Clinical Practice Committee Statement

ECMO in ED for Out of Hospital Cardiac Arrest

(4/23/2022)

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Executive Summary

Emergency departments (ED) and emergency medical services (EMS) are motivated to increase survival following sudden out of hospital cardiac arrest (OHCA).[1] Extracorporeal cardiopulmonary resuscitation (ECPR) has been promoted as an option but substantial uncertainty exists regarding how to select patients.[2] Recently, a single-center randomized controlled trial demonstrated increased survival with early extracorporeal membrane oxygenation (ECMO), compared to standard care.[3] Limited evidence demonstrates some emergency departments have successfully implemented ECPR.[4] The observational data is mixed. An overarching problem with existing data is the concept of competing risk. If OHCA patients are being moved to ECPR centers and this were to compromise the delivery of standard advanced cardiac life support measures to other patients, it is possible that ECPR strategies may decrease the survival of a population of OHCA patients. At this point in time, the existing evidence is not strong enough to recommend the use of ECPR for OHCA as a standard of care. Further research is needed, particularly on how the broader OHCA population would be affected.

Questions

In accordance with the AAEM template for structured clinical practice statements, we discussed the scope and plan for a literature review. Although ECMO has the potential to be applied to treat a range of conditions, such as refractory cardiogenic or pulmonary embolism-associated shock, we elected to focus on its use in refractory OHCA. Therefore, other indications for ED-based ECMO are not addressed in this statement.

Is ECMO more effective for refractory out of hospital cardiac arrest versus standard ACLS?

Although there have been some encouraging new studies, there is insufficient evidence to claim that ECPR is more effective than standard ACLS for OHCA at this time.

ECPR has been advanced as a method of increasing survival for OHCA.[5] Prior work has uniformly studied a highly-selected subset of this population, one with a short-downtime or witnessed cardiac arrest, shockable rhythm, younger age, and an absence of severe comorbidities. However, prior to the ARREST trial, the available literature consisted of observational and registry studies without randomization and frequently retrospective in nature.[3,6,7] The 2019 AHA Guidelines offer a weak recommendation for ECPR, stating, "ECPR may be considered for selected patients as rescue therapy when conventional CPR efforts are failing in settings in which it can be expeditiously implemented and supported by skilled providers,"[8] albeit acknowledging a high risk of bias and heterogeneity among existing studies.

The ARREST trial, the first randomized controlled trial based on the single center experience of the University of Minnesota, showed positive results for ECPR over conventional cardiopulmonary resuscitation (CCPR) among 30 patients. Enrollment criteria included an initial shockable rhythm, no return of spontaneous circulation (ROSC) after three shocks and transfer time of less than 30 minutes. 6/14 in the ECPR group survived to hospital discharge vs 1/15 in the CCPR group (one patient withdrew from the study).

The results of the ARREST trial lead us to question whether ECPR should become the new standard of care for refractory cardiac arrest in suitable candidates where it is available. However, the number of participants in the study was small and the trial was stopped early. Accordingly, the confidence intervals for ECPR vs CCPR survival to hospital discharge intersect each other (43%, 21.3-67.7% compared with 7%, 1.6–30.2%, respectively), so meaningful uncertainty remains about its true efficacy.

Further, the protocol involved coordination with interventional cardiologists that immediately took the patients in the ECPR group to the catheterization laboratory upon hospital arrival, regardless of the presence of ROSC, in order to initiate ECMO and revascularize occluded coronary arteries. The presence of ROSC at any point after 3 shocks had been administered was not an exclusion criteria for the study. This could potentially have skewed results in favor of ECPR, since patients that had achieved ROSC without ECMO likely would not receive coronary angiography as expeditiously as such patients in the ECMO treatment arm.

Other observational studies utilizing an assortment of systems for administration of ECPR have reported varying results. Hsu et al in a single center study of 30 patients from the University of Michigan, reported 0% survival in the 5/15 patients that received ECPR.[9] Bourgoin et al, showed better survival with ECPR with refractory shockable rhythms, based on a Parisian OHCA registry.[10] Lamhaut et al, also reporting on a Parisian registry utilizing mobile intensive care units showed higher survival with ECPR once stringent patient selection criteria and an aggressive (ECPR if > 20 minutes without ROSC) protocol were instituted.[11] Alm-Kruse et al, in another registry study from Oslo, demonstrated no improvement with ECPR, and possibly harm, although not statistically significant, despite selecting for patients with shockable rhythms, younger age, and shorter CPR times.[12]

A prospective observational study investigating the natural history of conventional resuscitation among theoretically ECMO-eligible patients may be helpful in setting a benchmark for assessing the effectiveness of ECPR programs.[13] 11% of 1237 patients were eligible for the cohort and 38% survived to hospital discharge, 30% with a good neurologic outcome. Such numbers are better than the commonly reported 14-31% range for survival in OHCA due to VF/VT and suggest a standard against which to compare outcomes from ECPR trials.[14,15,16]

As stated by some of the authors of the above papers, instituting an effective ECPR program requires the reorganization of the local prehospital system to rapidly triage patients who would benefit from early ECMO treatment. It is thought that shorter intervals before cannulation for ECMO are associated with better survival. This necessitates the initiation of emergency transport to an ECMO-capable center after a pre-specified on-scene time or other criteria indicating refractoriness to standard ACLS measures. In some programs, 15 minutes without ROSC was a criteria to initiate ECMO transport. What is not clear is what effect such reorganization of prehospital care would have on the overall survival of cardiac arrest patients. The Alm-Kruse study may be a cautionary one, in which post-ECPR implementation survival was actually lower among ECPR-eligible patients, compared to the pre-implementation time period, although the findings were not statistically significant.[12] The authors theorize that since patients have been shown to have worse outcomes with in-transport CPR, compared with on-scene CPR, the mandatory transport of patients after 10 minutes without ROSC potentially led to worse survival and may have had a paradoxically negative effect in the study.[17] The effect of transporting a larger number of patients with CPR in progress must be considered in light of a recent large multi-center propensity-matched observational study where intra-arrest transport was associated with worse overall and neurologically-intact survival.[18]

Conclusions

Encouraging data on ECMO for OHCA continues to trickle in, especially with the addition of the first randomized trial in 2020, but study participant numbers remain small and not sufficiently convincing to disturb the current equipoise. Therefore, ECMO for OHCA cannot be recommended as superior to standard ACLS, even in centers where it is available, until additional randomized trials reproduce the results of the ARREST trial. Further, improvements in survival with ECPR must not come at the expense of worse outcomes in the much larger total OHCA population.

References / Literature Review and Grading

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We followed the AAEM procedure for literature review. We first reviewed relevant guideline statements and then proceeded with a search of pubmed.

Guideline statements

AHA - ACLS -
https://www.ahajournals.org/doi/10.1161/CIR.0000000000000732?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

Literature review

Pubmed
ECMO AND “cardiac arrest” AND systematic[sb] (last 5 years, human) 35 total citations 13 potentially relevant

“ECPR” AND “cardiac arrest” clinical trials (since 2020) - 9 studies, 2 presenting primary results that are relevant (ARREST and Nakashima), 1 referring to design of relevant study (EROCA, first author HSU)

Note: Some additional literature was cited in the CPC Committee peer review process and is referenced, but not graded in this table as it was not identified by the literature search procedures.

Publication	GradeK	QualityK	GradeM	QualityM	Year	Comments	Additional Comments
Ooweneel, et al[19]	A	Adequate	A	Adequate	2016	Systematic review from 2016 of ECPR for OHCA, IHCA, and cardiogenic shock. 10 cohort studies with a control arm were included. Standardized outcome measures for both 30 day and 6 month survival. 13% higher long-term survival and 14% higher neurologically-intact survival in ECPR than in propensity-matched controls.	Included in and out of hospital, and refractory cardiogenic shock in MI (pre-arrest) - (positive - i.e. supports ECPR)
Holmberg, et al[20]	B	Poor	C	Poor	2018	Systematic review, including 15 observational studies of OHCA. Heterogeneity of outcome measures among studies. Overall low study quality. Meta-analysis could not be performed due to high risk of bias and heterogeneity of studies.	Meta-analysis of observational studies of OHCA and IHCA; adults and children - overall the authors rated this literature as inconclusive (neutral).
Twohig, et al[21]	A	Adequate	C	Adequate	2019	Systematic review of 17 studies of ECPR but only 9 observational studies compared ECPR to CCPR, 1 of which was prospective. Odds ratio favoring 30 day survival/hospital discharge in patients treated with ECPR with moderate to high risk of bias.	Meta-analysis of observational studies, generally at high risk of bias, but did have a strong signal in favor of ECPR (positive)

Miraglia, et al[6]	A	Good	B	Adequate	2020	Systematic review of 6 propensity-matched cohort studies of adult IHCA and OHCA. ECPR was associated with better 30 day and long-term neurological outcomes and survival when pooled IHCA and OHCA arrest data were used. No benefit for ECPR was seen for 30 day survival and neurologic outcomes in OHCA. Long-term survival and neurologic outcome may be better in OHCA.	ECPR of OHCA and IHCA, but only included studies with propensity score matching. Had a strong signal in favor of ECPR, but limited by lack of randomization. (Supportive)
Hsu, et al (EROCA)[9]	C	Adequate	C	Adequate	2021	Prospective single center University of Michigan feasibility trial randomizing OHCA patients to standard vs expedited transport and measuring arrival to ED within 30 minutes and frequency of initiation of ECPR. Included non-shockable rhythms. 12/15 eligible pts randomized to expedited transport. 5/15 pts received ECPR, with 0% survival.	Studied feasibility of early transport to an ECPR center. Did not directly randomize to ECPR versus control. Did not demonstrate feasibility. There was only one survivor in the whole study, who did not receive ECPR. (Not Supportive)

Yannopoulos, (ARREST)[3]	A	Outstanding	A	Outstanding	2020	Randomised open-label single center trial from University of Minnesota. Enrolled 30 adults with OHCA with initial rhythm of v fib or pulseless v tach and no ROSC after three shocks and transfer time of less than 30 min. Survival to hospital discharge: 6/14 in ECPR and 1/15 in standard ACLS group. CPC category 1 in 5/6 survivors in ECPR group. Study stopped early due to prespecified stopping criteria being met.	Trial was strongly positive, but the model required interventional cardiologists able to cannulate for ECMO 24-7 and only included shockable arrests out of hospital (supportive)
Nakashima, et al[22]	C	adequate	C	adequate	20199	Prospective multicenter observational study in Japan. < 45 min after emergency call, 15 min of CPR in ED then cannulation. Primary endpoint 6 month favorable neurologic outcome, defined CPC 1 or 2. 407 total patients, 250 with ECPR. Significantly higher number with VF/pVT in the ECPR group. Primary endpoint reached in VF/pVT group. No statistical benefit if conversion from VF/pVT to PEA before ECPR.	Basically compared sites that did ECPR to those that did not. As such, relatively high risk of bias (other site effects). (Supportive)

Bougouin, et al[10]	C	Adequate	C	Adequate	2019	Prospective registry of OHCA in Paris area, 2011-2018. 8% survival in 525 patients given ECPR prehospital,vs. 8.6% for CCPR. No significant advantage of ECPR for survival to hospital discharge. Significant selection bias in pts treated with ECPR. Did not examine long term or neurologically intact survival.	Did matching to address differences in baseline characteristics. Shockable rhythm associated with higher likelihood of a good outcome, but interaction (shockable / ECPR) not formally tested. In patients without ROSC and shockable rhythm there were 28 survivors in ECPR group and 3 in conventional CPR group. (neutral on primary outcome, possibly supportive in shockable)
Stub, et al (CHEER)[10,23]	C	Adequate	C	Adequate	2014	Single center prospective observational study from Australia of IHCA and OHCA. Initial vfib rhythm, bystander cpr within 10 min for OHCA, after 30 min of CCPR. Included intra-arrest therapeutic hypothermia of 33 degrees. 26 pts (11 OHCA and 15 IHCA). Survival to hospital discharge 45% OHCA and 60% in IHCA all with full neurologic recovery. No case control and possible significant selection bias. No report of long term outcomes.	No control group, combination of OHCA and IHCA. They were able to get patients on ecmo within an hour of collapse about half the time (median time to ecmo 40 in survivors and 78 in nonsurvivors). Gives proof of concept (over half survived using this approach). (Supportive)
Mosca, et al[24]	D	Poor	D	Poor	2016	Single center retrospective chart review study in New York City of 31 patients who underwent ECPR after CCPR for IHCA. Multiple possible confounders, minimal chart review methods. 42% survival	Hard to interpret, but likely supportive of the concept in appropriately selected patients. (supportive)

						at 1 year. No significant difference in > 45 or < 45 minutes duration of CCR prior to ECPR.	
Shinar, et al [4]	D	Adequate	D	Adequate	2019	Single community hospital in San Diego retrospective chart review study of combined 58 pts with IHCA and OHCA who had EP-initiated ECPR. 24% vs 14% adjusted survival to hospital discharge.	Seven year case series of community ED, with ED physician (no residents) initiated cannulation. In general provides some data that a motivated group of emergency physicians can initiate ECPR (supportive)
Lamhaut, et al [11]	C	Poor	C	Poor	2017	Prospective registry of OHCA in Paris area from 2011-2015 using mobile intensive care units and strict inclusion criteria. 154 total patients, 9% survival during early period and 28% during more stringent criteria in later period. Period 2 had initiation of ECPR after 20 min of no ROSC and with more favorable patient factors. No control group.	Survival improved during a quality improvement (involving ECPR and other components) however patient selection changed, which makes the improved survival harder to interpret. (supportive)

Reynolds, et al [13]	C	Good	C	Good	2017	Prospective multicenter North American observational cohort study of OHCA (PRIMED) with analysis of hypothetically ECPR-eligible subgroup for natural history of survival and neurologic outcome with conventional CPR. 11% or 1237 met eligibility criteria. 38% of these survived to hospital discharge and 30% with a good neurologic outcome. 1/3 failed to achieve ROSC and half of those with ROSC died in the hospital or were discharged with poor neurologic outcome.	This study provides a potential number of patients who might be eligible for ECPR given prolonged arrest in spite of professional resuscitation. Interestingly about 30% of this hypothetical population survived with a good neurological outcome (which is much higher than zero), which is a higher than expected good outcome proportion and lower than control group survival in the recent ARREST trial. (neutral)
Alm-Kruse, et al[12]	D	Adequate	D	Adequate	2021	Registry study of pre and post-ECPR protocol implementation at two Norwegian centers. No significant difference in survival pre vs post (30/48 vs 50/100 ECPR-eligible patients). In Post group, 14 actually received ECPR.	No difference in survival in this uncontrolled before and after study in Norway - but possible trend towards worse survival after implementing ECPR - low volume may have been a problem. (Negative, possibly harmful)

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