Outcomes of Veno-Arterial Extracorporeal Membrane Oxygenation for In-Hospital Cardiac Arrest

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Running Head: VA ECMO for In-Hospital Cardiac Arrest

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ABSTRACT

Veno-arterial extracorporeal membrane oxygenation (VA ECMO) is increasingly used in cardiac arrest. Currently, public registries report the outcomes of cardiac arrest regardless of the setting (out-of-hospital versus in-hospital). Meanwhile, in-hospital cardiac arrest represents a more favorable setting for ECMO-assisted cardiopulmonary resuscitation than out-of-hospital cardiac arrest. Survival to discharge varies, but looks promising overall, ranging from 18.9 to 65%, with the bulk of the studies reporting survival to discharge between 30% and 50%, with about one-third to half of the patients discharged with no or minimal neurologic deficit. Based on the reported outcomes, in-hospital cardiac arrests can become a next focus for studies on successful implementation of VA ECMO.

Key words: veno-arterial extracorporeal membrane oxygenation; VA ECMO; in-hospital cardiac arrests; ECPR; extracorporeal cardiopulmonary resuscitation
Veno-arterial extracorporeal membrane oxygenation (VA ECMO) is a life-saving technology. Effectively replacing both heart and lungs, it can stabilize patients for hours, days, and sometimes weeks, until the underlying process is reversed or controlled, or until other more durable technologies are applied. One of the indications for VA ECMO is cardiac arrest. VA ECMO initiated during active cardiopulmonary resuscitation (CPR) is known as extracorporeal CPR (ECPR). ECMO can be implanted within 10–15 minutes by a surgeon, interventional cardiologist, critical care specialist, or emergency room physician, while the patient is undergoing resuscitation. While cardiac arrest is considered a no-flow state, conventional CPR creates a low-flow state, and ECPR provides normal blood flow of 4-6 L/min.

The Extracorporeal Life Support Organization (ELSO) collects the data on outcomes of adult ECPR. The extracted data from three time intervals (2003-2006, 2007-2010, and 2011-2014) demonstrated a more than 10-fold increase in annual ECPR episodes, from 35 to over 400 per year. At the same time, overall survival was 29%, with no improvement from 2003 to 2014 (27%, 28%, and 30%, respectively).  

In the 2019 update of the American Heart Association (AHA) guidelines on resuscitation, ECMO is given a limited role. The guidelines state that “there is insufficient evidence to recommend the routine use of ECPR for patients with cardiac arrest. The use of ECPR can be considered in select patients as rescue therapy when conventional CPR efforts are failing, in settings where it can be expeditiously implemented and supported by skilled providers (Class IIb, Level of evidence C-LD). Given the resources, structure, and effort going into timely deployment of the ECMO team, and the very limited time window when ECMO can make a difference, this recommendation sounds wise and prudent.
However, neither data reported by ELSO nor the guidelines given by the AHA differentiate outcomes and recommendations for out-of-hospital and in-hospital cardiac arrest. Meanwhile, the potential of ECMO in these two settings is very different. Specifically, the following characteristics are typical for in-hospital but not for out-of-hospital cardiac arrest:

- Cardiac arrest is almost always witnessed
- Continuous electrocardiographic monitoring of many patients, especially those with cardiac conditions
- Providers trained in CRP are readily available
- Defibrillators and medications for advanced cardiac life support are readily available
- Code status is documented
- Catheterization laboratory and operating room are in proximity
- Specialists capable of initiating ECMO are available
- Decision about indications for ECMO can be quickly made after reviewing the records and speaking with the providers responsible for care of the patient.

In-hospital arrests, therefore, provide a much better setting for utilization of ECPR with a greater survival potential.

This review was written with the objective to assess the current outcomes of VA ECMO specifically for in-hospital cardiac arrest.

METHODS

We searched articles published in English on Pubmed, Google Scholar, and Cochrane database using terms “ECLS” or “Extracorporeal life support” or “Extracorporeal Membrane Oxygenation” or “ECMO” or “Extracorporeal Cardiopulmonary Resuscitation” or “Venoarterial ECMO” or “E-CPR” or “eCPR” AND “in-hospital cardiac arrest” or “cardiac arrest” as either
keywords or “MeSH terms.” We also manually searched the references of relevant articles. Although we did not limit the search to adult populations, papers about pediatric patient population were not selected for this review.

DETERMINANTS OF OUTCOMES IN CARDIAC ARREST

In any cardiac arrest, initial shockable rhythm favors survival, pulseless electrical activity (PEA) is worse, and asystole leaves little hope. In a study of over 50,000 cardiac arrests, the distribution of initial rhythm was as follows: ventricular tachycardia/ventricular fibrillation (VT/VF) -24%, PEA - 37%, and asystole -39%, with survival rates 37%, 12%, and 11%, respectively. Paradoxically, when VT/VF occurs in the course of CPR with initial PEA (27%) or asystole (25%), it decreases the chances for survival (14% vs. 7% for PEA without vs. with subsequent VT/VF; 12% vs. 8% for asystole without vs. with subsequent VT/VF). Other factors favoring survival include younger age and fewer comorbidities.

Another critical predictor of outcome is the duration of CPR until the return of spontaneous circulation (ROSC). The ROSC rate was 2.24 times better in the CPR of in-hospital cardiac arrest patients than in the CPR of out-of-hospital cardiac arrest (p=0.0012). For every 1-minute increase in the CPR duration, the ROSC rate decreased by 1% (p=0.0228), and the rate of survival to discharge decreased by 4%. Per “Get with the Guidelines-Resuscitation” registry in 64,339 patients with cardiac arrests, 48.5% achieved ROSC and 15.4% survived to discharge. For patients achieving ROSC, the median duration of resuscitation was 12 min (interquartile ratio 6-21) compared with 20 min (14-30) for non-survivors.
SURVIVAL IN OUT-OF-HOSPITAL CARDIAC ARREST VERSUS IN-HOSPITAL CARDIAC ARREST WITHOUT ECPR

Survival in out-of-hospital cardiac arrest is poor. Even with the wide use of automated external defibrillators and the vast network of courses, classes, and other educational endeavors targeting both medical professionals and the general public, with the aim to increase awareness and skill to perform a timely and good-quality CPR, most victims of out-of-hospital cardiac arrest die. For decades, survival stayed at about 4-5%. Per recent data, covering only cardiac arrests where emergency medical services were deployed, survival occurred in 11.3%, with a favorable functional outcome in 7.3%.

By other data, survival increased from 8.2% in 2006 to 10.4% in 2010.

More progress has been achieved for in-hospital cardiac arrest. The availability of professionally-trained staff on a 24/7 basis, crash carts on the floors and in the unit, readily available rapid response teams, shorter distances, continuous monitoring all favor survival of the victims of in-hospital cardiac arrest versus out-of-hospital cardiac arrest. The CPR of in-hospital cardiac arrest patients showed a 2.49 times higher survival to discharge rate than the CPR in out-of-hospital cardiac arrest patients (per results reported in South Korean population) (p=0.03).

In the National Registry of Cardiopulmonary Resuscitation, 73% of patients suffering in-hospital cardiac arrest were witnessed and monitored; 10% were monitored but not witnessed; 9% were witnessed but not monitored; and only 8% were neither witnessed nor monitored. Compared with those who were unmonitored/unwitnessed, each of the three groups of patients who were monitored and/or witnessed were more than twice as likely to survive to hospital discharge with a cerebral performance category of 1 or 2 (monitored/witnessed odds ratio [OR]
The estimated incidence of in-hospital cardiac arrest is one to six per 1000 admissions and survival to discharge ranges 15% -40%.

There has been a slow progress in outcomes of in-hospital cardiac arrests. In 1995-2004, only 6.6% victims survived to discharge (i.e. the outcomes did not differ from out-of-hospital cardiac arrest). In 2000-2009, the overall rate of survival to discharge was 17.0%, improving from 13.7% to 22.3% over time.

In 2017, survival to hospital discharge was 25% in the Get With The Guidelines registry. Among patients alive at hospital discharge, 85% were discharged with a favorable neurological outcome (cerebral performance category 1 or 2). These data create some background for assessing the utilization of ECMO for in-hospital cardiac arrest.

**OUTCOMES IN ECPR VERSUS CONVENTIONAL CPR**

Many studies, both prospective and retrospective, demonstrated superiority of ECPR over conventional CPR in terms of survival and neurological outcomes. However, the data are quite heterogeneous.

In a meta-analysis of the studies comparing ECPR with conventional CPR, there was no benefit of ECPR for survival to hospital discharge in out-of-hospital cardiac arrest. For all arrests (in-and out-of-hospital), neurological outcomes and long-term survival were better on ECMO.

The relative risk for survival to discharge with good neurological outcome on ECPR was 8.00, 95% CI 1.04–61.71 for out-of-hospital cardiac arrest and 2.72, 95% CI 1.21–6.13 for in-hospital cardiac arrest. In this study, the most favorable comparison was obtained at 3-6 months, however, after one year, the results became similar.
Improving circulation and oxygenation, ECPR may enhance cerebral blood flow and recovery of neurological function. Preservation of neurologic function was observed in 12.3% of patients in the ECPR group versus 1.5% in the conventional CPR group at 1 month (P<0.0001), and 11.2% vs 2.6% at 6 months (P=0.001), respectively. Neurological outcomes were positively affected by higher hemoglobin and lower lactic acid levels before ECMO (P = 0.02 and P < 0.001, respectively), as well as by a shorter time from cardiac arrest until ECMO insertion (P = 0.04).\textsuperscript{18}

After reporting crude results, several studies did a propensity matching of patients who did and did not receive ECLS during CPR for out-of-hospital cardiac arrest. In the matched cohorts, the discharge rate with minimal neurologic impairment in the ECPR group was significantly higher than that in the conventional CPR group (OR of mortality or significant neurologic deficit, 0.17; 95% CI, 0.04-0.68; p = 0.012). The difference persisted for six months after discharge.\textsuperscript{19} In the subgroup with cardiac origin of the arrest, ECPR also yielded better survival to discharge and up to 2-year survival with minimal neurologic impairment. Independent predictors of good neurological outcome were age ≤65 years (hazard ratio (HR) 0.46; 95% CI=0.26-0.81; p=0.008), CPR duration ≤35 min (HR=0.37; 95% CI=0.18-0.76; p=0.007), and subsequent cardiovascular intervention including coronary intervention or cardiac surgery (HR=0.36; 95% CI=0.18-0.68; p=0.002).\textsuperscript{20} In another propensity-matched cohort, survival at three months after in-hospital cardiac arrest was 29.2% in the group treated with ECPR compared with 8.3% in the conventional CPR group.\textsuperscript{19} Detailed data on survival at different follow-up time points demonstrated a cumulative survival rate in the ECMO group of 93.2% (at 24 h), 76.3% (3 days), 44.1% (14 days), 33.9% (30 days), 28.8% (6 months), and 18.6% (1 year). In the conventional group, corresponding outcomes were 38.1%, 31.0%, 21.2%, and
15.0%, 11.5% and 9.7%. Overall survival to discharge was 28.8% of ECPR patients and only 12.3% in the conventional CPR group. In another propensity-matched study, patients who eventually received ECPR had significantly higher APACHE II scores (p=0.03), increased norepinephrine dosages (p=0.03) and elevated levels of creatine kinase (p<0.0001), creatinine (p=0.04) and lactate (p=0.02) before CPR compared with those undergoing conventional CPR. After adjusting for these parameters, ECPR compared favorably with conventional CPR in terms of a 30-day survival (27% vs. 17%; p=0.01) and long-term survival (23.1% vs. 11.5%; p=0.008), with no significant difference in neurologic outcomes.

A trend towards the advantage of ECPR was seen in a subset of patients who experienced in-hospital cardiac arrest due to acute myocardial infarction. The survival rate was 34.9% for patients who received ECPR and 21.8% for those who received conventional CPR (p=0.4). Increased survival rates to hospital discharge were seen in patients with ST segment elevation (p<0.01), or had initial rhythm of ventricular tachycardia/ventricular fibrillation (VT/VF) during resuscitation (p=0.031).

EXTRACORPOREAL LIFE SUPPORT IN CARDIAC ARREST: WHAT DETERMINES THE OUTCOME?

The duration of conventional CPR is an important factor affecting outcomes of ECPR [13]. In the setting of out-of-hospital cardiac arrest, door-to-ECLS implantation time was significantly longer in non-survivors than in survivors [42.5 min (interquartile [IQR] 28.0-56.5) vs. 25.0 min (IQR 21.0-30.0), respectively, p < 0.01]. This factor was the only significant and independent predictor of 30-day mortality.
In fact, the time from the onset of CPR to beginning of ECLS is critical. There is a significant, negative, linear correlation between time to ECPR and survival (r=-0.266, p<0.001). By the data of Haneya et al., an interval of less than 15 minutes from CPR to ECLS resulted in a 70% chance of survival to discharge. This survival dropped to about 50% with time to ECLS 15-30 minutes, 27% for 30-45 minutes, and 11% for 45 to 60 minutes. Wengemayer et al. demonstrated a survival rate of 67% in CPR duration shorter than 2 minutes, and 29%, 10%, and 6% after 20-45, 45-60, and over 60 minutes, respectively. In both studies, patients with both in-and out-of-hospital cardiac arrest were included.

Not surprisingly, the duration of CPR until ECMO support was usually longer for out-of-hospital arrests compared to in-hospital arrests: 49.6 ± 5.9 vs. 72.2 ± 7.4 minutes, respectively, p = 0.001). Low-flow time strongly correlated with survival (p < 0.001) and was an independent predictor of mortality.

It is clear that the chances for success increase if ECPR is used in younger patients with shockable rhythm and short previous CPR-time. Because there are no guidelines, each ECMO program makes internal rules.

An unwitnessed arrest, lack of quality CPR within 5 minutes of the arrest, and asystole as an initial rhythm almost always excluded patients from consideration of ECPR. Also, patients are typically considered not to be an ECPR candidates if they have terminal malignancy, irreversible brain damage, liver cirrhosis, coagulation disorders/contraindications for systemic anticoagulation, multi-organ failure, “do not resuscitate” status, or if they are in end stage cardiomyopathy and do not have the prospect of receiving a heart transplantation or a durable left ventricular assist device. The presence of aortic dissection and severe peripheral artery disease, preventing cannulation, are considered a contraindication for
ECMO. Most authors favor early initiation of ECPR, with 10 minutes of conventional CPR without ROSC being the most commonly cited decision point.²⁵⁻²⁷

Age threshold for ECPR varies among programs: 80,⁵ 75,²⁸ 65,²⁹ or is not set at all.²⁵

Although the chances for survival exist even with prolonged CPR, the decision to initiate ECMO support should be made as early as possible in the course of resuscitation efforts.

ECLS is a process consisting of several steps. To place a coding patient on VA ECMO support, the following must be accomplished:

Activation of the ECLS team; bringing the equipment; sterile insertion of large bore peripheral arterial and venous catheters (in a pulseless patient, with chest compressions ongoing); starting the circuit. These steps require time, and all specialists and equipment should be available immediately-in house.

The importance of proper staffing is underscored by the study by Lee et al³⁰ who found that ECPR occurring on weekdays results in better survival than weekend cases (35.8% versus 21.5%, p = 0.041). After adjustment for age and sex, the difference persisted, with odds of survival to discharge being higher for patients who underwent ECPR on weekdays [OR 2.11, 95% CI: 1.05 to 4.24, p =0.036). Cannulation failure was also more frequent in the weekend group (1.5% versus 7.7%, p = 0.038), as well as other complications such as cannulation site bleeding (3.0% versus 10.8%, p = 0.041), limb ischemia (5.9% versus 15.6%, p = 0.026), and procedure-related infections (0.7% versus 9.2%, p = 0.005).

Several simple factors should be taken into consideration in the process of decision-making. Most authors used the following inclusion and exclusion criteria:¹²⁻¹⁴,¹⁹,²⁷,³¹

Inclusion Criteria: witnessed arrest; presumed cardiac origin; no ROSC during first 10-20 minutes of CPR; initial shockable rhythm.
Exclusion criteria: age > 75; known severe irreversible brain injury; known advanced malignancy or other terminal disease; traumatic origin of shock; uncontrolled bleeding; non-cardiac origin; poor level of activity before ECMO; Do Not Resuscitate status.

ECPR FOR IN-HOSPITAL CARDIAC ARREST: CURRENT OUTCOMES

Outcomes of patients who had ECPR for in-hospital cardiac arrest are summarized in Table 1.\textsuperscript{13-16,23,24,26,31-39} The outcomes are very promising, ranging from 18.9 to 65\%, with the bulk of the studies reporting survival to discharge between 30\% and 50\%, and about one-third to one-half of the patients discharged with no or minimal neurologic deficit. For evaluation of neurologic status, many centers used the Glasgow-Pittsburgh cerebral–performance categories (CPC) score: CPC 1 or 2: went home with good neurological outcome; CPC 3 or 4: went to a nursing home with poor neurological outcome; CPC 5: discharged on day of death. In the studies cited in the Table, scores 1 or 2 were considered good outcome, although there may be signs of moderate cerebral disability with score 2.

A systematic review of the studies on ECPR in cardiac arrest was done by Holmberg et al\textsuperscript{40} They demonstrated an overall positive effects of ECPR on immediate survival, long-term survival, and survival with a favorable neurologic outcome, with only one study showing positive results in all outcome categories.\textsuperscript{20} The authors also stated that the risk of bias in all the studies in their analysis was high due to confounding factors, that the quality of evidence was very low, and that there was inconclusive evidence to support or refute the use of ECMO in cardiac arrest.\textsuperscript{40}
Other authors suggest that ECMO can be beneficial for in-hospital cardiac arrest in selected patients, such as post cardiac surgery.\textsuperscript{41} Induced hypothermia has the potential of increasing survival and improving neurological outcomes post cardiac arrest\textsuperscript{42} and expanding the pool for ECPR.

These overall data indicate, from our standpoint, that in-hospital cardiac arrest should be a target for intense exploration in terms of applying the advanced technologies, including VA ECMO, to this potentially salvageable population.

**CONCLUSION**

In-hospital cardiac arrest represents a more favorable setting for ECPR than out-of-hospital cardiac arrest. With the lack of large-scale randomized studies, decisions on the use of ECPR for in-hospital cardiac arrest depend on published case series and non-randomized studies. Survival to discharge varies, but looks promising overall, ranging from 18.9 to 65%, with the bulk of the studies reporting survival to discharge between 30 and 50%, and about one-third to one-half of the patients discharged with no or minimal neurologic deficit. Agreement on patient selection criteria for ECPR of in-hospital cardiac arrest and conducting randomized studies appears to be next step in addressing survival in cardiac arrest. Overall, based on the reported outcomes, in-hospital cardiac arrests can become a next focus for studies of successful implementation of VA ECMO.
REFERENCES

1. Richardson AS, Schmidt M, Bailey M et al. ECMO Cardio-Pulmonary Resuscitation (ECPR), trends in survival from an international multicentre cohort study over 12-years. Resuscitation 2017;112:34-40.


### Table 1. Outcomes of Extracorporeal Cardiopulmonary Resuscitation for In-Hospital Cardiac Arrest

<table>
<thead>
<tr>
<th>Author, date, ref</th>
<th>N</th>
<th>Survival to Discharge N(%)</th>
<th>Time on ECMO (hours)</th>
<th>Mean CPR time (minutes)</th>
<th>Inclusion criteria</th>
<th>Good Neurological Outcomes by CPC 1-2 N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sung, 2006&lt;sup&gt;12&lt;/sup&gt;</td>
<td>22</td>
<td>9 (41)</td>
<td>39.4±52.6</td>
<td>43.3 ± 19.6</td>
<td>Good Neurological Outcomes by CPC 1 - 2 N (%): 9 (41)</td>
<td>9 (41)</td>
</tr>
<tr>
<td>Chen, 2008&lt;sup&gt;13&lt;/sup&gt;</td>
<td>59</td>
<td>17 (28.8)</td>
<td>110 ± 128</td>
<td>53 ± 37</td>
<td>Age &lt;75; Cardiac origin CPR &gt;10 min without sustained ROSC; witnessed arrest</td>
<td>14 (23.7)</td>
</tr>
<tr>
<td>Kagawa, 2010&lt;sup&gt;11&lt;/sup&gt;</td>
<td>38</td>
<td>13 (34) *</td>
<td>9 (5–62)</td>
<td>25 (21–43)</td>
<td>Age &lt;75; VF during CPR (not initial!); interval &lt; 15 min from the arrest to CPR; cardiac origin or pulmonary embolism; no ROSC within 20 min</td>
<td>10 (26)</td>
</tr>
<tr>
<td>Shin, 2011&lt;sup&gt;11&lt;/sup&gt;</td>
<td>85</td>
<td>29 (34.1)</td>
<td></td>
<td>42 ± 26</td>
<td>Age ≤80; witnessed; cardiac origin; no ROSC 10 minutes CPR</td>
<td>24 (28.2)</td>
</tr>
<tr>
<td>Avalli, 2012&lt;sup&gt;14&lt;/sup&gt;</td>
<td>24</td>
<td>11 (46)</td>
<td>5 (3–7) days</td>
<td>55 (40–70)</td>
<td>Age &lt;75</td>
<td>9 (38)</td>
</tr>
<tr>
<td>Lee, 2012&lt;sup&gt;15&lt;/sup&gt;</td>
<td>200</td>
<td>62 (31.0)</td>
<td>38 (20.5)</td>
<td>112.07 ± 154.50</td>
<td>No exclusions</td>
<td>No exclusions</td>
</tr>
<tr>
<td>Haneya, 2012&lt;sup&gt;14&lt;/sup&gt;</td>
<td>59</td>
<td>25 (42.4)</td>
<td>87± 81 (70; 26–120)</td>
<td>40 ± 28 (25; 20–50)</td>
<td>No exclusions</td>
<td>No exclusions</td>
</tr>
</tbody>
</table>

*Note: CPC = Cerebral Performance Category; ECMO = Extracorporeal Membrane Oxygenation; CPR = Cardiopulmonary Resuscitation; ROSC = Return of Spontaneous Circulation*
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Age (Range)</th>
<th>30-day Survival</th>
<th>Witnessed</th>
<th>30-Day Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bednarzyck, 2014</td>
<td>22</td>
<td>72.3 ± 45</td>
<td>48.8 ± 21</td>
<td>witnessed</td>
<td>10 (45%)</td>
</tr>
<tr>
<td>Park, 2014</td>
<td>152</td>
<td>67.5 ± 116</td>
<td>31 ± 17</td>
<td>witnessed</td>
<td></td>
</tr>
<tr>
<td>Wang, 2014</td>
<td>199</td>
<td>94 ± 122</td>
<td>44.4 ± 24.7</td>
<td>Age ≤80; witnessed</td>
<td>50 (25.1)</td>
</tr>
<tr>
<td>Peigh, 2015</td>
<td>23</td>
<td>6.2 ± 5.5 days</td>
<td>54 ± 30</td>
<td>Age ≤70</td>
<td>7 (30.5)</td>
</tr>
<tr>
<td>Stub, 2015</td>
<td>15</td>
<td>2 (1-5) days</td>
<td></td>
<td></td>
<td>9 (60)</td>
</tr>
<tr>
<td>Blumenstein, 2016</td>
<td>52</td>
<td>33(19-47)</td>
<td>witnessed</td>
<td>11 (78.6)</td>
<td></td>
</tr>
<tr>
<td>Dennis, 2016</td>
<td>25</td>
<td>17 (69)</td>
<td></td>
<td>No exclusions</td>
<td>13(52)</td>
</tr>
<tr>
<td>Wengenmeyer, 2017</td>
<td>74</td>
<td>49.8 ± 9.1</td>
<td>49.6</td>
<td>Age &lt;75; witnessed</td>
<td></td>
</tr>
<tr>
<td>Pabst, 2018</td>
<td>58</td>
<td>38.9 (±17.9)</td>
<td>No exclusions</td>
<td>17(29.3)</td>
<td></td>
</tr>
</tbody>
</table>

* 30-day survival

ECMO, extracorporeal membrane oxygenation; CPR, cardiopulmonary resuscitation;
CPC, cerebral performance categories; ROSC, restoration of spontaneous circulation; VF, ventricular fibrillation