, history of renal insufficiency, patient type (cardiac versus non cardiac and medical versus surgical) and duration of cardiac arrest had good discrimination and acceptable calibration for identifying patient's outcome.

Outcomes after OHCA.

Studies have shown that outcome after OHCA is consistently poorer than after IHCA. The largest study till date is by Bougouin et al where he compared 525 patients receiving either ECPR or CCPR. (10) The overall survival to discharge was 8% in ECPR group as compared to 9% in the CCPR group. This was inspite of the fact that the ECPR group had younger patients, received bystander CPR and had initial shockable rhythm. Interestingly, prehospital implementation of ECPR was associated with better outcome. The other factors associated with survival included an initial shockable rhythm and transient ROSC before ECMO. Although prehospital ECMO may raise optimism, the real world issues of instituting ECMO in unfamiliar settings have to be of great concern.

The ARREST trial was stopped at the first interim analysis by the data monitoring board after only 30 patients were recruited due to the posterior probability of superiority of ECPR. (11) In this single center study, the survival to discharge was 7% in the CCPR group as compared to 43% in the ECPR group. Although many patients in the ECPR could not walk at the time of discharge, at 6 months all survivors had good functional recovery. More organ failures were noted in the ECMO group.

In another highly complex and sophisticated single center study where suitable patients were identified early (cardiac arrest of cardiac etiology, immediate bystander CPR, short low flow time) following OHCA, selected patents were transported to an ECMO capable hospital on mechanical chest compressions. (12) The CCPR group received on site chest compressions. The primary outcome which was good neurological outcome at 180 days was 31.5% in the ECPR group and 22% in the CCPR group (p= 0.09) The difference did not reach statistical significance. Neurological recovery was again better at 30 days in the ECPR group (30.6% as compared to the CCPR group (18.6%)(p=0.02). Overall CPR time was longer in the ECPR group and targeted temperature management was more frequently used in the ECPR group. This study was again stopped at the request of the data and safety monitoring board when prespecified futility criteria were met. The authors concluded that the study was probably underpowered to meet a clinically relevant difference.

In another multi-center, randomized controlled trial from Netherlands, 160 patients with OHCA received either CCPR or were shifted to hospital for ECPR. (13) ECPR was instituted if patients had no ROSC within 15 minutes of arrest. The survival to hospital discharge with good neurological outcome occurred in 20% of patients with ECPR as compared to 16% in the CCPR group (p=0.52)

A moratorium on ECPR in OHCA was called by MacLaren et al in 2020. (14) The availability of immediate bystander, witnessed cardiac arrest, immediate institution of CPR, high quality CPR, decision for ECPR in case of sustained cardiac arrest, availability of immediate resources to either implement ECPR or transport patients to nearest hospital, the traffic in the city, availability of expert personnel to cannulate and start ECPR all prompted the authors from moving away from ECPR.

The answer to this was provided by a recent meta-analysis and trial sequential analysis of 14 studies which included both OHCA and IHCA. (15) The studies included the major ARREST, PRAGUE OHCA and the INCEPTION trials and included about 14,000 patients. The primary outcome of the meta-analysis was in hospital mortality with secondary outcome targeting neurological recovery at 30 days and 1 year. Overall, the meta-analysis showed that ECPR was associated with a reduction in in-hospital mortality (OR 0.63). The study for the first time revealed a reduction in mortality for OHCA (OR 0.67). ECPR was associated with a favorable neurological outcome at short term follow up and at 30 days. The long term outcome remained unchanged.

Patient specific factors associated with ECPR outcomes.

a) Age < 70 years
b) Witnessed arrest
c) Arrest to CPR time (no flow time) < 5 minutes
d) Initial cardiac rhythm: ventricular fibrillation (VF) or ventricular tachycardia (VT)
e) Arrest to ECMO initiation time (low flow time) < 60 minutes
f) ETCO2 during CCPR > 10 mmHg before initiation of ECPR
g) Intermittent ROSC or recurrent VF
h) Signs of life during CCPR may be a positive indicator of survival
i) Absence of significant comorbidities before cardiac arrest including severe congestive heart failure, obstructive pulmonary disease, end stage liver or renal failure.
j) No known aortic valve incompetence. (4)

Recent changes in AHA guidelines for ECPR.

The 2019 AHA guidelines suggested that "there is insufficient evidence to recommend the routine use of ECPR for cardiac arrest" and that it may be considered "*as rescue therapy in patients when conventional CPR is failing in settings in which it can be expeditiously implemented and supported by skilled providers*" (Class 11b, LOE: C-LD). (16)

The 2024 modification of the guidelines mentions that "*use of ECPR for patients with cardiac arrest refractory to standard ACLS is reasonable in select patients when provided within an appropriately trained and equipped system of care*". The recommendation has been changed to 2a with LOE B-R. This decision was influenced by the ARREST trial and the PRAGUE-OHCA trial. (11,12).

Patient specific factors associated with ECPR outcomes.

Timing of initiation.

ECPR should be considered as complementary to high quality CCPR given the association between bystander CPR and outcome. Most high-volume centers make a decision regarding ECPR within 10-20 minutes (6, 4). This is based on the finding that refractory arrest lasting more than 20 minutes is associated with a survival rate <5%. Too early cannulation for ECPR may result in a highly invasive procedure for a patient who could have responded to CCPR. Too late a decision may result in ischemia-reperfusion injury affecting the brain and other organ systems.

One of the basics principles in ECPR is to reduce the low flow times. Although the final decision regarding cannulation for ECPR may be taken in 10-20 minutes, the arrival of the ECMO team and the actual establishment of ECMO may take its time. Hence, it is advised that once a candidate is suitable for ECPR, the information to arrive at the site should be taken within the first 10 minutes. In patients with OHCA, either a "stay and play" principle or "scoop and run" policy should be adapted. Stay and play policies are unlikely to be useful in patients suitable for ECPR due to the difficulties associated with implementation of ECMO at unfamiliar places. High quality CPR using mechanical chest compression devices may be useful during transit. Early communication with the ECMO hospital should be established so that the ECMO team is ready on arrival. The recently published EROCA trail, a pilot study where EMS call to patient arrival in 30 minutes and EMS arrival to ECPR initiation of < 30 minutes could not achieve the targeted time in 80% of the cases for each of these objectives. (18) This study highlights the challenges in limiting low flow times.

In short for OHCA, the decision for ECPR should be taken within 10-20 minutes, time from OHCA to arrival at hospital should be < 30 minutes and arrival time to ECPR should be < 30 minutes.

Resource availability and system design.

ECPR programs require substantial investment, including a readily available primed sterile circuit (though most teams can prime within 15 minutes), a skilled cannulation and management team, and trained nursing staff.

ECPR can be initiated anywhere in the hospital, but this may require mobilizing resources; hence, designated areas such as the emergency department, cardiac catheterization lab, ICU, or operating room are easier to manage. The key is to minimize low-flow time and establish ROEC as early as possible.

For OHCA, effective ECPR systems require continuous communication between EMS and the ECMO center so the team is ready on patient arrival. A "hub and spoke model" may be used, where ROEC is established at the referral center and the patient is then transferred to a hub for ongoing ECMO management.

Post ROEC care of patient.

One of the most important issues is the post resuscitation care of the ECPR patient. Once flows are increased to > 3L per minute CCPR can be discontinued. ROEC is associated with significantly better coronary oxygen delivery and the patient becomes more susceptible to defibrillation attempts. If there is persistent VF after establishing ROEC, one or two attempts at defibrillation may be attempted. Persistent VF may be a sign of coronary occlusion, and the patient may need care in the cardiac laboratory.

Immediate post ROEC care includes the following:

a) Acute coronary occlusion accounts for the majority of the patients who develop cardiac arrest especially in the community. If an emergency ECG shows any evidence of coronary involvement, patients should have immediate access to the coronary angiography suite. An ECG immediately after ROEC may be difficult to interpret due to the global ischemia and the metabolic changes. If the initial ECG shows signs of ST elevation or regional changes suggestive of ischemia, the patients should be shifted immediately to the angiography suite. If the initial ECG shows no ST changes, a repeat ECG should be taken after 10-15 minutes to confirm. The cardiac angiography suite is also useful for assessment of pulmonary embolism. Percutaneous intervention even in the absence of ST elevation has been shown to have a beneficial effect on the duration of ECMO, neurological outcome and mortality (19)

b) As the femoral cannula will occupy most of the circumference of the femoral artery, distal limb ischemia is inevitable in patients on peripheral cannulation. A distal perfusion cannula should be placed within 4 hours of surgery. This may be perfused using the side arm of the aortic inflow cannula.

c) Targeted temperature management (TTM) is advocated after ROEC. The AHA Update in 2023 states that all patients who do not respond to verbal commands after ROSC irrespective of the location of arrest or presenting rhythm should have some form of TTM. However, there is no definition of what is meant by TTM although AHA updated guidelines suggest that the lowest temperature should be 32^0C. Although there are multiple studies that show TTM to be without benefit, the study by Lascarrou et al where 581 post cardiac arrest patients were randomized to either a TTM of 33^0C or 37^0C, showed significant benefit with the lower temperature (10.2% vs 5.7%).(20) While lower temperatures are associated with electrolyte imbalances, arrhythmias, coagulopathies and an increased incidence of ventilator associated pneumonia, it is protective for neuronal survival. Hyperthermia (> 37^{0}C) should be avoided as it leads to significant neuronal damage and cerebral injury.

d) Reperfusion injury to the brain and myocardium can occur when the patients are established on full ECMO flow. The perfusionist should gradually increase the ECMO flows to avoid these complications. The target MAP should be about 60 mmHg and below 80 mmHg.(4) The ventilation should be adjusted to ensure protective lung ventilation strategies with tidal volumes of 4-6 ml.kg, PEEP of 10 cmH2O, drive pressure of < 15 cmH2O and rates between 8-15 per minute. The oxygen delivered (FdO2) should be gradually increased to avoid reperfusion injury and PaO2 maintained between 100-150 mmHg. Sudden increase or decrease in PaCO2 are associated with neurological injury. The PaCO2 should be maintained > 30 mmHg. As the lungs gradually improve more work may be transferred to the lungs.

e) The centrifugal pump generates adequate pressure to drive the retrograde flow of blood into the ascending aorta. This results in oxygenated blood being delivered to the brain. In conditions when the lungs are bad and the left ventricular (LV) contractility is good, deoxygenated blood from the lungs will be pumped out of the LV and this can result in poorly oxygenated blood perfusing the brain. This can be diagnosed by sampling from the right radial arterial line which is a must in patients with peripheral ECMO.

f) An echocardiogram will reveal biventricular function, pericardial effusion, organized ventricular activity, and movement of the aortic valves. A POCUS gives additional information about pleural effusions and lungs status, position of the distal tip of the venous drainage cannula and free fluid in the abdominal cavity.

g) ECPR involves exposure to continuous anticoagulation, the chances of intracranial bleed in post ECPR patients on ECMO are higher than in other patients on ECMO.(5) The exact reason is not known. In suspected cases neuroimaging with CT scan may be required along with transcranial Doppler.

Ethical considerations

ECPR may increase the number of patients on ECMO without meaningful recovery (“bridge to nowhere”), though some may proceed to destination therapies such as left ventricular assist device or heart transplant. Others, with or without intact neurology, may remain ICU-bound without prospects of discharge.

If ECPR is viewed as an extension of CPR, clinicians may unilaterally terminate ECMO in futile cases; if seen as part of a transplant pathway, full life-sustaining support should continue until transplantation. There is currently no consensus.

As CCPR and ECPR become more common, ECPR discussions should be included in future conversations with relatives, especially in equipped centers.

Another area of controversy with ECPR is organ donation. ECPR is associated with an increased number of patients with brain death. In a meta analysis of 26 studies, Sandroni et al showed that the number of patients who were brain dead was significantly more after ECPR (27.9% vs 8.3%). (21) However, there was no significant difference in the rate of organ donation between CPR and ECPR. This potential for brain dead donors has serious implications in terms of initiation and withdrawal of ECPR. Although organ donation should never be the primary objective of ECPR, nonetheless ECPR may increase the number of donations in controlled circumstances.

ECPR in India.

Gulla et al in a survey showed that out of 63 respondents to a clinical questionnaire only 6 respondents had any experience with ECPR.(22)

Most of the respondents were intensivists. The most common indication for ECPR was failure of CCPR for more than 10 minutes and the decision to go on ECPR was taken by the intensivist. All ECPRs were done in private sectors. The first successful OHCA ECPR was done at Aster Medcity. (23) there are a number of issues related to widespread use of ECPR in India.

a) Lack of awareness about bystander CPR and ECPR. If the resources that can be used for developing a ECPR program can be utilized from training bystander CPR, the benefit in terms of successful resuscitation from cardiac arrest itself can be hugely different.

b) Financial issues: Most government hospitals do not have the resources to start a ECPR program. Most ECPRs so far has taken place at private and corporate hospitals who have the resources and the expertise to do such cases. The expenditure required for setting up such a system is too high and may not be profitable even at tertiary care centres

c) EMS system. ECPR needs a complete team involving the EMS and a full set of experts for cannulation, perfusion and nursing. EMS system has to be on par with similar systems that work in countries like Spain & France. Moreover, the traffic jams with narrow roads seen in most Indian cities will not make this a reality in India.

d) Poor quality of CPR. In most cases that can be converted into ECPR cases , the quality of bystander CPR may be so poor that it may end up in "bridge to nowhere" situation.

e) Cost constraints. As mentioned earlier, private hospitals can have the resources, but the vast majority of patients may not have the financial ability to generate such finances

f) Lack of clear guidelines. There are no clear guidelines for ECPR in India

g) Legal and ethical issues. There are numerous h) legal and ethical issues surrounding organ donation following ECPR. Moreover, the social media may take this in the wrong sense and criminalize the issue and concerned people

i) Inability to get informed consent from relatives. There are no state guidelines for ECPR. In an emergency the relatives may not be available, and the doctors may not be able to take a proper decision.

Summary

The awareness of ECMO and ECPR is gradually improving among the medical community in India. With the H1N1 pandemic followed by the Covid terror, a large number of centers in India have acquired the knowledge and skills to perform ECMO. Thousands of lives have been saved during this period.

ECPR should be an extension to efficient, high-quality CPR. Tertiary care centers have the capability and the resources to start using ECPR as extended CPR. Now, we are still in infancy and will take a few more years to doing more cases. Indian registry for ECPR would be a useful adjunct to this.

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