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Abstract

Out-of-hospital cardic arrest (OHCA) affects 134 per 100 000 citizens annually. Extracorporeal cardiopulmonary resuscitation (ECPR), providing mechanical circulatory support, may be a means to improve the likelihood of survival among those with refractory OHCA. In comparison to in-hospital ECPR candidates, those in the out-of-hospital setting tend to be sudden unexpected deaths in younger and healthier patients. The aims of this review are to summarize and identify the limitations of the evidence evaluating ECPR for OHCA, and to provide an approach for ECPR program application. Although there are many descriptions of ECPR-treated cohorts, we identified a paucity of robust data demonstrating ECPR effectiveness in comparison to conventional resuscitation. However, it is highly likely that ECPR, provided after a prolonged attempt with conventional resuscitation, does benefit select patient populations in comparison to conventional resuscitation alone. Whereas reliable data demonstrating the optimal patient selection criteria for ECPR are lacking, most implementations sought young previously healthy patients with immediate high quality CPR. Carefully planned development of ECPR programs, in high performing emergency medical systems at experienced ECMO centres, may be reasonable as part of systematic efforts to determine ECPR effectiveness and globally improve care. Protocol evaluation requires regional-level assessment, examining the incremental benefit of survival in comparison to standard care, while accounting for resource utilization.

Summary

ECPR may improve survival among those with refractory out-of-hospital cardiac arrest, but there is a paucity of robust data to estimate effectiveness. Available literature suggests that ECPR provided after prolonged conventional resuscitation, in comparison to conventional resuscitation alone, benefits select patient populations. Carefully planned development of ECPR programs at experienced ECMO centres may be reasonable as part of systematic efforts to determine ECPR effectiveness and globally improve care.

Introduction

Emergency medical services (EMS) attend 134 out-of-hospital cardiac arrests (OHCA) per 100 000 adult citizens yearly,[1] a proportion of whom are young previously healthy persons.[2] Unfortunately overall survival is low, with typically 5-15% surviving to hospital discharge.[1] Significant gains in survival have been reported in the past decade,[3] attributable in part to focus on early arrest recognition, bystander resuscitative efforts (including dispatcher-assisted), early defibrillation, improved professional rescuer efforts including high quality CPR, as well as advances and protocolization of post-arrest care.

The goal of cardiac arrest resuscitation is two-fold: (1) to maintain cerebral and systemic perfusion with early and effective chest compressions; and, (2) to achieve return of spontaneous circulation (ROSC). Unfortunately, while both are necessary conditions for neurologically favourable survival, neither are sufficient. For many ROSC is unachievable with conventional efforts, despite having cerebral circulation maintained with external cardiac massage; resuscitation efforts are thereby terminated, despite potential cerebral viability.

Extracorporeal membrane oxygenation (ECMO) has been used as a rescue therapy in resuscitation (ECPR), with reports of application for OHCA since the 1980s.[4] Theoretically, ECPR has the potential to overcome the requirement for ROSC, allowing the possibility of favourable neurological outcomes for those who have cerebral perfusion maintained. Initial reports—while demonstrating wide heterogeneity in outcomes—have shown promise.[5–7] However as existing data are observational, estimates of effectiveness are limited by significant differences in systems of care and biases.

In comparison to those with in-hospital arrests (IHCA), who presented to hospital due to preceding symptoms and/or other significant comorbidities, OHCA patients typically experience sudden unexpected cardiac deaths and tend to be younger, healthier, with better prognostic features.[8,9] The out-of-hospital setting includes a higher absolute number of cardiac arrests, where the ideal ECPR candidates may be best found.[2] However, achieving timely access of advanced invasive therapies to candidates in the out-of-hospital setting requires a complex logistical framework.

The aims of this review are to document the state of the evidence of ECPR for OHCA, reflecting on the limitations, and to provide an approach for ECPR protocol development. Building on previous work ECPR for IHCA,[10] this review will focus on the aspects unique to OHCA.

Review of the Literature

<u>Search Strategy, Data Extraction, and Quality Assessment</u>

To provide an overview of the evidence of ECPR efficacy for OHCA, we (EG) designed a search strategy (Appendix A) to identify systematic reviews (SR) and meta-analyses. From 2005 to May 29, 2017, we searched: Medline (Ovid), Embase (Ovid), Cochrane (Wiley), PubMed (NLM) and Web of Science (Thomson Reuters), with no language restrictions. We used text words in the title, abstract or keyword fields, and relevant subject indexing to retrieve systematic reviews or meta-analyses documenting the use of ECPR/ECMO for human cardiac arrest. Two reviewers (LH, IO-D) independently screened citations by title and abstract. Disagreements were resolved by consensus. Our population of interest was adult OHCA of presumed cardiac origin that proved refractory to conventional therapies. The intervention of interest was ECPR, defined as ECMO initiation during CPR. The outcomes of interest were survival and favourable neurological outcome at hospital discharge. Included studies were limited to systematic reviews or meta-analyses. We excluded studies that: included IHCA only or mixed IHCA and OHCA without subgroup analysis; included patients with cardiogenic shock only or mixed cardiac arrest and cardiogenic shock; or did not fulfill the criteria for high quality SRs.[11] Data from each review was then extracted according to predefined selection criteria. The two reviewers independently assessed the quality of included reviews using the 11-item validated AMSTAR tool.[12]

Results

Our systematic search produced 327 citations (Appendix 1 and Figure 1). After screening, we identified 12 SRs, 7 of which were excluded after full text retrieval,[4,13–18] leaving 5 included studies.[5,19–22]

Four of the systematic reviews limited study eligibility to those comparing ECPR to conventional resuscitation, [20,23–25] all including different combinations of five studies (Tables 1 and 2; Appendices 2 and 3). The Kim et al[20] review included the propensity score-matched comparisons of Kim et al[26] and Maekawa et al.[27] Neurological outcomes at hospital discharge (RR 8.00; 95% CI 1.04-61.71) and 3-6 month neurologic outcomes (RR 4.64; 95% CI 1.41-15.25) were superior in the ECPR group. Squires et al[25] included the same studies but did not attempt a meta-analysis.[26] Wang et al[23] also included these studies, with an additional third study (with 20 ECPR, 683 CCPR patients),[28] however included only unmatched data from all studies. They reported a significant difference in survival to discharge, favouring ECPR over the conventional group (RR 2.69; 95% CI 1.48-4.91). Ahn et al[24] included propensity matched data from Maekawa et al,[27] a prospective parallel group study,[29] and a large unmatched prospective observational cohort,[30] reporting that ECPR was not associated with improved outcomes.

Ortega-Deballon et al. included all studies that reported outcomes of ECPR-treated adult OHCA's, without restricting to comparative studies,[5] including 833 patients. Inclusion criteria generally included ages 10-75 years, a no-flow duration of <5-15 minutes, a presumed cardiac etiology, and no ROSC after 10-30 minutes. Overall, survival and favourable neurological outcomes were seen in

22% and 13%, respectively.

Limitations in Current Research

Risk of bias results in a low or very low quality evidence for ECPR in refractory OHCA.[31] Selection bias by clinicians for ECPR therapy is a major limitation, in addition to significant heterogeneity in the intervention provided and study populations.

The majority of systematic reviews included studies that compared those treated with either ECPR or conventional resuscitation, based on clinical decision. The results of these comparisons are highly dependent on the group chosen to be the control group. ECPR-eligible patients overall are known to have remarkably high survival when treated with convention resuscitation, based on criteria that mandate highly favourable prognostic features.[2,32] In contrast, those actually treated with ECPR comprise a systematically different population, restricted to those in refractory arrest despite full conventional efforts that have typically been ongoing for 60 minutes. Even if one creates a propensity-score matched group with the same mean duration of resuscitation efforts, the ECPR-treated group is still limited to those who have failed prolonged conventional efforts, in comparison to those for whom a proportion were successfully resuscitated.

In reality, two strategies should be compared: conventional resuscitation with the option to perform ECPR, or conventional resuscitation alone. Comparisons should include patients meeting the same criteria at a pre-specified duration of resuscitation, and thus the “ECPR protocol group” should include a proportion of those resuscitated via conventional means. A quasi-experimental study by Sakamoto and colleagues,[29] in which 46 tertiary hospitals in Japan were self-allocated to an ECPR arm and conventional care arm, enrolled 419 OHCA’s with initial shockable rhythms in refractory arrest at hospital arrival (mean enrolment time 30 minutes). They reported 12.3% and 2.6% neurologically intact survivors at 1 month in the ECPR-treating hospitals and conventional treating hospitals, respectively, supporting the incremental benefit of ECPR therapies in this system.

We identified several ongoing clinical trials that may provide higher quality evidence for the effectiveness of ECPR for OHCA.[33–38]

ECPR Effectiveness for Refractory OHCA: Completely Obvious or Entirely Unknown? (Table 3)

Previous studies define the limits of survivable CPR duration for patients who meet ECPR criteria, but who are treated exclusively with conventional resuscitation.[39,40] One North American study included 150 EMS agencies over a 3-year period and identified all patients who met an ECPR criteria but were treated with conventional resuscitation.[40] The probability of survival demonstrated a continual decline with increasing durations of elapsed resuscitative efforts. The longest duration until ROSC in a survivor with a favourable neurological outcome (mRS ≤ 3) was 47 minutes, suggesting beyond this there is no further benefit of conventional resuscitation. Conversely, existing data demonstrates positive outcomes among those treated with ECPR after 47 minutes duration of CPR,[18,41] strongly suggesting that ECPR after failed conventional resuscitation is superior to conventional resuscitation alone. ECPR thus allows a “second chance” to achieve circulation among those who have failed conventional therapy, thereby creating a bimodal distribution of resuscitation durations among survivors. Kim et al. compared outcomes stratified by duration of resuscitation in 444 conventionally-treated to 55 ECPR-treated OHCA’s.[26] Three-month neurologically intact survival in those treated with and without ECPR, respectively, with 41-60 minutes of CPR was 21% and 0%, and with 61-80 minutes was 18% and 0%. It is likely there are unreported or unmeasured differences between those chosen for ECPR and those not, however a lack of survivors in the group receiving conventional therapy makes it difficult to argue that this is an effective strategy after 40 minutes of CPR. The benefit of initiating ECPR earlier in the resuscitation, however, in comparison to conventional therapy, is less clear.

Some may argue, on the basis of these data, that the need for an ECPR randomized trial for those with prolonged refractory arrest would be comparable to the need for a trial randomizing those with renal failure to dialysis or placebo, or randomizing those skydiving to parachute or sham device.[42] Robust evidence demonstrating efficacy for dialysis and parachutes is similarly lacking, however it is clear that without these interventions the outcome is surely death. There are two caveats to this argument however. First, the initiation of ECPR requires transport to hospital, which has been shown to impair resuscitation quality.[43] Alterations to current protocols in favour of intra-arrest transport may thereby worsen overall outcomes, even if ECPR does confer benefit.[44] Currently, studies comparing ECPR to conventional therapies are limited to systems with “load and go” protocols,[20,26–29] limiting external validity to other models. Secondly, prognostication bias, in which clinicians cease resuscitations due to a predicted poor outcome, limit robust estimates of outcomes with CPR performed beyond 47 minutes, as for most patients efforts have already been terminated.[40] However, based on analyses of large datasets, survival with conventional resuscitation beyond this juncture appears to be very unlikely.[4,45]

EMS Differences and the Need for a True denominator

With the exception of reports of ECPR initiated in the prehospital setting,[46] the current literature is limited to outcomes of patients who have been transported to the hospital with ongoing CPR. Inclusion in studies has ranged from only those treated with ECPR during active CPR,[7] those treated with ECPR after OHCA (some with ROSC),[47] to those selected for ECPR (some without initiation due to ROSC or unsuccessful vascular access).[6] The most appropriate denominator, however, is the number of ECPR-eligible patients throughout the region (whether or not chosen for transport and/or ECPR initiation). The foundational questions are: what is the incremental benefit of adding ECPR services into a regional resuscitation system of care? Is there a role for ECPR to improve the overall OHCA survival, or at least in a specific subgroup of these patients? Is the infrastructure investment required for these outcomes justified?

The initial quality of care provided by the EMS in ECPR reports is typically unreported, which likely plays a large role in outcomes. Significant differences in systems may include level of provider, hospital transport policies, readiness to implement ECPR at the hospital, and conventional resuscitation/CPR quality (before and in-hospital). One of the largest studies examining ECPR-treated patients within a system reported a median EMS on-scene time of seven minutes and overall functional survival of 1.6%.[28] With these stark differences to North American systems (considerably longer scene time and overall survival typically several fold higher[48,49]) external validity ECPR outcomes is unclear. Furthermore, it is possible that systems with high rates of successful conventional resuscitation and overall survival may garner minimal incremental benefit from ECPR, as in most candidates ROSC was successfully achieved.

Who Are Ideal Candidates for ECPR?

ECPR deployment is typically highly selective,[5,18] with clinicians treating only patients believed to have the possibility of good outcomes, usually focusing on relatively young healthy patients with short no-flow durations, in order to minimize the risk of treating those with preceding irreversible cerebral injury. Therefore, our ability to ascertain the best ECPR candidates beyond these highly selected groups is limited. The alternative strategy, a wide application of ECPR resulting in data to determine the optimal eligibility criteria, has not been conducted, likely due to resource constraints.

Many ECPR protocols exclude patients with non-shockable initial rhythms, a group for whom the probability of ROSC with conventional efforts is low.[5] However, therein lies the paradox: ECPR-eligible patients with initial shockable rhythms already achieve excellent outcomes with conventional therapy (87% in one region survived to ward admission[2]) and could be disadvantaged by altering treatment strategies. Conversely, those with non-shockable rhythms may have more incremental benefit from ECPR given the poor survival with current best practices (and potentially the greatest number of net survivors given the higher incidence), albeit likely with lower proportional survival in comparison to shockable comparators. Among those with non-shockable rhythms, reliable strategies are required to identify those with arrest etiologies amenable to ECPR treatment.

A meta-analysis of prognostic factors for success with ECPR reported favourable outcomes in 15%.[18] Survivors were more likely to have shorter low-flow durations, initial shockable rhythms, and higher pH and lower lactate values on hospital arrival. The authors classified the evidence as low or very low quality. Unfortunately significant variability among survivors and non-survivors with respect to laboratory values such as pH and lactate preclude robust "cut-off values" to inform candidacy. Furthermore, tools for ECPR eligibility assessment are ideally available to prehospital providers, such that unnecessary transports are not undertaken in those deemed to be poor candidates upon hospital arrival.

Potential Absolute Benefits

The overall incremental benefit of ECPR to the survivorship in a health region may be modest. One study in Vancouver (population approximately one million) reported that 10% of OHCAs met the local ECPR criteria, of whom one third were refractory to conventional resuscitation and thus may have benefited from ECPR (approximately 12 per year).[2] This estimate would be lower if restricted to shockable rhythms. A report from Vienna found that 6% of OHCA fulfilled their criteria for ECPR.[50] Estimates of ECPR candidates may vary in different regions depending on the proportion of OHCA patients successfully resuscitated, patient demographics, and population density.

A recent large North American EMS-based study found that overall 4.0% were ECPR-eligible and refractory to resuscitation.[40] Interestingly, this study demonstrated the likelihood survival with favourable neurological status with increasing durations until ROSC remained approximately steady at 30% between 15 and 40 minutes of CPR. Assuming that establishment of mechanical perfusion could achieve a success rate that is at best, equal to that of conventional ROSC after similar durations, this gives an estimate of the maximum potential benefit of ECPR. Further, it demonstrates the neurological resilience of ECPR-candidates with prolonged CPR.

Resource Implications and Readiness

OHCA patients treated with ECPR require resource intensive management, which may not be feasible in all locales. In contrast, OHCA patients who do not have ROSC are pronounced dead in the prehospital setting or in the emergency department, with a relatively low cost. In the prehospital setting, ECPR implementation requires modification of protocols and training, which should seek to achieve the greatest chance of ROSC prior to transport, while at the same time minimizing delays for ECMO initiation.[39,51]

The hospital setting requires a team of appropriately skilled practitioners to be emergently alerted and attend to a patient in cardiac arrest, followed by the requisite infrastructure and resources for post-arrest ECMO care.[10] In settings where these services already exist, the additional resources to treat ECPR candidates appear to be reasonable. One study reported a median duration of ECMO of 2 days (IQR 1-5 days), and a median hospital stay of 13 days (IQR 1.3-22);[6] other reports are similar.[52,53] Although this short hospital stay is resource intensive, young previously healthy patients with many potential years of life to be gained may warrant this investment. Cost-benefit analyses might explore what number of ECPR-treated survivors is a reasonable use of resources.

Donation-Related Considerations

When employing advanced resuscitation treatments, the first and foremost priority is saving the patient's life with the goal of neurologically favourable survival. However, while treatment advances have led to improvements in survival, the most common outcome remains death,[1] with many patients suffering irreversible anoxic brain injury. While organ donation has not traditionally been reported in OHCA studies the 2015 ILCOR recommendations now state: "We recommend that all patients who have restoration of circulation after CPR and who subsequently progress to death be evaluated for organ donation… We suggest that patients who fail to have restoration of circulation after CPR and who would otherwise have termination of CPR efforts be considered candidates for kidney or liver donation in settings where programs exist."[49] Anoxic brain injury after resuscitated cardiac arrest has evolved to be the most common etiology of devastating brain injury leading to organ donation in Canada.[54] As abdominal and thoracic vital organs can recover despite irreversible brain injury after resuscitated cardiac arrest,[55] patients who suffer cardiac arrest, including those treated with ECPR, may be eligible for organ donation. Organ donation should be considered and reported routinely as an outcome of any ECPR study, and included in cost evaluations.

A Framework for ECPR Application

Canadian experience with ECPR for OHCA is limited. While there have been reports describing the use of ECPR for IHCA,[56,57] only one study has described the experience with a formal OHCA ECPR protocol.[52]

Although there are significant limitations in the literature regarding estimates of efficacy, it is highly likely that ECPR after prolonged conventional resuscitation for select patients is superior to conventional resuscitation alone. Nonetheless, acknowledging the state of the evidence, widespread application may not yet warranted. We suggest that implementation may be suitable in carefully developed programs with the goal of further learning, whether in the form of observational registries or a clinical trial. We suggest the following framework for ECPR program development and implementation (Table 4):

1. The decision to implement ECPR within an OHCA system of care should be made at the regional level. Whereas to a clinician who receives a patient at hospital after preceding prolonged efforts it is clear that the only avenue for possible survival is now ECPR initiation, this is likely not the ideal vantage point or time to assess the overall merit of systematically offering this treatment option. Rather, a regional population-based evaluation of incremental benefit, potential harm of hospital transport, and resource utilization is a more ideal structure to evaluate impact.

2. An ECPR program with an OHCA system of care requires careful planning that will typically span a year or more. Multiple disciplines within and exterior to the hospital require consultation and collaboration, ideally including patient and public involvement. Whereas clinicians employing ECMO on an ad hoc basis attempt to create an ECMO initiation scheme while CPR is ongoing, ideally all aspects of a protocol are meticulously planned well in advance of any case.

3. Acknowledging that robust data delineating those most likely to benefit from ECPR is lacking, it is most reasonable to focus efforts on relatively healthy victims of sudden unexpected cardiac arrest, for whom cerebral perfusion has been maintained with early and high quality CPR.

4. Due to the potential risks to the success of conventional resuscitation while

focusing on the prospect of ECPR treatment, it is imperative that careful steps are taken to acknowledge and mitigate this potential harm. High quality initial conventional on-scene resuscitative efforts, which will resuscitate most ECPR-eligible patients,[2] should not be compromised. Previous data can inform the ideal time to transport these patients, which may differ based on patient circumstances and initial cardiac rhythm.[39,40] Further, strategies to maintain all aspects of high quality resuscitation during transport should be pursued; mechanical chest compression devices may assist with this goal.

5. The incorporation of ECPR into an OHCA system of care should be reserved for already high-performing systems. The EMS should be equipped with quality monitoring programs that demonstrate success in delivering high quality conventional resuscitation. ECPR may be a way to glean additional OHCA survivors, however highly selective application in a small proportion of cases is unlikely to lead to significant changes in total outcome statistics. The public health priority should remain widespread improvements in the basics of prehospital resuscitation and optimization of all aspects of the chain of survival[49] prior to implementing selective resource-intensive programs.

6. Prehospital and hospital-based cooperative planning is essential in order to carefully select candidates, and develop the most appropriate protocols for how and when to transport. Ideally there will be few patients for whom conventional resuscitation is altered but are later classified as non-candidates. Patient selection may be best facilitated by a smaller group of paramedics in tiered paramedic systems, in consultation with hospital-based clinicians.[52] As existing data suggests a low likelihood of survival when initiated on ECPR beyond 75 minutes of CPR,[5,7,26] a reliable system of prehospital protocol activation may be critical to achieve the rapid deployment of ECMO required for positive outcomes.[52]

7. Hospital-based providers should have the requisite training and sufficient volume of experience to maintain competency. Within published reports,

differing practitioners have been successful at performing cannulation, and in differing locations.[5–7,37,58] Whereas these aspects need to be individualized to the institution, the essential piece is the requisite skills and volume of cases to develop and maintain competence. Similarly, team-based competence is essential for ECPR initiations. Due to the rarity of these cases, and the relative large human resource pool, regular ECPR simulation training is likely essential for institutional competency and excellence.[52] The term "crash onto ECMO" is an example of a poor conceptual model, which condones an ill-prepared chaotic procedure. Rather, centers employing this modality should strive to have the same regimented, safe, efficient, and effective implementation of other invasive procedures.

8. Quality monitoring of all phases of care within an ECPR program is essential with detailed evaluations of each case to identify areas requiring improvement.[52] Prehospital records should be reviewed to ensure high quality resuscitation was continued during extrication and transport. As resuscitation durations prior to ECPR initiation are correlated with outcomes,[18] metrics detailing time intervals from EMS dispatch to ECMO flows, and door-to-ECMO flows, should be reviewed.

9. Program evaluation should track outcomes, in comparison to historical or concurrent controls, at the regional level to quantify the incremental gain in survivors and resource utilization. For example, after ECPR services have been incorporated into a regional OHCA strategy, a system may report: "In comparison to the previous year [or a neighbouring region], among ECPR-eligible patients the proportion of those who achieved ROSC with conventional resuscitation and survived to hospital discharge was similar. In addition, there were XX ECPR-treated patients who survived to discharge, increasing the overall survival among ECPR-eligible patients to XX%". Whenever possible, the families of non-survivors should be offered the opportunity for organ donation; organ donation should be reported as an outcome of an ECPR program.

Conclusion

The incremental benefit and cost-effectiveness of incorporating ECPR into regional OHCA resuscitation systems of care remains unclear. However, it is highly likely that ECPR treatment, in select patients with OHCA refractory to prolonged attempts of conventional resuscitation, is superior to conventional efforts alone. Carefully planned development of ECPR programs in high performing EMS systems at experienced ECMO centres with the requisite skills, training, and resources may be reasonable as part of ongoing efforts to improve systems of care and to gather more data regarding the incremental effectiveness of this intervention.

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Figure 1: Study Flow Diagram

Table 1: Characteristics of Included Systematic Reviews

Characteristics	Kim 2016[20]	Wang 2107[23]	Ahn 2016[24]	Squiers 2016[22]	Ortega-Deballon 2016[5]
Time Period	August 1965 - February 2015	January 2000 - December 19, 2015	? - December 22, 2015	Start of MEDLINE – December 1, 2015	January 1, 2005 - May 25, 2015
Inclusion Criteria	1. Adult (≥ 16yrs) 2. IHCA or OHCA 3. Compared ECPR vs CCPR 4. Reported survival and neurologic outcomes	1. Studies with n ≥ 15 2. IHCA or OHCA	1. Studies of adults with CA of cardiac origin 2. IHCA or OHCA	1. Study design with highest LOE for ECMO 2. Cohort Studies with n ≥ 15; case series n ≥ 100	1. Studies of adults with CA of cardiac origin 2. Endorsed recommendations
Exclusion Criteria	1. Studies with only ECPR or CCPR 2. Cases with cardiogenic shock or post-cardiac surgery 3. Pediatric patients (age < 16 years) 4. Events caused by trauma, avalanche, hanging and/or drowning 5. Do-Not-Attempt Resuscitation	1) Studies that did not include survival to discharge or CPC status 2) Language other than English	1) Language other than English	1) Language other than English 2) Animal studies	1) Studies that included patients with cardiac arrest of non-cardiac origin (e.g. trauma, massive bleeding, hypothermia, poisoning, near drowning, etc.) 2) Animal studies
Included Studies (total n= ECPR:CCPR)	2 studies with propensity matching (76:76; matched cohorts used)	3 studies; 2 with propensity matching (128:1236; umatched cohorts used)	3 studies; 2 with propensity matching (604:538; matched cohorts used when possible)	2 studies with propensity matching (76:76; matched cohorts used)	20 primary studies of ECPR with no comparator groups (ECPR-treated n=833)

Characteristics	Kim 2016[20]	Wang 2107[23]	Ahn 2016[24]	Squiers 2016[22]	Ortega-Deballon 2016[5]
Primary/ Secondary Outcomes	Survival to hospital discharge and good neurologic outcome at discharge.	Survival rate to discharge/ Long-term neurological outcome (CPC) score	Survival and neurological outcome (GOS or CPC) at hospital discharge or later	Survival to hospital discharge	Description of ECPR practices Survival and neurological outcome (GOS or CPC) at hospital discharge or later Organ donation potential
Main Findings for OHCA patients	1. No beneficial effect of ECPR on survival to discharge but superior at 3-6 mo 2. Superior neurological outcomes at discharge and 3-6 mo for ECPR	Superior survival to discharge for ECPR	No beneficial effect of ECPR for survival or neurologic outcomes	No meta-analysis performed	Overall survival for ECPR is 22%, including 13% with CPC 1 or 2
AMSTAR score	10	10	10	7	8

* Quality of the evidence is with respect to study design. Prospective or retrospective observational studies are considered low quality evidence[6].

ECPR – Extracorporeal cardiopulmonary resuscitation; CCPR – Conventional cardiopulmonary resuscitation; CA - cardiac arrest; IHCA – In hospital cardiac arrest; OHCA – Out of hospital cardiac arrest; ECMO – Extracorporeal membrane oxygenation; CPC - Cerebral performance category; GOS- Glasgow Outcome Scale; LOE – Level of evidence

Table 2: Characteristics of Individual Studies Included in Meta-Analyses

Study	Included in			Period and country	Study Type	Population (n)	Main Finding
	Wang[19]	Ahn[21]	Kim[20]				
Maekawa 2013[27]	Yes (unmatched cohort)	Yes	Yes	2000-2004 Japan	Prospective Single centre Observational Matched	ECPR (53/24*) CCPR (109/24*)	ECPR may improve neurologic outcome
Sakamoto 2014[29]	No	Yes	No	2008-2012 Japan	Prospective Multi-centre Observational	ECPR (260) CCPR (194)	Bundle of TH, IABP & ECPR associated with improved neurologic outcome
Kim 2014[26]	Yes (unmatched cohort)	No	Yes	2006-2013 Korea	Prospective Single centre Observational Matched	ECPR (55/52*) CCPR (444/52*)	Bundle of TH & ECPR may improve neurologic outcome
Lee 2015 [30]	Yes	No	No	2009-2014 Korea	Retrospective Single centre Observational	ECPR (20) CCPR (683)	Comparable survival for ECPR vs CCPR.
Choi 2016 [28]	No	Yes**	No	2009-2013 Korea	Retrospective Multi-centre Matched	ECPR (320*) CCPR (36 227/320*)	No difference in survival for ECPR vs CCPR

* Number in matched cohort

**Ahn et al[21] meta-analysis used 1:1 propensity score matched cohort from Choi et al[28] with adjusted for co-variables: year, age, gender, initial arrest rhythm, community urbanization, arrest location, witnessed status, bystander CPR, EMS defibrillation, ED level, response time, on-scene time, transport time, therapeutic hypothermia, and reperfusion therapy.

ECPR – Extracorporeal cardiopulmonary resuscitation ; CCPR – Conventional cardiopulmonary resuscitation; TH – Therapeutic hypothermia; IABP – intra

Table 3: Uncertainties Regarding ECPR for OHCA

- ECPR Effectiveness for Refractory OHCA: Completely Obvious or Entirely Unknown?

  There are no RCT's to inform of effectiveness. However, among those who have undergone prolonged attempts at conventional resuscitation, at which point survival with further conventional treatment is extremely unlikely, there are survivors among those treated with ECPR, suggesting that there is a benefit.

- EMS Differences and the Need for a True denominator

  Differences in EMSs make external validity of ECPR reports difficult to ascertain. The key question is: what is the incremental benefit of adding ECPR services into a regional system of care for OHCA resuscitation?

- Who Are Ideal Candidates for ECPR?

  ECPR programs typically select relatively young healthy patients with rapid CPR initiation, based on previous data demonstrating successful outcomes with conventional resuscitation. Our knowledge of the best ECPR candidates beyond these highly selected groups is limited.

- Potential Absolute Benefits

  The overall incremental benefit of ECPR to the survivorship in a health region is likely to be relatively low, with a low proportion OHCA's typically considered eligible. Among ECPR-eligible candidates it is unlikely that positive outcomes will surpass 30%.

- Resource Implications and Readiness

  ECPR programs are resource-intensive, however the additional resources required in settings with existing ECMO capabilities may be appropriate when targeting young previously healthy patients with many potential years of life to be gained.

- Donation-Related Considerations

  Families of non-survivors should be offered the opportunity for organ donation. Organ donation should be reported as a secondary outcome of any evaluation of ECPR.

Table 4: A Framework for ECPR Application

1. The decision to implement an ECPR protocol for OHCA should be made at the regional level, with input from all stakeholders including the general public.

2. All components and phases of an ECPR protocol should be carefully planned prior to any cases.

3. It is reasonable to focus efforts on relatively healthy victims of sudden unexpected cardiac arrest, for whom cerebral perfusion has been maintained with early and high quality CPR.

4. Careful steps are required to mitigate the potential harm to conventional resuscitation while focusing on the prospect of ECPR treatment.

5. The incorporation of ECPR into OHCA systems of care should be reserved for already high-performing systems with quality monitoring programs. The overall public health priority should remain improvements in the basics of OHCA resuscitation including enhancing bystander response and high quality professional efforts.

6. Prehospital and hospital-based cooperative planning is essential in order to carefully select candidates, and develop the most appropriate protocols for how and when to transport.

7. Hospital-based providers should have the requisite training and sufficient volume of experience to maintain competency and deliver ECPR therapy with the same safe and effective manner of other invasive procedures.

8. Quality monitoring of all phases of care within an ECPR program is essential with detailed evaluations of each case to identify areas requiring improvement.

9. Program evaluation should track patient outcomes, in comparison to historical or concurrent controls, at the regional level to quantify the incremental gain in survivors and resource utilization.

Figure 1: Study Flow Diagram