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THE BRASS TACKS: CONCISE REVIEWS OF PUBLISHED EVIDENCE

Extracorporeal cardiopulmonary resuscitation for refractory out-of-hospital cardiac arrest

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NNT color recommendation	Yellow (unclear benefits)
Summary heading	Extracorporeal cardiopulmonary resuscitation did not improve favorable neurological status at the shortest follow-up and at 6 months or reduce in-hospital mortality when compared to conventional ACLS
Benefits in NNT	No one was helped (no additional favorable neurological status, no reduction in in-hospital mortality)
Benefits in percentages	No one was helped
Harms in NNT (NNH)	Not assessed
Harms in percentages	Not assessed
Efficacy endpoints	Favorable neurological status at the shortest follow-up and at 6 months, reduced in-hospital mortality
Harm endpoints	Not assessed
Who was in the studies	418 participants in three trials of adult patients with OHCA

NARRATIVE

Out-of-hospital cardiac arrest (OHCA) is a significant cause of morbidity and mortality, with survival rates less than 10%.[1–4] Early high-quality chest compressions and appropriate defibrillation for shockable rhythms improve the likelihood of return of spontaneous circulation (ROSC).[4–7] Unfortunately, over 50% of patients are not responsive to standard OHCA therapies and require prolonged cardiopulmonary resuscitation (CPR).[2] Refractory cardiac arrest is defined as prolonged failure to obtain ROSC despite conventional CPR in the absence of hypothermia.[8] These patients in particular have poor outcomes, with less than 5% having neurologically favorable survival if ROSC is not obtained within 45 min of arrest.[2]

The addition of venoarterial extracorporeal membrane oxygenation to CPR, known as extracorporeal CPR (ECPR), may be used in select patients when conventional therapies have failed.[5–7] ECPR includes the initiation of venoarterial extracorporeal membrane oxygenation (VA ECMO) during CPR. VA ECMO is a mechanical support device in which blood is removed from a cannula in the venous system (e.g., femoral vein), runs through a circuit that mimics gas exchange, and is returned to the arterial system via a cannula in the arterial system (e.g., femoral artery).[9–11] Currently, there is uncertainty regarding the effect of ECPR compared to standard advanced cardiac life support (ACLS) therapies on survival and neurologic outcomes.[9,10]

A systematic review published in 2018 evaluated 25 observational studies: 15 were adult OHCA, seven were adult in-hospital cardiac arrest (IHCA), and three were pediatric IHCA.[10] This systematic review found the risk of bias to be critical with significant confounding, the evidence quality was very low, and there was significant heterogeneity.[10] These factors precluded the authors from drawing significant conclusions. Herein, we summarize a systematic review of randomized controlled trials (RCTs) evaluating the use of ECPR in refractory OHCA.[11]

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The systematic review discussed here included three RCTs ($n=418$ participants) of adult patients with OHCA.[11] Included trials randomized patients to ECPR versus conventional ACLS therapies. The review excluded nonrandomized studies, abstracts without published full text, and studies including IHCA. The outcomes of interest were survival with a favorable neurologic status at the shortest follow-up, survival with a favorable neurologic status at 6 months, and in-hospital mortality. As the time period varied between studies, the authors defined the outcome using the shortest reported follow-up period. The shortest reported follow-up was at hospital discharge in one study and at 30 days in the other two studies. All included studies defined a favorable neurologic outcome as a cerebral performance category (CPC) scale of 1 or 2, which corresponds to no major deficits or some deficits but with the ability to still perform activities of daily living, respectively.

Mean age of included patients ranged from 54 to 59 years. Myocardial infarction was the leading cause of OHCA in the Prague OHCA (50%) and INCEPTION (77%) trials.[12,13] The Prague OCHA trial included both shockable and nonshockable rhythms,[13] while ARREST and INCEPTION included only shockable rhythms.[12,14] Duration of cannulation and total time from collapse to initiation to ECPR varied from 7 to 59 min in ARREST, 20–74 min in INCEPTION, and 12–61 min in Prague OHCA.[12-14] Of patients randomized to the ECPR arm, ECPR was started in 64% of patients in Prague OHCA, 66% in INCEPTION, and 86% in ARREST.[12-14] The rate of crossover was 8% in Prague OCHA and 5% in the INCEPTION trial, though no patients randomized to ACLS in the ARREST trial received ECPR.[12-14]

This meta-analysis found that ECPR in refractory OHCA did not improve survival with a favorable neurologic outcome at the shortest follow-up (26.4% vs. 17.2%, risk ratio [RR] 1.47, 95% confidence interval [CI] 0.91–2.40) or at 6 months (28.3% vs. 18.6%, RR 1.48, 95% CI 0.88–2.49).[11] In-hospital mortality did not differ between ECPR and conventional ACLS (RR 0.89, 95% CI 0.74–1.07). Subgroup analysis of patients with shockable rhythm at presentation found no significant benefit at shortest follow-up (RR 1.62, 95% CI 0.95–2.76) and at 6 months (RR 1.50, 95% CI 0.90–2.50).[11]

CAVEATS

There are several important considerations when interpreting these results. First, all studies were open label, there was variable levels of adherence, and there were significant differences in sample sizes. Only 64%–86% of patients randomized to ECPR received the intervention. Second, two of the three RCTs (INCEPTION and Prague OHCA) had crossover between allocations, ranging from 5% to 8% of patients.[12,13] Third, the ARREST trial was stopped early due to ECPR superiority,[14] which may have overinflated the observed effect size, further contributing to bias. On the other hand, the Prague OHCA trial was stopped early due to futility, which may have provided underpowered results.[13] Fourth, there was difference in definition of refractory cardiac arrest, and INCEPTION did not utilize a mandated emergency medical services protocol for OHCA, which has been associated with improved survival in OHCA.[12] Fifth, there were significant differences in the included trials regarding performance of ECPR, with the ARREST trial reporting a shorter duration of cannulation (7 min compared to 12–20 min) and time from collapse to circulatory support (59 min compared to 61 and 74 min).[14] There was also moderate to high degrees of statistical heterogeneity. Though it was stopped early, the ARREST study suggests that high-volume ECPR centers may reduce the time of cannulation and time to initiation of circulation, though it is controversial whether this is associated with improved patient outcomes.[14,15] Importantly, ECPR requires dedicated training, teams, and centers, and ECPR is not currently feasible in the majority of health care settings or centers. Of note, the prehospital system response to OHCA is integral to improving the quality of OHCA care and bystander CPR rates.

Based on current data it is unclear whether implementation of routine ECPR use in refractory OHCA improves favorable neurological status or reduces mortality.[11] Therefore, we have selected a color recommendation of yellow (unclear benefits) for the use of ECPR in adult patients with OHCA versus conventional ACLS. ECPR demonstrates promise, but further data are needed using clear definitions of refractory OHCA and protocols for OHCA management, determining which patients are appropriate for ECPR, and delineating the technical procedure of ECPR. Studies with adequate blinding and strict study protocol adherence are also necessary.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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