A comprehensive regional clinical and educational ECPR protocol decreases time to ECMO in patients with refractory out-of-hospital cardiac arrest

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ABSTRACT

Objective: Extracorporeal membrane oxygenation within CPR (ECPR) may improve survival for refractory out-of-hospital cardiac arrest (OHCA). We developed a prehospital, emergency department (ED), and hospital-based clinical and educational protocol to improve the key variable of time-to-ECPR (TTE).

Methods: In a single urban health region we involved key prehospital, clinical, and administrative stakeholders over a 2-year period, to develop a regional ECPR program with destination to a single urban tertiary care hospital. We developed clear and reproducible inclusion criteria and processes, including measures of program efficiency. We conducted seminars and teaching modules to paramedics and hospital-based clinicians including monthly simulator sessions, and performed detailed reviews of each treated case in the form of report cards. In this before-and-after study we compared patients with ECPR attempted prior to, and after, protocol implementation. The primary outcome was TTE, defined as the time of initial professional CPR to establishment of extracorporeal circulation. We compared the median TTE for patients in the two groups using the Wilcoxon signed rank test.

Results: Four patients were identified prior to the protocol and managed in an ad hoc basis; for nine patients the protocol was utilized. Overall favourable neurological outcomes among ECPR-treated patients were 27%. The median TTE was 136 minutes (IQR 98 - 196) in the pre-protocol group, and 60 minutes (IQR 49 - 81) minutes in the protocol group ($p = 0.0165$).

Conclusion: An organized clinical and educational protocol to initiate ECPR for patients with OHCA is feasible and significantly reduces the key benchmark of time-to-ECPR flows.

RÉSUMÉ

Objectif: L'oxygénation par circulation extracorporelle (OCEC) en cours de réanimation cardiorespiratoire (RCR) peut améliorer la survie dans les cas d'arrêt cardiaque extrahospitalier (ACEH) réfractaire. Aussi avons-nous élaboré un protocole clinique et éducatif reposant sur le milieu préhospitalier, le service des urgences et le milieu hospitalier afin d'améliorer la principale variable temporelle liée à la RCR + OCEC.

Méthode: Des représentants importants des milieux préhospitalier, clinique et administratif ont travaillé, sur une période de deux ans, à l'élaboration d'un programme de RCR + OCEC dans une région sanitaire urbaine en vue du transport de malades vers un seul centre hospitalier de soins tertiaires, situé en ville. Ont été établis des critères d'inclusion et des processus précis et reproductibles, y compris des mesures d'efficacité du programme. Nous avons tenu des séminaires, préparé des modules d'enseignement à l'intention des ambulanciers paramédicaux et des cliniciens hospitaliers, organisé des séances mensuelles de formation par simulation, et procédé, sous forme de fiche, à l'examen détaillé de chacun des cas traités. Dans cette étude de type avant-après, il y a eu comparaison des patients soumis à des tentatives de RCR + OCEC avant et après la mise en œuvre du protocole. Le principal critère d'évaluation consistait en la mesure du temps écoulé avant la RCR + OCEC, défini comme le temps passé depuis le début des manœuvres de RCR par des professionnels jusqu'à l'établissement de la circulation extracorporelle. Nous avons comparé le temps médian écoulé avant la RCR + OCEC dans les deux groupes de patients à l'aide du test de Wilcoxon pour observations appariées.

Résultats: Quatre patients ont été retenus avant la mise en œuvre du protocole et pris en considération de façon

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ponctuelle, tandis que neuf autres patients ont été soumis au protocole. La proportion de résultats neurologiques favorables chez les patients traités par la RCR + OCEC a atteint, dans l'ensemble, 27 %. Le temps médian écoulé avant la RCR + OCEC était de 136 minutes (écart interquartile [EIQ] : 98-196) dans le groupe antérieur à la mise en œuvre du protocole et de 60 minutes (EIQ : 49 - 81) dans le groupe soumis au protocole (p = 0,0165).

Conclusion: Les résultats de l'étude montrent qu'il est possible d'élaborer un protocole clinique et éducatif sur la pratique de la RCR + OCEC chez les patients victimes d'un ACEH, et que celui-ci permet de réduire considérablement la principale valeur de référence liée au temps écoulé avant la RCR + OCEC.

Keywords: extracorporeal membrane oxygenation, heart arrest, cardiopulmonary resuscitation

INTRODUCTION

North American emergency medical services (EMS) attend to 134 cases of out-of-hospital cardiac arrest (OHCA) per 100,000 adult citizens annually,[1,2] with survival ranging from 3%-16%.[1,2] Emerging data have suggested that extracorporeal cardiopulmonary resuscitation (ECPR), a form of veno-arterial extracorporeal membrane oxygenation (ECMO) implanted during cardiac arrest, may improve survival in certain patients with refractory OHCA.[3-6]

Several centres have described ECPR experiences; although inclusion criteria—chiefly, younger patients with both rapid arrest recognition and initiation of cardiopulmonary resuscitation (CPR)—have been similar, outcomes have varied.[4-12] Positive outcomes appear to be strongly correlated with the time from arrest-to-ECPR initiation: survival is rare if this number exceeds 75 minutes.[4,5,7-12] In ECPR studies comparing in-hospital arrests with OHCAs, patients in the latter group—despite often demonstrating better prognostic characteristics such as a younger age and higher proportion of shockable rhythms—demonstrate significantly worse outcomes than their hospitalized counterparts,[7,8] likely in part because of the substantial increase in the time to ECPR initiation.

While the community is the most likely place for a sudden unexpected cardiac arrest in a previously healthy patient, the ideal ECPR candidate, there are logistical challenges in optimizing arrest-to-ECPR intervals for out-of-hospital patients with refractory arrest. At our institution, we recognized that in the small number of OHCAs that were treated with ECPR, the times required to initiate ECMO were prolonged. Further, as our prehospital system prioritizes on-scene resuscitation, with patients in refractory arrest uncommonly transported to the hospital, few could be considered for this therapy. For this reason, we developed a formal regional clinical ECPR protocol for OHCAs, the first of its kind in Canada, to improve the access and efficiency of ECPR initiation. The protocol included prehospital and hospital integration for early identification and transport of ECPR candidates, with rapid ECPR initiation upon hospital arrival for those who remained in refractory arrest. To achieve this, we instituted an intensive educational and quality improvement program, involving all members of the ECPR initiation team from each phase of care, to optimize time metrics. The primary goal of the ECPR service was to achieve expedited initiation of ECPR for appropriate patients; the aim of this study was to measure the change in times to ECPR initiation after protocol implementation.

METHODS

Study design and setting

This study was an observational before-and-after design examining the performance of a clinical protocol, which took place in a single health region including the cities of Vancouver and North Vancouver and the district municipalities of North Vancouver and West Vancouver, in the province of British Columbia (BC). The total land area is approximately 380 km^2 and contains a population of approximately 800,000 (73% between the ages of 15 and 65)[13] and four emergency departments (ED). The study hospital is St Paul's Hospital, a regional cardiac referral centre, which includes 24-hour access to cardiothoracic surgical services and cardiac catheterization, as well as cardiac transplant and ventricular assist device programs. The cardiovascular surgery program has provided ECPR services at St. Paul's Hospital since 2000 on a case-by-case basis, but with no formal protocol prior to the protocol described in this manuscript.[14] The ED treats approximately 85,000 patients annually.

This study protocol was submitted to and reviewed by the University of British Columbia (UBC)/Providence Healthcare Research Ethics Board but was deemed exempt from the requirements for researcher ethics approval both in accordance with UBC Policy and the provisions of the Tri-Council Policy because it was a classified as a quality improvement project.

Prehospital care

In BC, coordinated EMS is provided by municipal fire departments (FD) and the provincial Ambulance Service (BCAS). FD first responders are trained in basic life support (BLS)[15] including automated external defibrillators (AED). There are approximately 20 BLS[15] paramedic teams and four advanced life support (ALS)[17] paramedic teams on-duty at any given time; the latter attend to approximately 98% of OHCAs.[18] BCAS policy requires that all patients treated by EMS must undergo resuscitative efforts for at least 30 minutes prior to termination unless contrary to family wishes or a "do not resuscitate" order is identified.[19] Transport of patients who do not regain a pulse (ROSC) in the prehospital setting is rare.[18]

Development of hospital-based care protocols

In January 2014, discussions commenced regarding the establishment of a regional ECPR service for OHCA based at St. Paul's Hospital. It was acknowledged that ECPR services were already being utilized for OHCA, but quite infrequently and on an ad hoc basis, that there was no established eligibility criterion and that ECMO initiation times were prolonged. A committee was created involving administrative and clinical representatives from the health authority's senior leadership team, emergency medicine, cardiac surgery, perfusion services, cardiac anesthesiology, interventional cardiology, and critical care. The feasibility, potential benefits, resource utilization, and costs of such a formal program for OHCA ECPR application were discussed, and analyses were developed and published.[20,21] The committee endorsed the proposal, which was approved by the hospital administration in June 2015. Over the next six months, a formal OHCA ECPR hospital-based protocol was developed that commenced in January 2016. The stated overall vision was to improve the proportion of neurologically intact survivors among young previously healthy victims of sudden unexpected OHCA, through rapid identification of appropriate candidates and initiation of ECPR in the ED for a short duration of intensive therapy. The key goal metric of the protocol was time-to-ECMO (TTE) flows within 75 minutes, but preferably within 60 minutes, of initial professional resuscitative efforts. The inclusion and exclusion criterion are described in Figure 1. All required equipment and materials for ECPR initiation, including an ECMO unit, were acquired and housed in the ED resuscitation bay.

Activate *Code-ECPR* for those in refractory cardiac arrest if following criteria are met:

Inclusion Criteria (meets all of the following):

- Age ≤ 65 yr
- Witnessed Arrest (by bystander or EMS)
- Early CPR (bystander initiated OR time from 911 call to EMS CPR < 10 min)
- Cause of arrest is one of the following:
  - No obvious non-cardiac cause
  - Overdose of cardiac toxin (including beta-blockers, calcium channel blockers, tricyclic antidepressants, or digoxin), or
  - Hypothermia (with T < 32°C)*

Exclusion Criteria (meets any of the following):

- Any other cause of cardiac arrest
- Inappropriate for ICU admission
- Pre-Existing major organ system failure (incl. CHF, COPD, dialysis-dependent, liver failure, major neurological deficits)
- Active malignancy
- EMS arrival > 40 minutes from initial professional resuscitation

*Hypothermia-related arrests may be eligible for ECPR even if other inclusion criteria are not met, provided the patient is appropriate for ICU admission.

Figure 1. ECPR Criteria.

Development of novel prehospital ECPR protocol

In June 2015, discussions began with the senior leadership at BCAS. As arrests typically run for 30 minutes without transport to the hospital for those who did not achieve ROSC,[19,21] this new protocol required a major change. The prehospital phase of the protocol was developed, along with a training program for paramedics in the region, and was based on a six-step Kern approach.[22] One Lucas mechanical chest compression device (Physio-Control, Inc., Lund, Sweden) was acquired for each ALS team. The training package was sent to all paramedics: 1) a manual outlining the ECPR protocol; 2) a manual describing the operation of the Lucas device; 3) video instructions for the Lucas device; and 4) hypothetical case examples of potential ECPR patients. In addition, all ALS paramedics underwent: 1) standardized in-person training of the protocol and operation of the Lucas chest compression device; and 2) a test to confirm competency. A Lucas-compatible mannequin was placed in each ALS station for interval training. Pocket cards detailing the inclusion and exclusion criteria, as well as the prehospital portion of the protocol, were given to each paramedic.

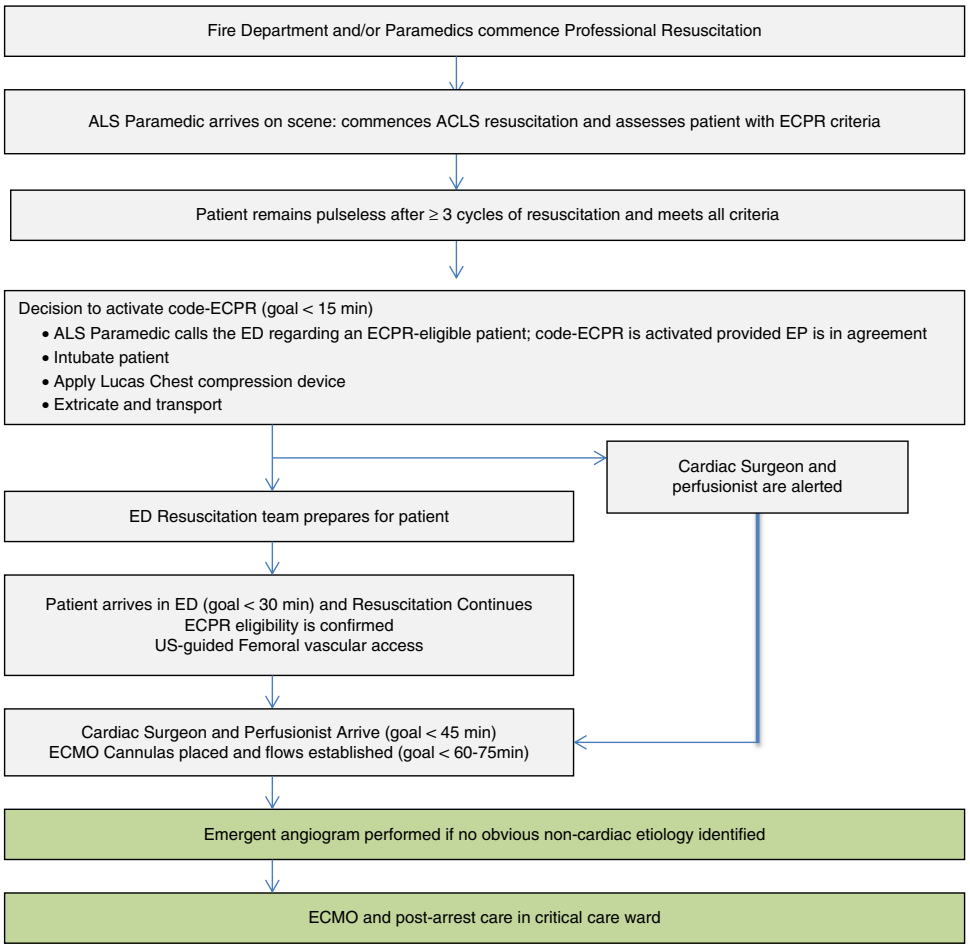

Figure 2. ECPR Protocol Scheme.

The protocol is shown in Figure 2. For all patients meeting the criteria, the ALS paramedic called the on-duty St. Paul's emergency physician (EP). The criteria were reviewed, and if candidacy was confirmed, the EP activated "code-ECPR." Paramedics intubated the patient (if not already performed), applied the Lucas compression device, extricated, and then transported the patient to St. Paul's Hospital with ongoing ACLS resuscitation.

ED and hospital-based protocol

Upon receiving a call from an ALS paramedic, the EP completed a standardized form to ensure the patient was appropriately included; if so, the EP initiated "code-ECPR." The ED unit clerk notified the on-call cardiovascular surgeon and perfusionist (in-hospital from 6:00 a.m. to 6:00 p.m., and within 30 minutes of the hospital at other times), as well as cardiac anesthesiology, intensive care, the cardiac surgery intensive care unit (ICU) nurse leader, and the hospital clinical coordinator. The ED team, consisting of two EPs, four nurses, and one respiratory therapist, assembled in the resuscitation bay prior to patient arrival, and various duties were assigned (Online Appendix 1). Upon patient arrival, the patient was again assessed using the eligibility criteria. One EP began placing single-bore 16-gauge catheters in the artery and vein using US guidance. In addition, a bedside US was performed to assess for reversible OHCA causes. Upon arrival, the cardiovascular surgeon assumed leadership of cannulation, inserting the ECMO cannulas with the EPs assisting and using a bedside US to assist with wire placement. ECMO flows were then commenced. Unless an obvious noncardiac cause was identified, an emergent coronary angiogram was performed. Online Appendix 2 details the strategy for ongoing ECMO management. All patients for whom withdrawal of

life-sustaining therapies was planned were considered for donation.

Medical and nursing education

Beginning in June 2015, we organized monthly stakeholder meetings to create a curriculum that was open to feedback and continuous iterative improvements. We sent monthly electronic messages to all ED staff regarding the protocol and invited contributions. At monthly departmental and educational rounds, various committee members gave ten-minute sessions relating to various protocol aspects.

We organized ECPR simulations involving prehospital and ED providers monthly since October 2015 and included ALS prehospital notification, code-ECPR activation, ED preparation and delegation of roles, paramedic arrival (with a mannequin on an EMS stretcher and ongoing mechanical chest compressions) and transfer of care, ED ACLS resuscitation, and US visualization of femoral vessels with US-guided catheterization. New medical supplies were used in each simulation to enhance verisimilitude. We used an adapted mannequin with a custom-made ballistic gel over a tubing insert to cannulate and place ECMO cannulas. At the conclusion of each session, a debriefing session was held, and the simulation director and program leaders provided feedback. Simulations were recorded for further analysis.

Quality improvement model

The Model for Improvement Framework of Deming's System of Profound Knowledge was utilized to achieve and sustain the primary outcome.[23] Real-time data were measured using run charts, with additional analysis to examine any particular cause variation noted.[23] We attempted to interview all participants after the ECPR activations, including all involved physicians and surgeons, nurses, perfusionists, and respiratory therapists.

Report cards

A designated quality and safety team was constructed to perform a standardized, detailed review of all "code-ECPR" activations that included interviews of participants, a synopsis of the event, calculation of time intervals, areas of success, and areas for improvement. We assembled template report cards (see Online Appendix 3) and sent them to all stakeholders and all ED staff members.

Selection of participants and analysis groups

This study included consecutive patients with nontraumatic refractory OHCA who had ECPR initiation attempted in the ED. Patients were excluded if sustained ROSC was achieved prior to ECPR initiation attempt.[24] We dichotomized patients based on whether they were treated prior to or after protocol implementation. We included patients who were treated up to two years prior to and within the first seven months of the commencement of the ECPR protocol.

Outcome measures and variable definitions

The primary outcome was the TTE, defined as the time of first professional resuscitative efforts to the commencement of ECMO flows. All cases were included in the analysis, regardless of whether adequate ECMO flows were achieved. In addition, we described the outcomes of the ECPR-treated patients at hospital discharge: 1) favourable neurologic outcomes defined as a cerebral performance category 1–2; and 2) survival.[25]

Data collection

All prehospital data including commencement of first EMS CPR, patient characteristics, Utstein variables,[25] and treatments were recorded on standardized BCAS template charting (in use since prior to the pre-protocol period). Perfusion services have used a standard template form for all ECMO initiations since before the pre-protocol time period; this template includes data entry for the time ECMO flows were first initiated. We collected data from these sources onto a standardized Excel spreadsheet, which was used to populate the ECPR report cards (Online Appendix 3). The overall number of OHCAs in the region was determined using the BC Resuscitation Outcomes Consortium OHCA Registry.[26]

Data analysis

We used Microsoft Excel 2008 (Microsoft Corp, Redmond, WA, USA) and R version 3.2.4 with the "exactRankTests" package (Foundation for Statistical Computing, Vienna, Austria) for data entry and analysis. QI Macros for Excel 2013 (KnowWare

International, USA) and statistical process control charts were used for quality improvement monitoring. We compared the median TTE for patients in the two groups using the Wilcoxon signed-rank test.

RESULTS

Characteristics of study subjects

The overall number of adult nontraumatic EMS-treated OHCAs in the region prior to and after the protocol implementation was 953 and 353, respectively. There were four and nine ECPR cases attempted prior to and after protocol commencement, respectively. The median age was 44 (IQR 35-58); two (15%) were female, and 62% had initial shockable cardiac rhythms (Table 1).

Main results

Patient characteristics are shown in Table 1. Of the pre-protocol patients, all had adequate ECMO flows established, and one (25%) survived (Table 2). One patient in the pre-protocol phase was transported to a different ED within the region and then transferred with ongoing CPR to St. Paul's hospital for ECPR initiation. After protocol implementation, ECPR was attempted in nine patients (all transported directly to St. Paul's), seven of whom had adequate ECMO flows established and two of whom survived. Of the two patients who could not have adequate ECMO flows established (thus precluding ECPR treatment), both were found to have aortic dissection on autopsy. All survivors had favourable neurological outcomes at hospital discharge. Two patients, both in the protocol group, were determined to be organ donation candidates; for one, an appropriate recipient was identified, and organs were donated (two kidneys, pancreas, and liver).

The median TTE flows prior to protocol implementation was 136 minutes (IQR 98-196 minutes), in comparison to 60 minutes during the protocol period (IQR 49-81 minutes, $p = 0.017$) (Table 2). The difference remained significant after removal of the one patient who was not transported directly to the ECPR-performing institution ($p = 0.027$). A run chart can be seen in Figure 3. The median door-to-ECPR time pre-protocol was 104 minutes (IQR 53-138), and after the protocol implementation, it was 28 minutes (IQR 20-45, $p = 0.011$).

Table 1. Patient characteristics and treatment data of ECPR attempts

	Pre-Protocol	Protocol
	n or median (% or IQR)	n or median (% or IQR)
Number	4	9
Age	38 (32-44)	46 (35-61)
Past Medical History		
None	1 (25)	3 (33)
Coronary artery disease	0	2 (22)
Mental health	1 (25)	2 (22)
Inflammatory bowel disease	1 (25)	1 (11)
COPD	1 (25)	1 (11)
Bystander CPR	3 (75)	6 (67)
Witnessed		
Bystander	2 (50)	6 (67)*
EMS	1 (25)	2 (22)*
Initial rhythm		
VF	3 (75)	5 (55)
PEA	1 (25)	2 (22)
Asystole	0	2 (22)
Etiology of arrest		
Hypothermia	2 (50)	2 (22)
ACS	1 (25)	3 (33)
Unknown	1 (25)	1 (11)
Aortic dissection	-	2 (22)
Electrolyte	-	1 (11)
Time of Resuscitation		
0601-1800	4 (100)	3 (33)
1801-0600	0	7 (77)
Time from first EMS CPR to ED Arrival		
Prehospital Resuscitation (minutes)	43 (26-66)	32 (25-44)
Hospital Duration		
ECMO, days†	0.86 (0.16-4.84)	1.10 (0.57-2.77)
ED/Critical Care, days	3.42 (0.20–8.57)	1.65 (0.17-13.99)
Total Hospital stay, days	3.42 (0.20-8.57)	1.65 (0.18-27.84)
Interventions		
Angiogram	1 (25)	4 (44)
Fasciotomy	1 (25)	1 (11)
CABG	1 (25)	0
Laparotomy	0	1 (11)
Complications		
Compartment syndrome requiring a fasciotomy	1 (25)	1 (11)
Vascular injury	0	1 (11)
Intracranial hemorrhage	0	1 (11)
Liver laceration	0	1 (11)

ACS = acute coronary syndrome; CABG = coronary artery bypass graft; CPR = cardiopulmonary resuscitation; ECMO = extracorporeal membrane oxygenation; EMS = emergency medical systems; PEA = pulseless electrical activity; VF = ventricular fibrillation.
*One protocol period patient who had an unwitnessed arrest was treated with ECPR; he fell out of a boat with companions and then arrested soon afterwards; he was considered a hypothermia-related arrest and thus was not required to meet all criteria; and he was a nonsurvivor.
†Patients for whom adequate ECMO flows were unable to be established were excluded from this statistic.

The median duration of ECMO treatment among survivors and non-survivors (excluding those for whom adequate ECMO flows were not established) was 1.10 days (IQR 1.02-2.77) and 0.86 days (IQR 0.37-3.07 days), respectively. The median duration of the total

Table 2. Patient outcomes

	Pre-Protocol	Protocol
	n or median (% or IQR)	n or median (% or IQR)
Time to ECMO flows (minutes)	136 (98-196)	60 (49-81)
Door to ECMO flows (minutes)	104 (53-138)	28 (20-45)
ECPR-treated outcomes at hospital DC		
Survival (n, %)	1/4 (25)	2/7 (29)
Favourable neurological outcome	1/4 (25)	2/7 (29)
Eligible organ donors	0/4 (0)	2/9 (22)

DC = discharge; ECMO = extracorporeal membrane oxygenation; ECPR = extracorporeal membrane oxygenation cardiopulmonary resuscitation.

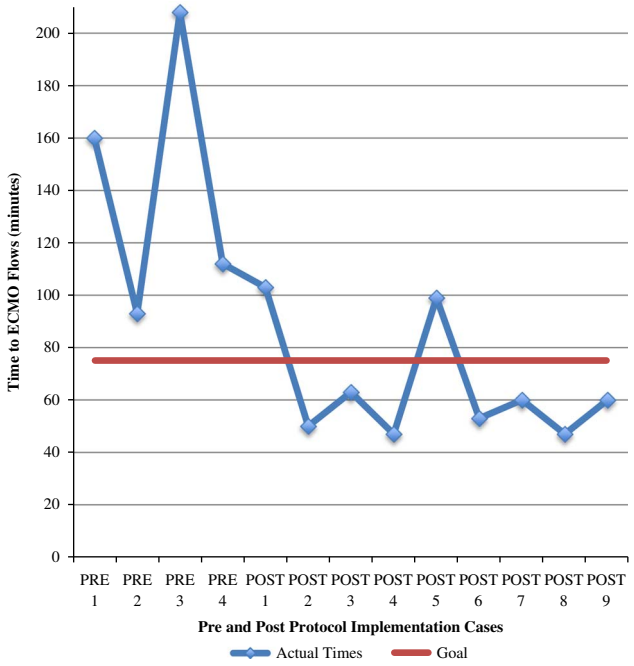

Figure 3. Run-Chart of ECPR Attempts in the Pre- and Post-Protocol time periods demonstrating Time-to-ECMO metrics.

hospital stay for survivors and non-survivors was 9.38 days (IQR 4.25-120.9) and 0.91 days (IQR 0.03-5.78), respectively.

DISCUSSION

We sought to improve outcomes from refractory OHCA in our region, specifically focusing on young victims of sudden unexpected cardiac arrest. We developed and implemented a structured formal multidisciplinary ECPR protocol involving prehospital resuscitation, prehospital-hospital coordination, pre-rehearsed ED management including the establishment of extra-corporeal membrane oxygenation, standardized post-arrest management, and ongoing education; the goal of this protocol was to achieve ECMO initiation in under 75 minutes from first paramedic contact. We found that there was a large decrease in the elapsed resuscitation duration to the establishment of ECMO flows after our protocol implementation. Importantly, during the pre-protocol period, when patients received unstructured care, the median 136-minute TTE exceeded a reasonable time frame that patients might be expected to survive; conversely, the median 60-minute TTE under the organized protocol is more likely to lead to positive outcomes. Our protocol, including the educational aspects and the description of the development process, might assist other hospitals in determining the feasibility of achieving required time metrics to provide ECPR therapy to patients with OHCA.

During the pre-protocol time, few OHCAs were treated with ECPR, likely because of the following: 1) the lack of a formal protocol; 2) the prehospital resuscitation paradigm focused on on-scene resuscitation; and 3) the infrequent intra-arrest patients transported to the hospital were sent to the closest hospital as opposed to one where a protocol would be developed. During this time, ECPR was only considered after failed ED resuscitative efforts that made acceptable TTE metrics virtually impossible, especially during times in which non-ED personnel were not in the hospital. While comparing time metric differences in the pre-hospital and hospital phases of care, it appears the greatest decrease was in the hospital phase. However, an essential component of this hospital-based improvement was prehospital activation of the protocol that allowed critical preparation to occur and mobilization of non-ED personnel to attend the ED—an especially key component as the majority of cases occurred outside of daytime hours in which non-ED personnel were offsite.

We previously reported an estimate of the number of potential ECPR candidates in our region and found that of those with initial shockable rhythms, the outcomes were already excellent, with 87% surviving to admission to a hospital ward.[20] Acknowledging these data, we were cognizant of the risk of worsening this high survival rate while building the protocol. Our examination of time-to-ROSC survival curves determined the optimal transport time to mitigate harm to patients who might have good outcomes with conventional resuscitation.[21]

To achieve the benefit of ACLS therapies both on-scene and during transport, we required that ALS paramedics attend to patients prior to transport for ECPR. This might have delayed hospital transport; however, we believed this would mitigate the risk of worsening baseline outcomes by maintaining all elements of our current conventional treatment algorithm at the scene and during transport. Our reliance on ALS-concentrated decision-making placed the experience with fewer but more experienced personnel, reducing training time and resources. In addition, we made mechanical CPR a prerequisite for transport and thus outfitted each ALS team with a mechanical chest compression device. While there is no evidence that mechanical chest compression devices are superior to manually performed CPR if applied to all OHCAs,[27] these devices have been shown to perform superior CPR quality during ambulance transport.[28,29]

The low volume of ECPR candidates is a threat to developing and maintaining competency in an ECPR protocol for OHCA within prehospital and ED settings. Our educational and simulation program sought to develop and maintain team-based familiarity with the procedure. Volumes may be higher in other settings with less strict inclusion criteria, those with existing outcomes including fewer patients who achieve ROSC, or those with differing population demographics or density.

Although not the primary objective of our efforts, our data indicates that the application of ECPR for OHCA in Canada may result in additional opportunities for organ procurement; this has the potential to benefit additional patients, and the cost-benefit of transplantation might offset the resource-intensive nature of ECPR therapy. In addition, the opportunity to donate, which would not otherwise be possible, may be an important source of consolation to bereaved families. Consistent with any patient with severe brain injury, our program incorporates the consideration of organ donation only after the decision of patient disposition as part of comprehensive end-of-life care. In contrast to OHCA ECMO programs in which ECMO is initiated with the primary purpose of supporting organ function for uncontrolled donation after cardiac death,[30,31] we believe that our donation practice does not represent conflict of interest.

Overall, our proportion of positive outcomes among those treated with ECPR was 27%. These data are consistent with previous reports.[32] Acknowledging the low sample sizes of ECPR-treated cases series, the undifferentiated mix of cardiac arrest patients with varied etiologies and baseline characteristics, and clinician selection bias, confidence in estimates of true effectiveness in terms of survival and comparisons with other sites or between different time periods are difficult to ascertain. The inclusion of non-shockable rhythms in our protocol also likely influenced our outcomes. Whereas those with refractory arrest after initial shockable rhythms might be better candidates, we elected to include patients with initial non-shockable rhythms as we hoped this therapy would be a way to improve the poor prognosis of this group. Overall, we found that non-survivors had modest impacts on resource utilization in terms of ECMO treatment durations and overall hospital stays.

LIMITATIONS

This is a single-region protocol, conducted from a single hospital with extensive experience in cardiovascular emergencies and prior ad hoc ECMO experience, but no previous formal in-hospital ECMO protocol. As such, our protocol, patients, and results might be difficult to replicate. In addition, our prehospital system, with long-standing experience in new protocols,[33-35] might differ from other settings. However, we offer a description of our experience and a template upon which other interested sites might build to accommodate the various demands of their individual EMS, region, EDs, and hospitals. It is possible that eligible patients were not correctly identified and not treated with the protocol. Although the outcomes of this study might be compared with outcomes of similar patients treated with equal durations of attempted conventional resuscitation,[21] this study is unable to make conclusions about ECPR efficacy.

From an analytic standpoint, our small sample size might limit enthusiasm. However, the post-protocol improvement in TTE is so profound that it is difficult to conceive what is because of chance alone. Patients with a 136-minute TTE are unlikely to have meaningful recovery after ECPR treatment[7,9]; the 60-75 minute zone is likely an appropriate benchmark.

CONCLUSIONS

An organized clinical and educational protocol to initiate ECPR for patients with OHCA is feasible and significantly reduces the key benchmark of time-to-flow.

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SUPPLEMENTARY MATERIAL

To view supplementary material for this article, please visit https://doi.org/10.1017/cem.2017.376

REFERENCES

1. Nichol G, Thomas E, Callaway CW, et al. Resuscitation Outcomes Consortium Investigators. Regional variation in out-of-hospital cardiac arrest incidence and outcome. *JAMA* 2008;300(12):1423-31.
2. Go AS, Mozaffarian D, Roger VL, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2014 update: a report from the American Heart Association. *Circulation* 2014;129(3):e28-292.
3. Morimura N, Sakamoto T, Nagao K, et al. Extracorporeal cardiopulmonary resuscitation for out-of-hospital cardiac arrest: A review of the Japanese literature. *Resuscitation* 201;82(1):10-4.
4. Wang CH, Chou NK, Becker LB, et al. Improved outcome of extracorporeal cardiopulmonary resuscitation for out-of-hospital cardiac arrest—a comparison with that for extracorporeal rescue for in-hospital cardiac arrest. *Resuscitation* 2014;85(9):1219-24.
5. Leick J, Liebetrau C, Szardien S, et al. Door-to-implantation time of extracorporeal life support systems predicts mortality in patients with out-of-hospital cardiac arrest. *Clin Res Cardiol* 2013;102(9):661-9.
6. Stub D, Bernard S, Pellegrino V, et al. Refractory cardiac arrest treated with mechanical CPR, hypothermia, ECMO and early reperfusion (the CHEER trial). *Resuscitation* 2014;1-7.
7. Haneya A, Philipp A, Diez C, et al. A 5-year experience with cardiopulmonary resuscitation using extracorporeal life support in non-postcardiotomy patients with cardiac arrest. *Resuscitation* 2012;83(11):1331-7.
8. Avalli L, Maggioni E, Formica F, et al. Favourable survival of in-hospital compared to out-of-hospital refractory cardiac arrest patients treated with extracorporeal membrane oxygenation: an Italian tertiary care centre experience. *Resuscitation* 2012;83(5):579-83.
9. Le Guen M, Nicolas-Robin A, Carreira S, et al. Extracorporeal life support following out-of-hospital refractory cardiac arrest. *Crit Care* 2011;15(1):R29.
10. Maekawa K, Tanno K, Hase M, Mori K, Asai Y. Extracorporeal cardiopulmonary resuscitation for patients with out-of-hospital cardiac arrest of cardiac origin: a propensity-matched study and predictor analysis. *Crit Care Med* 2013; 41(5):1186-96.
11. Nagao K, Kikushima K, Watanabe K, et al. Early induction of hypothermia during cardiac arrest improves neurological outcomes in patients with out-of-hospital cardiac arrest who undergo emergency cardiopulmonary bypass and percutaneous coronary intervention. *Circ J* 2010;74(1):77-85.
12. Kim SJ, Jung JS, Park JH, et al. An optimal transition time to extracorporeal cardiopulmonary resuscitation for predicting good neurological outcome in patients with out-of-hospital cardiac arrest: a propensity-matched study. *Crit Care* 2014;18(5):535.
13. Statistics Canada. Focus on Geography Series, 2011. Census. Ottawa; 2012.
14. Lamarche Y, Chow B, Bédard A, et al. Thromboembolic events in patients on extracorporeal membrane oxygenation without anticoagulation. *Innovations (Phila)* 2010;5(6):424-9.
15. Kleinman ME, Brennan EE, Goldberger ZD, et al. Part 5: Adult basic life support and cardiopulmonary resuscitation quality: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2015;132(18 Suppl 2):S414-35.
16. Link MS, Berkow LC, Kudenchuk PJ, et al. Part 7: Adult advanced cardiovascular life support: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2015;132(18 Suppl 2):S444-64.
17. Grunau B, Reynolds JC, Scheuermeyer FX, et al. Comparing the prognosis of those with initial shockable and non-shockable rhythms with increasing durations of CPR: informing minimum durations of resuscitation. *Resuscitation* 2016;101:50-6.
18. BC Ambulance Service Policy. Resuscitation of Critically Ill Patients, Vol. 2. Vancouver: BC Emergency Health Services; 2010. Policy Number 6.4.13.
19. Grunau B, Scheuermeyer FX, Stub D, et al. Potential candidates for a structured Canadian ECPR program for out-of-hospital cardiac arrest. *CJEM* 2016;18(6):453-60.
20. Grunau B, Reynolds J, Scheuermeyer F, et al. Relationship between time-to-ROSC and survival in out-of-hospital cardiac arrest ECPR candidates: when is the best time to consider transport to hospital? *Prehosp Emerg Care* 2016; 20(5):615-22.
21. Kern DE, Thomas P, Hughes M. Curriculum development for medical education: a six-step approach. 2nd ed. Baltimore: The John's Hopkins University Press; 2009.
22. Langley GJ, Nolan KM, Nolan TW, Norman CL. The Improvement Guide, A Practical Approach to Enhancing Organizational Performance. 2nd ed. San Francisco: Jossey-Bass Publishers; 2009.
23. Jacobs I, Nadkarni V, Bahr J, et al. International Liaison Committee on Resuscitation. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation

registries. A statement for healthcare professionals from a task force of the international liaison committee on resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa). *Resuscitation* 2004;63(3):233-49.

24. Perkins GD, Jacobs IG, Nadkarni VM, et al. Utstein Collaborators. Cardiac Arrest and Cardiopulmonary Resuscitation Outcome Reports: Update of the Utstein Resuscitation Registry Templates for Out-of-Hospital Cardiac Arrest: A Statement for Healthcare Professionals From a Task Force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia); and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. *Resuscitation* 2015;96:328-40.
25. Morrison LJ, Nichol G, Rea TD, et al. ROC Investigators. Rationale, development and implementation of the Resuscitation Outcomes Consortium Epistry-Cardiac Arrest. *Resuscitation* 2008;78(2):161-9.
26. Rubertsson S, Lindgren E, Smekal D, et al. Mechanical chest compressions and simultaneous defibrillation vs conventional cardiopulmonary resuscitation in out-of-hospital cardiac arrest: the LINC randomized trial. *JAMA* 2014; 311(1):53-61.
27. Fox J, Fiechter R, Gerstl P, et al. Mechanical versus manual chest compression CPR under ground ambulance transport conditions. *Acute Card Care* 2013;15(1):1-6.
28. Lyon RM, Crawford A, Crookston C, Short S, Clegg GR. The combined use of mechanical CPR and a carry sheet to maintain quality resuscitation in out-of-hospital cardiac arrest patients during extrication and transport. *Resuscitation* 2015;93:102-6.
29. Dalle Ave AL, Shaw DM, Gardiner D. Extracorporeal membrane oxygenation (ECMO) assisted cardiopulmonary resuscitation or uncontrolled donation after the circulatory determination of death following out-of-hospital refractory cardiac arrest-An ethical analysis of an unresolved clinical dilemma. *Resuscitation* 2016;108(0):87-94.
30. Manara AR, Dominguez-Gil B, Pérez-Villares JM, Soar J. What follows refractory cardiac arrest: Death, extracorporeal cardiopulmonary resuscitation (E-CPR), or uncontrolled donation after circulatory death? *Resuscitation* 2016;108:A3-5.
31. Ortega-Deballon I, Hornby L, Shemie SD, Bhanji F, Guadagno E. Extracorporeal resuscitation for refractory out-of-hospital cardiac arrest in adults: A systematic review of international practices and outcomes. *Resuscitation* 2016;101:12-20.
32. Aufderheide TP, Nichol G, Rea TD, et al. Resuscitation Outcomes Consortium (ROC) Investigators. A trial of an impedance threshold device in out-of-hospital cardiac arrest. *N Engl J Med* 2011;365(9):798-806.
33. Nichol G, Leroux B, Wang H, et al. ROC Investigators. Trial of continuous or interrupted chest compressions during CPR. *N Engl J Med* 2015;373(23):2203-14.
34. Kudenchuk PJ, Brown SP, Daya M, et al. Resuscitation Outcomes Consortium Investigators. Amiodarone, lidocaine, or placebo in out-of-hospital cardiac arrest. *N Engl J Med* 2016;374(18):1711-22.
35. Stiell IG, Nichol G, Leroux BG, et al. ROC Investigators. Early versus later rhythm analysis in patients with out-of-hospital cardiac arrest. *N Engl J Med* 2011;365(9):787-97.

ST. PAUL'S HOSPITAL
ECPR SERVICE

	PREPARATION	ROLE
RN 1	• Discuss roles with team • Move central fence between Resus 1 and 2 ~ one meter to create more space (see red markings on floor). • Move bed towards the center of the room (see red markings on floor). • Get appropriate paperwork out for charting. • Complete ECPR Preparation Checklist.	• Responsible for documenting the code. • Ensures ACLS algorithm is being followed – timing of defibrillation, chest compression pauses, and medication administration. • Control noise level in room and perform crowd control respectfully. • Sees the big picture in the room.
RN 2	• Get LUCAS out of case and ready for use. • Set up regional oximetry ensuring RN1 can visualize screen. • Ensure monitor is turned on with defibrillation pads attached to monitor. • Place ultrasound next to patient's right arm.	• Place patient on LUCAS device if not already on LUCAS. Troubleshoot as necessary. • Place patient on regional oximetry device. • Place patient on monitor and put defibrillation pads on patient. • Assist EP2 with US-guided vascular cannulation as necessary
RN 3	• Get epinephrine out of medication cart • Draw up 5000 units of heparin and label appropriately. • Prime arterial line • Help EP2 set up central line table (see below). • Spike two bags of cold saline. • Ensure IO device within reach if needed.	• Ensure pre-hospital IVs are patent with IV fluids running. • Start another IV if necessary. • Draw up and give medications as needed throughout code.
RN 4	• Help EP1 set up the CV Surgeon table (see below). • Ensure groin shaver, sterile marker, and chorhexadine is ready • Get any materials needed from outside the room.	• Help transfer patient onto hospital stretcher. • Expose patient and place in hospital gown. • Shave and help sterilize groin • Help with IV access if necessary. • Gather additional equipment and assist as needed. • Set up arterial line when needed.
EP 1	• Discuss roles with team • Place metal ECPR table at the foot of the bed. • Cover with sterile drape and place 60ml catheter tip syringe (filled with sterile saline), two large piles of 4x4 gauze, and two sterile gowns on top of the drape. Cover with a second sterile drape. All materials are in CV Surgeon box on ECMO table.	• Team Leader for entire resuscitation • Take report from Paramedics. • Airway management • Communicate with and introduce CV Surgeon to team. • Perform US visualization of wires and/or cannulae after insertion
EP 2	• Prepare central line supplies for US-guided femoral access of artery and vein. • Materials in the EP box on ECMO table. • Be dressed in sterile gown and gloves, prepared to cannulate, when patient enters the room.	• Sterilize groin after shave, place double groin angiogram drape, and • US identification of femoral vein and artery • Place single bore CVC into femoral artery and vein. • Draw blood from central line to be sent to lab. • Assist CV surgeon as needed with cannulation.
RT	• Ensure necessary airway equipment is readily available for when patient arrives. • Set up ETC02 monitor.	• Take over airway management on patient arrival. • Ventilate with 100% oxygen through established ETT or using BVM if patient is not intubated. • Attach ETCO2 monitoring. Inform RN1 of values when initiating ETCO2 monitoring and prn.

Providence HEALTH CARE

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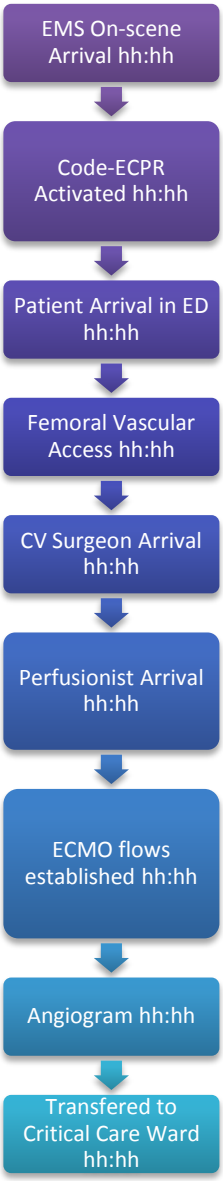
How you want to be treated.

The St. Paul's Hospital ECPR Service for Out-Of-Hospital Cardiac Arrest
REPORT CARD

***Objective**:* To Improve the survival of patients in the community with sudden unexpected cardiac arrest
ECPR Service Goal: EMS On-scene Arrival time to ECPR flows < 60-75 minutes

PATIENT CHARACTERISTICS		
Provincial Health Number		[redacted]
Age		
Date of arrest		
Initial arrest rhythm		
Bystander CPR		
Arrest witnessed? (No vs Bystander vs EMS)		
Presumed cause of arrest		
PREPARATION		
Was the protocol initiated pre-hospital?		
Were all ED pre-arrival tasks completed?		
Did the activation fit criteria?		
TIME INTERVALS*		
EMS on-scene arrival to:	ED notification (goal < 15 min)	
	ED arrival (goal < 30 min)	
	ECMO flows (goal < 60-75 min)	
ED Arrival to:	Femoral Access (goal < 15 min)	
	ECMO flows (goal < 30 min)	
ECMO flow to angiogram (goal < 60 min)		
Time family provided updated		

CLINICIANS	
ALS Paramedics	
ED Nurses	
ED Physicians	
CV Surgeons (s)	
Perfusionist (s)	
Social Worker	
Interventional Cardiologist	
Cardiac Anesthesiologist	
Intensivists(s)	



*** Basic Time Interval Goals Scheme:** EMS-Arrival (time 0) → EMS call ED & code-ECPR activated (goal<15min) → Pt arrival in ED (goal<30 min) → Fem vessels have been cannulated (goal<45 min) → ECMO flows established (goal<60-75 min)

CASE DESCRIPTION

- _
- _
- _

AREAS FOR IMPROVEMENT

- _
- _
- _
- _
- _

WHAT WENT WELL

Event analysis

Problem identified	Problem impact	Ideas for improvement
•	•	•
•	•	•
•	•	•
•	•	•

References:

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Review

Extracorporeal Cardiopulmonary Resuscitation for Refractory Out-of-Hospital Cardiac Arrest: The State of the Evidence and Framework for Application

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ABSTRACT

Out-of-hospital cardiac arrest (OHCA) affects 134 per 100,000 citizens annually. Extracorporeal cardiopulmonary resuscitation (ECPR), providing mechanical circulatory support, may improve the likelihood of survival among those with refractory OHCA. Compared with in-hospital ECPR candidates, those in the out-of-hospital setting tend to be sudden unexpected arrests in younger and healthier patients. The aims of this review were 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 showing ECPR effectiveness compared with conventional resuscitation. However, it is highly likely that ECPR, provided after a prolonged attempt with conventional resuscitation, does benefit select patient populations compared with conventional resuscitation alone. Although reliable data showing the optimal patient selection criteria for ECPR are lacking, most implementations sought young previously healthy

RÉSUMÉ

L'arrêt cardiaque hors de l'hôpital (ACHH) touche 134 citoyens sur 100 00 par année. La réanimation cardiorespiratoire extracorporelle (RCR-E), qui offre une assistance circulatoire mécanique, pourrait permettre d'améliorer la survie chez ceux qui ont un ACHH réfractaire. Comparativement à la RCR-E à l'hôpital, la RCR-E hors de l'hôpital entraîne généralement des morts subites inopinées chez des patients plus jeunes et en meilleure santé. Les objectifs de la présente revue étaient de résumer et de déterminer les limites des données probantes qui évaluent la RCR-E lors d'ACHH, et de proposer une approche pour l'application du programme de RCR-E. Bien qu'il existe de nombreuses descriptions de cohortes traitées par RCR-E, nous trouvons peu de données fiables qui montrent l'efficacité de la RCR-E par rapport à celle de la réanimation classique. Toutefois, il est fort probable que la RCR-E offerte après une tentative prolongée de réanimation classique constitue un avantage pour certaines populations de patients par rapport à la réanimation classique seule. Bien qu'il manque de

Emergency medical services (EMS) attend 134 out-of-hospital cardiac arrests (OHCAs) 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 cardiopulmonary resuscitation (CPR), as well as advances and protocolization of postarrest care.

The goal of cardiac arrest resuscitation is twofold: (1) to maintain cerebral and systemic perfusion with early and effective chest compressions; and (2) to achieve return of spontaneous circulation (ROSC). Unfortunately, although

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patients with rapid high-quality cardiopulmonary resuscitation. Carefully planned development of ECPR programs, in high-performing emergency medical systems at experienced extracorporeal membrane oxygenation 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 compared with standard care, while accounting for resource utilization.

données fiables montrant les critères optimaux de sélection des patients admis à la RCR-E, la plupart de ces réanimations étaient pratiquées sur de jeunes patients auparavant en bonne santé qui avaient subi une réanimation cardiorespiratoire immédiate de haute qualité. L'élaboration de programmes de RCR-E minutieusement planifiée, dans des systèmes de soins d'urgence de haute performance de centres expérimentés dans l'oxygénation par membrane extracorporelle (ECMO, de l'anglais *extracorporeal membrane oxygenation*), serait raisonnable dans le cadre des efforts systématiques pour déterminer l'efficacité de la RCR-E et améliorer les soins à l'échelle mondiale. L'évaluation du protocole exige une évaluation à l'échelle régionale, qui examine les avantages supplémentaires de la survie par rapport aux soins courants en tenant compte de l'utilisation des ressources.

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 (extracorporeal cardiopulmonary 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—although showing wide heterogeneity in outcomes—have shown promise.[5-7] However, because existing data are observational, estimates of effectiveness are limited by significant differences in systems of care and biases.

Compared with in-hospital cardiac arrests (IHCAs) who presented to hospital because of preceding symptoms and/or other significant comorbidities, OHCA patients typically experience sudden unexpected cardiac arrests 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 might 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 were to document the state of the evidence of ECPR for OHCA, reflect on the limitations, and to provide an approach for ECPR protocol development. Building on previous work ECPR for IHCA,[10] this review is focused on the aspects unique to OHCA.

Review of the Literature

Search strategy, data extraction, and quality assessment

To provide an overview of the evidence of ECPR efficacy for OHCA, we (E.G.) designed a search strategy (Supplemental Appendix S1) to identify systematic reviews (SRs) and meta-analyses. From 2005 to May 29, 2017, we searched: MedLine (Ovid), Embase (Ovid), Cochrane (Wiley), PubMed (National Library of Medicine), and Web of Science (Thomson Reuters), with no language restrictions. We used text words in the title, abstract, or key word fields, and relevant subject indexing to retrieve SRs or meta-analyses documenting the use of ECPR/ECMO for human cardiac arrest. Two reviewers (L.H., I.O.-D.) independently screened citations according to 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 SRs 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 fulfil the criteria for high quality SRs.[11] Data from each review were then extracted according to predefined selection criteria. The 2 reviewers independently assessed the quality of included reviews using the 11-item validated **A** **M**ea**s**urement **T**ool to **A**ssess Systematic **R**eviews (AMSTAR) tool.[11]

Results

Our systematic search produced 327 citations (Supplemental Appendix S1 and Fig. 1). After screening, we identified 12 SRs, 7 of which were excluded after full text retrieval,[4,12-17] leaving 5 included studies.[5,18-21]

Four of the SRs limited study eligibility to those that compared ECPR with conventional resuscitation,[18-21] all including different combinations of 5 studies (Tables 1 and 2; Supplemental Appendixes S2 and S3). The review by Kim et al.[19] included the propensity score-matched comparisons of Kim et al.[24] and Maekawa et al.[22] Neurological outcomes at hospital discharge (relative risk [RR], 8.00; 95% confidence interval [CI], 1.04-61.71) and 3- to 6-month neurologic outcomes (RR, 4.64; 95% CI, 1.41-15.25) were superior in the ECPR group. Squiers et al.[21] included the same studies but did not attempt a meta-analysis.[24] Wang et al.[18] also included these studies, with an additional third study (with 20 ECPR and 683 conventional CPR patients),[26] however, included 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.[20] included propensity matched data from Maekawa et al.,[22] a prospective parallel group study,[23] and a large

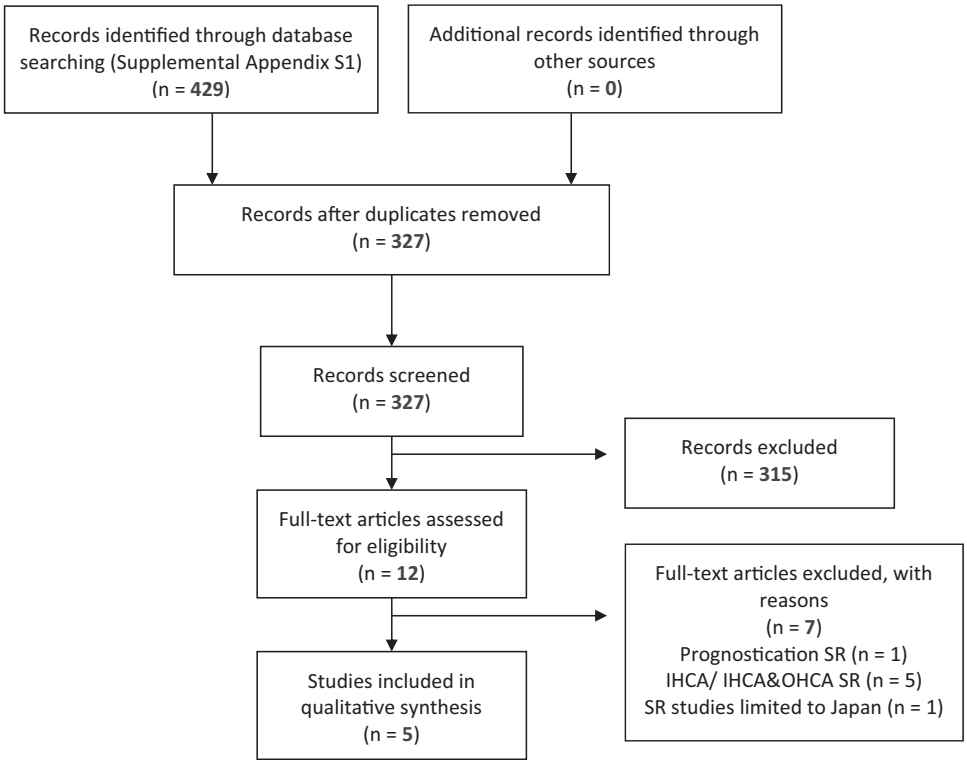

Figure 1. Study flow diagram. IHCA, in-hospital cardiac arrest; OHCA, out of hospital cardiac arrest; SR, systematic review.

unmatched prospective observational cohort,[25] and reported that ECPR was not associated with improved outcomes.

Ortega-Deballon et al. included all studies that reported outcomes of ECPR-treated adult OHCAs, without restricting to comparative studies,[5] and included 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 resulted in a low or very low quality of evidence for ECPR in refractory OHCA.[27] Selection bias by clinicians for ECPR therapy is a major limitation, in addition to significant heterogeneity in the intervention provided and study populations.

Most SRs included studies that compared those treated with ECPR, to those treated exclusively with conventional resuscitation, on the basis of 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 rates when treated with convention resuscitation, on the basis of criteria that mandate highly favourable prognostic features.[2,28] 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 in whom prolonged conventional efforts have failed, compared with those for whom a proportion were successfully resuscitated.

In reality, 2 strategies should be compared: conventional resuscitation with the option to perform ECPR, or conventional resuscitation alone. Comparisons should include patients who meet the same criteria at a prespecified duration of resuscitation, and thus the "ECPR protocol group" should include a proportion of those resuscitated via conventional means. A quasiexperimental study by Sakamoto and colleagues,[23] in which 46 tertiary hospitals in Japan self-allocated to either an ECPR arm or a conventional care arm, enrolled 419 patients with OHCA with initial shockable rhythms in refractory arrest at hospital arrival (mean enrollment 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 might provide higher-quality evidence for the effectiveness of ECPR for OHCA.[29-34]

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

Previous studies define the limits of survivable CPR duration for patients who meet ECPR criteria, but who are treated exclusively with conventional resuscitation.[28,35] 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.[28] The probability of survival showed a continual decline with increasing durations of elapsed resuscitative efforts. The

Table 1. Characteristics of included systematic reviews

Characteristics	Kim et al.[19]	Wang et al.[18]	Ahn et al.[20]	Squiers et al.[21]	Ortega-Deballon et al.[5]
Time period	August 1965 to February 2015	January 2000 to December 19, 2015	NR to December 22, 2015	Start of MedLine to December 1, 2015	January 1, 2005 to May 25, 2015
Inclusion criteria	1. Adult (16 years or older) 2. IHCA or OHCA 3. Compared ECPR vs CCPR 4. Reported survival and neurologic outcomes	1. Studies with n $\geq$ 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 $\geq$ 15; case series n $\geq$ 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 postcardiac surgery 3. Pediatric patients (age younger than 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 noncardiac origin (eg, 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; unmatched 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)
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 months 2. Superior neurological outcomes at discharge and 3-6 months 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 was 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]

AMSTAR, **A M**ea**s**urement **T**ool to **A**ssess Systematic **R**eviews; CA, cardiac arrest; CCPR, conventional cardiopulmonary resuscitation; CPC, cerebral performance category; ECPR, extracorporeal cardiopulmonary resuscitation; GOS, Glasgow Outcome Scale; IHCA, in-hospital cardiac arrest; LOE, level of evidence; NR, not reported; OHCA, out of hospital cardiac arrest.

Table 2. Characteristics of individual studies included in meta-analyses

Study	Included in: Wang et al.[18]	Ahn et al.[20]	Kim et al.[19]	Period and country	Study type	Population (n)	Main finding
Maekawa et al.[22]	Yes (unmatched cohort)	Yes	Yes	2000-2004 Japan	Prospective single-centre observational matched	ECPR (53/24*) CCPR (109/24*)	ECPR might improve neurologic outcome
Sakamoto et al.[23]	No	Yes	No	2008-2012 Japan	Prospective multicentre observational	ECPR (260) CCPR (194)	Bundle of TH, IABP, and ECPR associated with improved neurologic outcome
Kim et al.[24]	Yes (unmatched cohort)	No	Yes	2006-2013 Korea	Prospective single-centre observational matched	ECPR (55/52*) CCPR (444/52*)	Bundle of TH and ECPR might improve neurologic outcome
Lee et al.[25]	Yes	No	No	2009-2014 Korea	Retrospective single-centre observational	ECPR (20) CCPR (683)	Comparable survival for ECPR vs CCPR
Choi et al.[26]	No	Yes†	No	2009-2013 Korea	Retrospective multicentre matched	ECPR (320*) CCPR(36 227/320*)	No difference in survival shown for ECPR vs CCPR

CCPR, conventional cardiopulmonary resuscitation; CPR, cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation; ED, emergency department; EMS, emergency medical services; IABP, intra-aortic balloon pump; TH, therapeutic hypothermia.

*Number in matched cohort.

†The meta-analysis from Ahn et al.[20] used 1:1 propensity score matched cohort from Choi et al.[26] adjusted for covariables: year, age, sex, 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.

longest duration until ROSC in a survivor with a favourable neurological outcome (modified Rankin Scale [mRS $\leq$ 3]) was 47 minutes, suggesting beyond this there is no further benefit of conventional resuscitation. Conversely, existing data show positive outcomes among those treated with ECPR after 47 minutes of CPR,[17,36] 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 in whom conventional therapy has failed, thereby creating a bimodal distribution of resuscitation durations among survivors. Kim et al. compared outcomes stratified according to duration of resuscitation in 444 conventionally treated patients with 55 ECPR-treated OHCA patients.[24] 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 who received 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, compared with conventional therapy, is less clear (Table 3).

Some might argue, on the basis of these data, that the need for an ECPR randomized trial for those with prolonged refractory arrest would be comparable with the need for a trial randomizing those with renal failure to dialysis or placebo, or randomizing those skydiving to parachute or sham device.[37] Robust evidence showing efficacy for dialysis and parachutes is similarly lacking, however, it is clear that without these interventions the outcome is surely death. There are 2 caveats to this argument, however. First, the initiation of ECPR requires transport to hospital, which has been shown to impair resuscitation quality.[38] Alterations to current protocols in favour of intra-arrest transport might thereby worsen overall outcomes, even if ECPR does confer benefit.[39] Currently, studies that compared ECPR with conventional therapies are limited to systems with "load and go" protocols,[19,22-24,26] limiting external validity to other models. Second, prognostication bias, in which clinicians cease resuscitations because of a predicted poor outcome, limit robust estimates of outcomes with CPR performed beyond 47 minutes, because for most patients efforts have already been terminated.[28] However, on the basis of analyses of large data sets, survival with conventional resuscitation beyond this juncture appears to be very unlikely.[40,41]

Table 3. Uncertainties regarding ECPR for OHCA

- ECPR effectiveness for refractory OHCA: completely obvious or entirely unknown?
  There are no RCTs to inform of efficacy. 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, on the basis of previous data showing 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 OHCAs 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 nonsurvivors should be offered the opportunity for organ donation. Organ donation should be reported as a secondary outcome of any evaluation of ECPR.

CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; EMS, emergency medical services; OHCA, out of hospital cardiac arrest; RCT, randomized controlled trial.

EMS Differences and the Need for a True Denominator

With the exception of reports of ECPR initiated in the prehospital setting,[42] 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),[43] to those selected for ECPR (some without initiation because of 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 might 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 on ECPR-treated patients within a system reported a median EMS on-scene time of 7 minutes and overall functional survival of 1.6%.[26] With these stark differences to North American systems (considerably longer scene time and overall survival typically several-fold higher[44,45]) external validity of ECPR outcomes is unclear. Furthermore, it is possible that systems with high rates of successful conventional resuscitation and overall survival might garner minimal incremental benefit from ECPR, because in most candidates ROSC was successfully achieved.

Who Are Ideal Candidates for ECPR?

ECPR deployment is typically highly selective,[5,17] 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, 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 because of resource constraints.

Many ECPR protocols exclude patients with nonshockable initial rhythms,[5] a group for whom the probability of ROSC with conventional efforts is low.[40] 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 nonshockable rhythms may have more incremental benefit from ECPR on the basis of poor survival with current best practices (and potentially the greatest number of net survivors because of the higher incidence), albeit likely with lower proportional survival compared with shockable comparators. Among those with nonshockable 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%.[17] 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 nonsurvivors with respect to laboratory values such as pH and lactate preclude robust "cutoff 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 might be modest. One study in Vancouver (population approximately 1 million) reported that 10% of patients with OHCA met the local ECPR criteria, of whom one-third were refractory to conventional resuscitation and thus might have benefited from ECPR (approximately 12 per year).[2] This estimate would be lower if restricted to shockable rhythms. A study from Vienna reported that 6% of OHCAs fulfilled their criteria for ECPR.[46] Estimates of ECPR candidates may vary in different regions depending on the proportion of OHCA patients successfully resuscitated, patient demographic characteristics, and population density.

A recent large North American EMS-based study reported that overall 4.0% were ECPR-eligible and refractory to resuscitation.[28] Interestingly, this study showed the likelihood of survival with favourable neurological status with increasing duration 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 those with conventional ROSC after similar duration, this gives an estimate of the maximum potential benefit of ECPR. Further, it shows the neurological resilience of ECPR candidates with prolonged CPR.

Resource Implications and Readiness

OHCA patients treated with ECPR require resource-intensive management, which might 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 before transport, while at the same time minimizing delays for ECMO initiation.[17,35]

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 postarrest 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 ECMO duration of 2 days (interquartile range, 1-5 days), and a median hospital stay of 13 days (interquartile

range, 1.3-22 days)[6]; other reports are similar.[47,48] Although this short hospital stay is resource-intensive, young previously healthy patients with many potential years of life to be gained might warrant this investment. Cost-benefit analyses might explore what number of ECPR-treated survivors is a reasonable use of resources.

Donation-Related Considerations

When using advanced resuscitation treatments, the first and foremost priority is saving the patient's life with the goal of neurologically favourable survival. However, although treatment advances have led to improvements in survival, the most common outcome remains death,[1] with many patients suffering irreversible anoxic brain injury. Although organ donation has not traditionally been reported in OHCA studies, the 2015 International Liaison Committee on Resuscitation (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."[45] 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.[49] Because abdominal and thoracic vital organs can recover despite irreversible brain injury after resuscitated cardiac arrest,[50] patients who suffer cardiac arrest, including those treated with ECPR, might 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.

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 before 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 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 that require improvement.
9. Program evaluation should track patient outcomes, compared with historical or concurrent controls, at the regional level to quantify the incremental gain in survivors and resource utilization.

CPR, cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation; OHCA, out of hospital cardiac arrest.

A Framework for ECPR Application

Canadian experience with ECPR for OHCA is limited. Although there have been reports on the use of ECPR for IHCA,[51,52] only 1 study has described the experience with a formal OHCA ECPR protocol.[47]

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 be 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 effect.
2. An ECPR program within 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 who use 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 are 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. Because of 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 might differ on the basis of patient circumstances and initial cardiac rhythm.[35,36] Further, strategies to maintain all aspects of high-quality resuscitation during transport should be pursued; mechanical chest compression devices might 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 show success in delivering high-quality conventional resuscitation. ECPR might 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[45] before implementing selective resource-intensive programs.

6. Prehospital and hospital-based cooperative planning is essential 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 might be best facilitated by a smaller group of paramedics in tiered paramedic systems, in consultation with hospital-based clinicians.[47] Because existing data suggest a low likelihood of survival when ECPR is initiated beyond 75 minutes of CPR,[5,7,24] a reliable system of prehospital protocol activation might be critical to achieve the rapid deployment of ECMO required for positive outcomes.[47]
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.[5-7,33,53] 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. Because of the rarity of these cases, and the relative large human resource pool, regular ECPR simulation training is likely essential for institutional competency and excellence.[47] The term, "crash onto ECMO" is an example of a poor conceptual model, which condones an ill-prepared chaotic procedure. Rather, centres that use 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 that require improvement.[47] Prehospital records should be reviewed to ensure high-quality resuscitation was continued during extrication and transport. Because resuscitation duration before ECPR initiation is correlated with outcomes,[17] metrics detailing time intervals from EMS dispatch to ECMO flows, and door-to-ECMO flows, should be reviewed.
9. Program evaluation should track outcomes, compared with 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 might report: "Compared with 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 nonsurvivors 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 might be reasonable as part of ongoing efforts to improve systems of care and to gather more data regarding the incremental effectiveness of this intervention.

Disclosures

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References

1. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics—2014 update: a report from the American Heart Association. Circulation 2014;129:e28-292.
2. Grunau B, Scheuermeyer FX, Stub D, et al. Potential candidates for a structured Canadian ECPR program for out-of-hospital cardiac arrest. CJEM 2016;18:453-60.
3. Chan PS, McNally B, Tang F, Kellermann A; CARES Surveillance Group. Recent trends in survival from out-of-hospital cardiac arrest in the United States. Circulation 2014;130:1876-82.
4. Morimura N, Sakamoto T, Nagao K, et al. Extracorporeal cardiopulmonary resuscitation for out-of-hospital cardiac arrest: a review of the Japanese literature. Resuscitation 2011;82:10-4.
5. Ortega-Deballon I, Hornby L, Shemie SD, Bhanji F, Guadagno E. Extracorporeal resuscitation for refractory out-of-hospital cardiac arrest in adults: a systematic review of international practices and outcomes. Resuscitation 2016;101:12-20.
6. Stub D, Bernard S, Pellegrino V, et al. Refractory cardiac arrest treated with mechanical CPR, hypothermia, ECMO and early reperfusion (the CHEER trial). Resuscitation 2015;86:88-94.
7. Leick J, Liebetrau C, Szardien S, et al. Door-to-implantation time of extracorporeal life support systems predicts mortality in patients with out-of-hospital cardiac arrest. Clin Res Cardiol 2013;102:661-9.
8. Kagawa E, Inoue I, Kawagoe T, et al. Assessment of outcomes and differences between in- and out-of-hospital cardiac arrest patients treated with cardiopulmonary resuscitation using extracorporeal life support. Resuscitation 2010;81:968-73.
9. Avalli L, Maggioni E, Formica F, et al. Favourable survival of in-hospital compared to out-of-hospital refractory cardiac arrest patients treated with extracorporeal membrane oxygenation: an Italian tertiary care centre experience. Resuscitation 2012;83:579-83.
10. Singal RK, Singal D, Bednarczyk J, et al. Current and future status of extracorporeal cardiopulmonary resuscitation for in-hospital cardiac arrest. Can J Cardiol 2017;33:51-60.

11. Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol 2007;7:10.

12. Cardarelli MG, Young AJ, Griffith B. Use of extracorporeal membrane oxygenation for adults in cardiac arrest (E-CPR): a meta-analysis of observational studies. ASAIO J 2009;55:581-6.

13. Cheng R, Hachamovitch R, Kittleson M, et al. Complications of extracorporeal membrane oxygenation for treatment of cardiogenic shock and cardiac arrest: a meta-analysis of 1,866 adult patients. Ann Thorac Surg 2014;97:610-6.

14. Ouweneel DM, Schotborgh JV, Limpens J, et al. Extracorporeal life support during cardiac arrest and cardiogenic shock: a systematic review and meta-analysis. Intensive Care Med 2016;42:1922-34.

15. Xie A, Phan K, Tsai YC, Yan TD, Forrest P. Venoarterial extracorporeal membrane oxygenation for cardiogenic shock and cardiac arrest: a meta-analysis. J Cardiothorac Vasc Anesth 2015;29:637-45.

16. Lehot JJ, Long-Him-Nam N, Bastien O. Extracorporeal life support for treating cardiac arrest [in French]. Bull Acad Natl Med 2011;195:2025-33 [discussion: 2033-2036].

17. Debaty G, Babaz V, Durand M, et al. Prognostic factors for extracorporeal cardiopulmonary resuscitation recipients following out-of-hospital refractory cardiac arrest. A systematic review and meta-analysis. Resuscitation 2017;112:1-10.

18. Wang GN, Chen XF, Qiao L, et al. Comparison of extracorporeal and conventional cardiopulmonary resuscitation: a meta-analysis of 2 260 patients with cardiac arrest. World J Emerg Med 2017;8:5-11.

19. Kim SJ, Kim HJ, Lee HY, Ahn HS, Lee SW. Comparing extracorporeal cardiopulmonary resuscitation with conventional cardiopulmonary resuscitation: a meta-analysis. Resuscitation 2016;103:106-16.

20. Ahn C, Kim W, Cho Y, et al. Efficacy of extracorporeal cardiopulmonary resuscitation compared to conventional cardiopulmonary resuscitation for adult cardiac arrest patients: a systematic review and meta-analysis. Sci Rep 2016;6:34208.

21. Squiers JJ, Lima B, DiMaio JM. Contemporary extracorporeal membrane oxygenation therapy in adults: fundamental principles and systematic review of the evidence. J Thorac Cardiovasc Surg 2016;152:20-32.

22. Maekawa K, Tanno K, Hase M, Mori K, Asai Y. Extracorporeal cardiopulmonary resuscitation for patients with out-of-hospital cardiac arrest of cardiac origin: a propensity-matched study and predictor analysis. Crit Care Med 2013;41:1186-96.

23. Sakamoto T, Morimura N, Nagao K, et al. Extracorporeal cardiopulmonary resuscitation versus conventional cardiopulmonary resuscitation in adults with out-of-hospital cardiac arrest: a prospective observational study. Resuscitation 2014;85:762-8.

24. Kim S, Jung J, Park J, et al. An optimal transition time to extracorporeal cardiopulmonary resuscitation for predicting good neurological outcome in patients with out-of-hospital cardiac arrest: a propensity-matched study. Crit Care 2014;18:535.

25. Lee SH, Jung JS, Lee KH, et al. Comparison of extracorporeal cardiopulmonary resuscitation with conventional cardiopulmonary resuscitation: is extracorporeal cardiopulmonary resuscitation beneficial? Korean J Thorac Cardiovasc Surg 2015;48:318-27.

26. Choi DS, Kim T, Ro YS, et al. Extracorporeal life support and survival after out-of-hospital cardiac arrest in a nationwide registry: a propensity score-matched analysis. Resuscitation 2016;99:26-32.

27. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64:383-94.

28. Reynolds JC, Grunau BE, Elmer J, et al. Prevalence, natural history, and time-dependent outcomes of a multi-center North American cohort of out-of-hospital cardiac arrest extracorporeal CPR candidates. Resuscitation 2017;117:24-31.

29. ClinicalTrials.gov. Emergency cardiopulmonary bypass for cardiac arrest. Available at: https://clinicaltrials.gov/ct2/show/NCT01605409. Accessed May 4, 2017.

30. ClinicalTrials.gov. Early initiation of extracorporeal life support in refractory OHCA. Available at: https://clinicaltrials.gov/ct2/show/NCT03101787. Accessed May 4, 2017.

31. ClinicalTrials.gov. A comparative study between a pre-hospital and an in-hospital circulatory support strategy (ECMO) in refractory cardiac arrest. Available at: https://clinicaltrials.gov/ct2/show/NCT02527031. Accessed May 12, 2017.

32. ClinicalTrials.gov. ECPR for refractory out-of-hospital cardiac arrest. Available at: https://clinicaltrials.gov/ct2/show/NCT03065647. Accessed May 12, 2017.

33. ClinicalTrials.gov. Hyperinvasive approach in cardiac arrest. Available at: https://clinicaltrials.gov/ct2/show/NCT01511666. Accessed June 18, 2017.

34. ClinicalTrials.gov. BC ECPR trial for out-of-hospital cardiac arrest. Available at: https://clinicaltrials.gov/ct2/show/NCT02832752. Accessed May 12, 2017.

35. Grunau B, Reynolds J, Scheuermeyer F, et al. Relationship between time-to-ROSC and survival in out-of-hospital cardiac arrest ECPR candidates: when is the best time to consider transport to hospital? Prehosp Emerg Care 2016;3127:1-8.

36. Fjølner J, Greisen J, Jørgensen MR, et al. Extracorporeal cardiopulmonary resuscitation after out-of-hospital cardiac arrest in a Danish health region. Acta Anaesthesiol Scand 2017;61:176-85.

37. Smith GC, Pell JP. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. BMJ 2003;327:1459-61.

38. Krarup NH, Terkelsen CJ, Johnsen SP, et al. Quality of cardiopulmonary resuscitation in out-of-hospital cardiac arrest is hampered by interruptions in chest compressions—a nationwide prospective feasibility study. Resuscitation 2011;82:263-9.

39. Christenson J, Andrusiek D, Everson-Stewart S, et al. Chest compression fraction determines survival in patients with out-of-hospital ventricular fibrillation. Circulation 2009;120:1241-7.

40. Reynolds JC, Grunau BE, Rittenberger JC, et al. Association between duration of resuscitation and favorable outcome after out-of-hospital cardiac arrest: implications for prolonging or terminating resuscitation. Circulation 2016;134:2084-94.

41. Goto Y, Funada A, Goto Y. Relationship between the duration of cardiopulmonary resuscitation and favorable neurological outcomes after out-of-hospital cardiac arrest: a prospective, nationwide, population-based cohort study. J Am Heart Assoc 2016;5:e002819.

42. Lamhaut L, Hutin A, Puymirat E, et al. A pre-hospital extracorporeal cardio pulmonary resuscitation (ECPR) strategy for treatment of refractory out hospital cardiac arrest: an observational study and propensity analysis. Resuscitation 2017;117:109-17.

43. Ha TS, Yang JH, Cho YH, et al. Clinical outcomes after rescue extracorporeal cardiopulmonary resuscitation for out-of-hospital cardiac arrest. Emerg Med J 2017;34:107-11.

44. Grunau B, Taylor J, Scheuermeyer FX, et al. External validation of the universal termination of resuscitation rule for out-of-hospital cardiac arrest in British Columbia. Ann Emerg Med 2017;70:374-81.e1.

45. Callaway CW, Soar J, Aibiki M, et al. Part 4: advanced life support: 2015 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. Circulation 2015;132(16 suppl 1):S84-145.

46. Poppe M, Schober A, Weiser C, et al. The incidence of "load&go" out-of-hospital-cardiac arrest-candidates for emergency department utilization of emergency-extracorporeal life support. A one-year review. Resuscitation 2015;91:131-6.

47. Grunau B, Carrier S, Bashir J, et al. A comprehensive regional clinical and educational ECPR protocol decreases time to ECMO in patients with refractory out-of-hospital cardiac arrest. CJEM 2017;19:424-33.

48. Haneya A, Philipp A, Diez C, et al. A 5-year experience with cardiopulmonary resuscitation using extracorporeal life support in non-postcardiotomy patients with cardiac arrest. Resuscitation 2012;83:1331-7.

49. Kramer AH, Baht R, Doig CJ. Time trends in organ donation after neurologic determination of death: a cohort study. CMAJ Open 2017;5:E19-27.

50. Orioles A, Morrison WE, Rossano JW, et al. An under-recognized benefit of cardiopulmonary resuscitation: organ transplantation. Crit Care Med 2013;41:2794-9.

51. Lamarche Y, Cheung A, Ignaszewski A, et al. Comparative outcomes in cardiogenic shock patients managed with Impella microaxial pump or extracorporeal life support. J Thorac Cardiovasc Surg 2011;142:60-5.

52. Bednarczyk JM, White CW, Ducas RA, et al. Resuscitative extracorporeal membrane oxygenation for in hospital cardiac arrest: a Canadian observational experience. Resuscitation 2014;85:1713-9.

53. Bellezzo JM, Shinar Z, Davis DP, et al. Emergency physician-initiated extracorporeal cardiopulmonary resuscitation. Resuscitation 2012;83:966-70.

Supplementary Material

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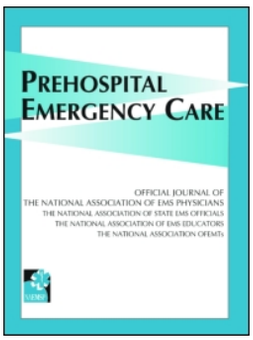

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Relationship between Time-to-ROSC and Survival in Out-of-hospital Cardiac Arrest ECPR Candidates: When is the Best Time to Consider Transport to Hospital?

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Abstract

Objective: Extracorporeal cardiopulmonary resuscitation (ECPR) may improve outcomes for refractory out-of-hospital cardiac arrest (OHCA). Transport of intra-arrest patients to hospital however, may decrease CPR quality, potentially reducing survival for those who would have achieved return-of-spontaneous-circulation (ROSC) with further on-scene resuscitation. We examined time-to-ROSC and patient outcomes for the optimal time to consider transport. **Methods**: From a prospective registry of consecutive adult non-traumatic OHCA's, we identified a hypothetical ECPR-eligible cohort of EMS-treated patients with age $\leq$ 65, witnessed arrest, and bystander CPR or EMS arrival $<$ 10 minutes. We assessed the relationship between time-to-ROSC and survival, and constructed a ROC curve to illustrate the ability of a pulseless state to predict non-survival with conventional resuscitation. **Results**: Of 6,571 EMS-treated cases, 1,206 were included with 27% surviving. Increasing time–to–ROSC (per minute) was negatively associated with survival (adjusted OR 0.91; 95%CI 0.89–0.93%). The yield of survivors per minute of resuscitation increased from commencement and started to decline in the 8th minute. Fifty percent and 90% of survivors had achieved ROSC by 8.0 and 24 min, respectively, at which times the probability of survival for those with initial shockable rhythms was 31% and 10%, and for non-shockable rhythms was 5.2% and 1.6%. The ROC curve illustrated that the 16th minute of resuscitation maximized sensitivity and specificity (AUC = 0.87, 95% CI 0.85–0.89). **Conclusion:** Transport for ECPR should be considered between 8 to 24 minutes of professional on-scene resuscitation, with 16 minutes balancing the risks and benefits of early and later transport. Earlier transport within this window may be preferred if high quality CPR can be maintained during transport and for those with initial non-shockable rhythms. **Key words:** cardiac arrest; cardiopulmonary resuscitation; extracorporeal membrane oxygenation; emergency medical services

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Introduction

Emergency Medical Services (EMS) in North America attend 134 cases of out-of-hospital cardiac arrest (OHCA) per 100,000 adult citizens annually, with survival rates ranging from 3%–16%.[1,2] Since most conventional resuscitative therapies are available in the prehospital environment, transporting patients with OHCA refractory to standard resuscitation to hospital, without implementing additional treatment strategies, is of questionable benefit and potentially endangers paramedic safety.[3,4]

Circulatory support with extracorporeal cardiopulmonary resuscitation (ECPR) may improve the chances of survival of select patients with cardiac arrest refractory to conventional resuscitation. ECPR is the incorporation of veno-arterial extracorporeal membranous oxygenation (ECMO) into cardiac arrest resuscitation, and has been used since 1966.[5] Mounting observational data suggest that ECPR is a beneficial therapy for select patients with OHCA, with most protocols focusing on younger patients with rapid arrest recognition and CPR initiation.[6–9]

An emergency medical system considering utilization of ECPR for refractory OHCA must balance two potentially competing factors: CPR quality and early access to ECPR. First, extrication and transport of patients with refractory arrest are associated with pauses in chest compressions,[10] which has been associated with decreased survival.[11] Thus, earlier transport for those who would have achieved return of spontaneous circulation (ROSC) with continued on-scene conventional resuscitation may worsen outcomes. EMS systems that employ longer durations of attempted prehospital resuscitation, with low rates of transport to hospital for refractory cardiac arrest, have demonstrated superior outcomes than comparators.[1,4,12] On

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the other hand, lower arrest-to-ECPR intervals are associated with improved neurological outcomes and the majority of neurologically intact survivors have ECPR established within 60–75 min.[7,8,13–18] Acknowledging that a minimum of 15–30 min is typically required to cannulate and commence ECPR,[8,9] patients would likely have to arrive at hospital no more than 45 min after cardiac arrest to achieve this time goal. Thus, earlier transport for those who will not achieve ROSC with continued on-scene conventional resuscitation, for the purpose of hospital-based ECPR therapy, would likely result in improved outcomes.

Unfortunately, at the beginning of resuscitation one does not know who will achieve ROSC with conventional resuscitation. For this reason, we sought to demonstrate the survival curves for ECPR-eligible patients to determine if there was a natural inflection point during conventional resuscitation when further prehospital efforts yielded little additional benefit, but still fell within the time frame of transport to an ECPR-capable center. We reviewed a cohort of OHCA patients in a provincial EMS system fulfilling a set of hypothetical ECPR criteria to describe the relationship of time-to-ROSC and outcomes, in order to inform decision-making when considering transport to hospital for ECPR.

METHODS

Study Setting

This study took place in the four major metropolitan regions in the province of British Columbia: Victoria, Vancouver, the Fraser Valley, and Kelowna. These communities contain a collective population of approximately 3.3 million (72% of the total provincial population)[19] and each contain at least one hospital with ECMO capacity. There were no ECPR programs or use of mechanical CPR devices during the study period.

The provincial British Columbia Emergency Health Services (BCEHS) and individual municipal fire department first responders provide coordinated prehospital emergency medical care through a 9-1-1 emergency service. All fire department personnel are trained in basic cardiopulmonary life-support[20] including the use of automated external defibrillators (AED). BCEHS is organized in teams of two paramedics per vehicle, with either basic (BLS) or advanced (ALS) life-support certification. BCAS policy dictates which patients must be provided resuscitative treatments (see Appendix 1).[21] There was no termination of resuscitation guideline used by the BCEHS during the study period.

The institutional ethics review boards of Providence Health Care and the University of British Columbia approved this study.

Study Design and Selection of Participants

All consecutive non-traumatic OHCA occurring in the study regions were prospectively identified and data collected as part of the Resuscitation Outcomes Consortium[22] cardiac arrest registry between 2007 and 2011 inclusive. Based on previous ECPR protocols[9,23,24] and other data,[25,26] we constructed a hypothetical post-hoc ECPR-eligible cohort, including patients if the following set of criteria were met: (1) age 18–65 years (inclusive); (2) witnessed arrest; and (3) bystander CPR (performed by laypersons or EMS if the arrest was EMS-witnessed) or EMS arrival in less than 10 min. Patients were excluded from analysis if there was no attempt at resuscitation.

Data Collection

All prehospital data, including time-stamped diagnostics, treatments administered, patient characteristics, and prehospital outcomes, were prospectively collected from standardized EMS template charting and survival at hospital discharge was recorded.[22]

Outcome Measures and Variable Definitions

The primary endpoint was survival to hospital discharge.[27] The primary independent variable of interest was time-to-ROSC, defined as the interval between the initiation of chest compressions by a professional rescuer and first ROSC. ROSC was defined as a palpable pulse in any vessel for any length of time. Patients were categorized by initial rhythm: (1) "shockable," including ventricular fibrillation, pulseless ventricular tachycardia, and unknown rhythms that were shocked with the AED; and, (2) "non-shockable" including pulseless electrical activity, asystole, and unknown rhythms that were not shocked by the AED.

Data Analysis

We used Microsoft Excel 2008 (Microsoft Corp, Redmond, WA, USA) and Statistica™ (Dell Corp, Round Rock, Texas, USA) for analysis. Categorical variables are reported as percentages and 95% confidence intervals. Continuous variables are presented as means with standard deviations (if normally distributed) or medians with interquartile ranges (IQR). We used unmatched logistic regression to evaluate the association between survival and time-to-ROSC. Unadjusted odds ratios and 95% confidence intervals are based on univariable models. We then adjusted for covariates known to be associated with outcomes in OHCA: age, gender, arrest in a public location, bystander CPR, initial rhythm, time to EMS arrival, and EMS-witnessed arrest.[28,29]

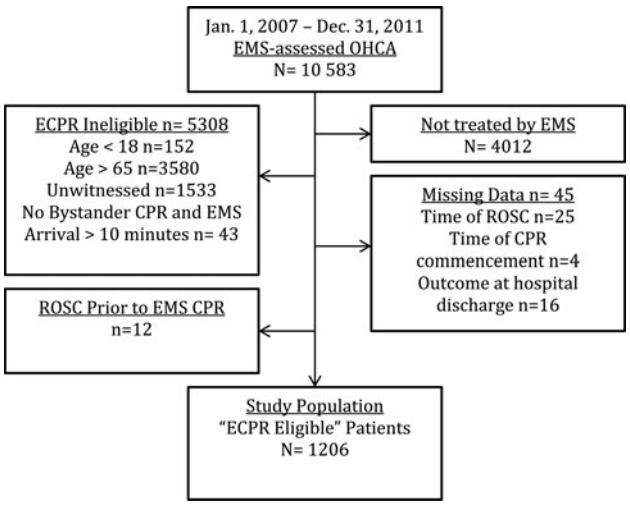

FIGURE 1. Study flow.

To visualize and describe our dataset, we constructed several curves. First, among survivors we demonstrated the proportion of patients with ROSC prior to successive one-minute increments of professional resuscitation. Based on previous work,[28] we highlighted the durations of professional resuscitation at which time 50%, 75%, 90%, and 99% of survivors had achieved ROSC. Second, among those who remained pulseless at increasing time junctures from the commencement of resuscitation, we illustrated the proportion who survived to hospital discharge.

We constructed a receiver operating characteristic (ROC) curve to illustrate the ability of a pulseless state (a "positive test") to predict non-survival with conventional resuscitation, at incremental time junctures of resuscitation. The true positive rate was the proportion of those in a pulseless state who did not survive to hospital discharge. The false positive rate was the proportion of those in a pulseless state who survived to hospital discharge. We determined the time juncture in the resuscitation that yielded the best test performance.

RESULTS

Characteristics of Study Subjects

Of 10,583 consecutive EMS-assessed cases of OHCA in the study period, 6,571 were treated by EMS (overall 12% of EMS-treated cases survived to hospital discharge). A total of 1206 patients met our set of hypothetical ECPR criteria and were included in this study (Figure 1).

Main Results

Patient characteristics of the full ECPR-eligible cohort and subgroups characterized by initial rhythm are shown in Table 1. The median age was 55 years (IQR 47–60), and 75% were male. Of 753 (62%) patients with ROSC, 750 (99.6%) achieved ROSC in the prehospital setting. A total of 195 patients (16%) had transport to hospital initiated prior to achieving ROSC. The median duration of resuscitation prior to termination in those who did not achieve ROSC was 37 min (IQR 30–47 min). The median time-to-ROSC among survivors and non-survivors at hospital discharge was 8.1 min (IQR 4.7–14.0) and 17.1 min (IQR 11.0–24.0), respectively. Overall, 328 (27%) survived to hospital discharge (Table 2).

In adjusted models, increasing time-to-ROSC (per minute) was negatively associated with survival to hospital discharge (adjusted OR = 0.91; 95% CI = 0.89–0.93; Table 3). Figure 2A demonstrates the proportion of survivors who achieved ROSC prior to incremental time junctures. The yield of survivors per minute of resuscitation increased from

TABLE 1. Characteristics of study population

	Full Cohort		Initial Shockable Rhythms		Initial Non-Shockable Rhythms	
	n or median (% or IQR)	Missing	*n* or median (% or IQR)	Missing	*n* or median (% or IQR)	Missing
Number	1206		569*		616*	
Age (years)	55 (47–60)	0	55 (49–60)	0	54 (45–60)	0
Male sex	908 (75)	0	473 (83)	0	417 (68)	0
Public Location	395 (33)	1	568 (44)	1	140 (23)	0
Bystander Witnessed	960 (80)	0	497 (87)	0	444 (72)	0
Bystander CPR	622 (65†)	0	337 (68†)	0	268 (60†)	0
Witnessed by EMS	246 (20)	0	72 (13)	0	172 (28)	0
9-1-1 Call to EMS arrival, min	6.7 (5.3–8.6)	0	6.3 (5.2–8.2)	0	7.2 (5.4–8.8)	0
ALS Involvement	1098 (90)	0	519 (91)	0	551 (89)	0
Advanced Airway	1200 (81)	6	567 (81)	2	612 (80)	4
Initial Shockable Rhythm	569 (48)	21	569 (100)	0	0 (0)	0
Epinephrine Administered	858 (72)	17	368 (66)	10	471 (77)	7
Epinephrine Dose, mg	5 (2–7)		4 (2–7)		5 (3–7)	
Transported to Hospital	891 (74)	0	474 (83)	0	401 (65)	0

*Patients with missing data on initial rhythm were excluded from the subgroups based on initial rhythm.
†EMS-witnessed arrests excluded from the denominator of this proportion.
IQR = interquartile range; CPR = cardiopulmonary resuscitation; EMS = emergency medical services; min = minutes; ALS = advanced life support paramedic.

TABLE 2. Patient outcomes

	Full Cohort *n* or median (% or IQR)	Initial Shockable Rhythms* *n* or median (% or IQR)	Initial Non-Shockable Rhythms* *n* or median (% or IQR)
ROSC	753(62)	428(75)	310(50)
Time To ROSC (minutes)	13.0(7.2–20.8)	12.0(6.8–19.2)	15.3(7.8–23.0)
Survival to Hospital Discharge	328(27)	255(45)	67(11)

*Patients with missing data on initial rhythm were excluded from the subgroups based on initial rhythm.
ROSC = return of spontaneous circulation.

commencement, peaked in the seventh minute, and started declining in the eighth minute. Figure 3 demonstrates the probability of survival to hospital discharge among patients in a persistent pulseless state, at increasing junctures since the commencement of resuscitation (both for the full cohort and stratified by initial rhythm). The time junctures at which 50%, 75%, 90%, and 99% of survivors had achieved ROSC were 8.0, 14.0, 23.7, and 38.8 min, at which point the probability of survival among pulseless patients was 17% (95% CI 15–19%), 10% (95% CI 8.2–12%), 5.4% (95% CI 3.6,7.2%), and 0.84% (95% CI 0.02–1.7%), respectively.

The ROC curve, describing the ability of the pulseless state to predict non-survival, illustrates that the 16th minute of resuscitation maximizes sensitivity and specificity (area under the curve = 0.87, 95% CI 0.85–0.89; Figure 4). At this juncture 9.0% (95% CI 6.9–11%) of those who remained pulseless survived to hospital discharge.

Of the 569 patients with initial shockable rhythms, 75% achieved ROSC and 45% survived to hospital discharge (Table 2). The time junctures at which 50%, 75%, 90%, and 99% of survivors had achieved ROSC were 8.5, 14.7, 23.0, and 39.0 min, respectively. Of the 616 patients with initial non-shockable rhythms, 50% achieved ROSC and 11% survived to hospital discharge. The time junctures at which 50%, 75%, 90%, and 99% of survivors had achieved ROSC were 6.1, 12.8, 23.9, and 36.0 min, respectively.

DISCUSSION

ECPR is a complex therapy requiring time-sensitive initiation; however, it holds promise for a subset of patients with rapid high quality CPR (to maintain cerebral perfusion), for whom ROSC is not achievable with conventional resuscitation. The challenge is to determine how and when to identify patients who will prove refractory to conventional resuscitation, and who may have an increased chance of survival if transported to hospital for ECPR.

We explored the relationship between time-to-ROSC and survival among potential ECPR candidates—younger patients with early CPR initiation after OHCA—and estimated the incremental benefits of increasing durations of conventional resuscitation. Our data indicate that there is no clear juncture in the resuscitation at which the likelihood of survival drops precipitously, but rather starting in the 8th min there is a slow transition to progressively lower yield of further conventional efforts. Although no single time juncture was identified, the timeframe of 8–24 min after commencement of professional resuscitation appears to be a reasonable window to consider transport to hospital for ECPR for several reasons. In the 8th min of resuscitation, the incremental benefit of conventional therapies had started to decline, and at the end of this minute 50% of survivors had already achieved ROSC. By 24 min, 90% of survivors had already achieved ROSC and further on-scene efforts approach the logistical limits that would still allow a patient to be transported to hospital within a collapse-to-ECPR interval compatible with survival.[7]

Our ROC curve indicates that a lack of a pulse at 16 min (which falls in the middle of the 8–24 min window) has the best performance for predicting non-survival, which balances the risk of earlier transport to

TABLE 3. Logistic regression models for survival to hospital discharge

Variable (referent)	Crude OR (95% CI)	Adjusted OR (95% CI)
Gender (female)	1.6(1.14 – 2.26)	1.43(0.95 – 2.17)
Age in years (per year increase)	1.00(0.98 – 1.02)	0.99(0.97 – 1.01)
Public location	1.88(1.39 – 2.55)	1.08(0.75 – 1.57)
Bystander CPR*	1.42(1.02 – 1.98)	1.25(0.83 – 1.89)
Witnessed by EMS	1.29(0.89 – 1.85)	1.52(0.91 – 2.51)
Time from 9-1-1 call to EMS arrival (per minute increase)	0.94(0.89 – 0.99)	0.94(0.88 – 0.99)
Initial Shockable rhythm	5.35(3.83 – 7.46)	5.75(3.89 – 8.49)
Time to ROSC (per minute increase)	0.91(0.89 – 0.93)	0.91(0.89 – 0.93)

*By Layperson or EMS if EMS-witnessed.
CPR = cardiopulmonary resuscitation; EMS = emergency medical services; ROSC = return of spontaneous circulation.

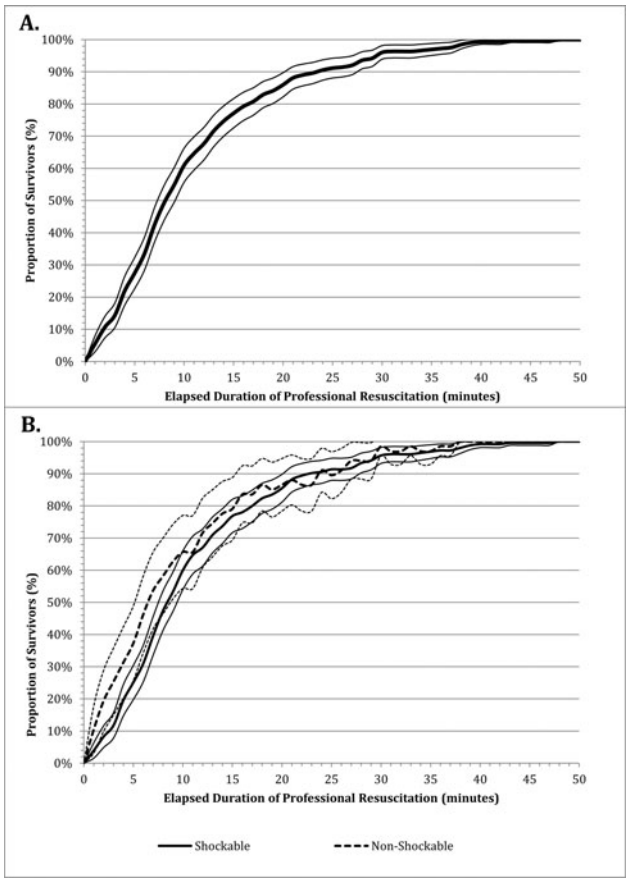

FIGURE 2. Proportion of survivors achieving ROSC prior to incremental durations of resuscitation (with 95% CI), among (A) the full cohort and (B) dichotomized by initial cardiac rhythm.

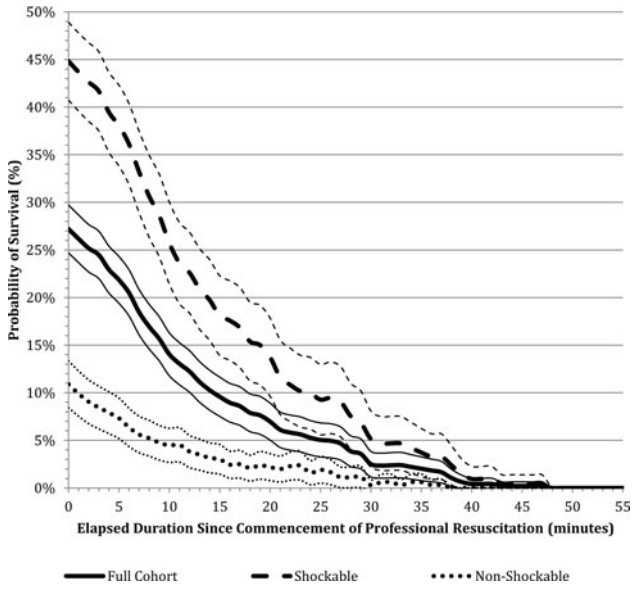

FIGURE 3. Probability of survival among pulseless patients, at increasing durations of time since commencement of resuscitation (with 95% CI).

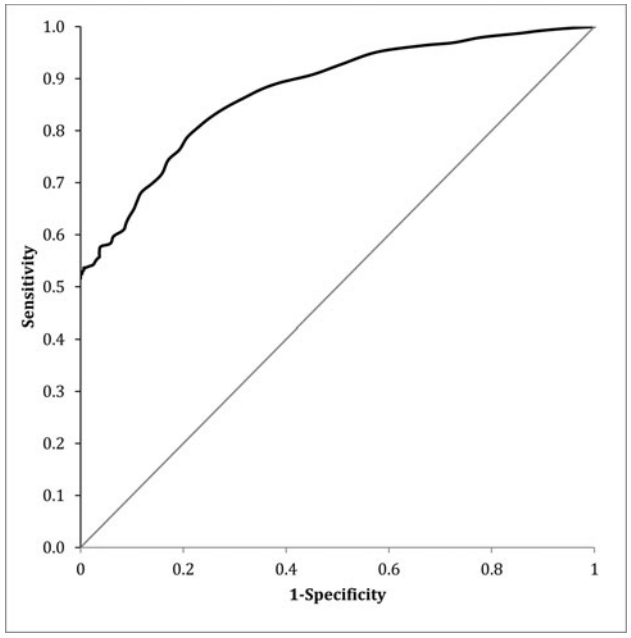

FIGURE 4. ROC curve for *No Pulse* as a positive test to predict non-survival at increasing time junctures from commencement of resuscitation.

a patient who would have achieved ROSC with further on-scene conventional therapies, and the risk of later transport to an ECPR-eligible patient who will never achieve ROSC. However, this assumes that the risks of earlier and later transport are equally important, which may not be the case for most patients. When considering when to transport within the 8–24 min time window two critical patient level factors deserve consideration: (1) the quality of CPR that can be performed during extrication and transport and (2) the initial cardiac rhythm. CPR quality is a crucial variable in resuscitation and can vary substantially, especially during extrication and transport.[11,30,31] If one can be confident in consistent high-quality transport CPR, then transport of an ECPR candidate to hospital should take place after 8 min of failed high-quality conventional efforts. If high-quality CPR during transport cannot be assured, depending on the quality impact, consideration should be made for later transport within the 8–24 min window, or continued on-scene resuscitation until termination. Mechanical chest compression devices may play a key role in maintaining CPR quality for ECPR-eligible patients that are transported to hospital.[32] However, as studies comparing the outcomes of patients treated with these high-cost devices to manual CPR have demonstrated worse[33,34] or neutral results,[35–37] EMS systems may lack enthusiasm to incorporate mechanical compression systems into routine management.

One novel aspect of our study is the stratification of survival curves by shockable and non-shockable initial cardiac rhythms. Although the proportion of survivors achieving ROSC prior to increasing durations of

resuscitation was similar (Figure 2B), there were large differences in the probability of survival of those who remained pulseless (Figure 3). After 8 min of resuscitation, the probability of survival among those with initial shockable rhythms dropped only to 31%; however, among those with non-shockable rhythms fell to 5.2%. As the probability of survival for shockable patients at 8 min remains relatively high, longer on-scene conventional resuscitation may be preferable unless transport CPR quality can be ensured. Conversely, the probability of survival for patients with non-shockable rhythms fell to 5.2%, demonstrating the small benefit of additional on-scene efforts. Importantly, survival of non-shockable patients treated with ECPR have been reported as high as 29%–35%,[8,9,13] and thus prioritizing early transport of patients with non-shockable rhythms may be appropriate.

In addition, two system related factors may warrant consideration: (1) the outcomes of conventional resuscitation within the EMS system; and (2) the outcomes of the local ECPR system; both of which have been shown to vary considerably in different regions.[1,9,15] If the EMS baseline outcomes with conventional resuscitation are poor and the local ECPR system has high rates of positive outcomes, this would favor earlier transport for ECPR therapies. However, if this were the case, system quality improvement in fundamental conventional resuscitation may yield a greater benefit than a resource-intensive ECPR program. Conversely, if a local ECPR program yields few survivors, then one should prioritize conventional resuscitation and ensure continual high-quality CPR, with possible later transport to an ECPR site if persistent refractory arrest.

When considering the possible benefits of incorporating ECPR into a local algorithm for refractory OHCA, the analysis must take place at the overall EMS system level. Whereas previous studies have reported the outcomes of patients who were transported to hospital and treated with ECPR, this negates the impact on the rest of the system including the possible detrimental effect of intra-arrest transport on CPR quality. Furthermore, there are additional resource-intensive logistical factors that require planning, albeit for a relatively small number of patients who would be eligible. Experience gleaned from the development STEMI protocols in the recent years may have high yield for ECPR protocols, including the prehospital identification of eligible patients, prehospital ECPR team activation, and bypass of other hospitals to designated ECPR centers[38–40] In-hospital ECPR teams that could be rapidly mobilized would be required. These protocols would need to prioritize rapid arrest-to-ECMO times, however with the recognition that there would be a proportion of false positive prehospital activations for those who would achieve ROSC in the intervening time prior to actual cannulation.

Previous studies have estimated the time juncture in resuscitation at which one might consider ECPR, however no studies have specifically examined the patient subset that would be considered eligible for this therapy. Potential ECPR candidates may be systematically different from the general population of OHCA patients in regard to time-to-ROSC and outcomes. Reynolds et al. analyzed data from 1,042 OHCA patients, of whom 11% survived to hospital discharge. They reported that within 16.1 min of CPR, 90% of patients with a favorable functional outcome had achieved ROSC; the probability of a good functional outcome among those still receiving chest compressions at this juncture was 1%.[28] Arima et al. examined a cohort of 172 patients with initial shockable rhythms and demonstrated decreasing rates of survival with increasing durations to ROSC. Of those with resuscitation for > 30 minutes, only 1.4% had favorable outcomes.[34] From a cohort of patients who were transported to hospital, of whom 10% were chosen for ECPR, Kim et al. constructed a ROC curve from those not treated with ECPR and concluded the ideal time to consider ECPR was 21 min.[18]

No published prospective randomized trials have compared ECPR to conventional care. Outcomes of highly selected patients treated with ECPR—whom clinicians deemed unlikely to survive with conventional therapies—have been published, but the lack of comparator groups makes the true benefit of ECPR difficult to ascertain. The best outcomes are seen with early ECPR initiation;[13] however, a proportion of these could have achieved ROSC with conventional means. It is also unclear whether achieving earlier perfusion through ECPR, in patients who would achieve later ROSC with conventional resuscitation, confers benefit. Our data demonstrate the outcomes of potentially ECPR-eligible patients treated with conventional methods, and could be used as an estimate of the probability of survival with conventional resuscitation, to compare to patients treated with ECPR in other studies. In our study, although a single survivor regained ROSC at 47 min, the vast majority of survivors achieved ROSC much earlier. As previous data indicate that ECPR performed on patients with OHCA tend to be initiated at or after the 45-min juncture,[7,9] it appears likely that ECPR does confer benefit over conventional resuscitation when initiated at this time.

The aim of this study was not to determine the effectiveness of ECPR therapy or on-scene conventional resuscitation, but rather sought to guide management decisions in EMS systems considering the possible risks of early transport to hospital, in view of the potential benefits of transport to hospital for ECPR. For this reason we considered survival to be a more appropriate and conservative primary outcome than neurological outcomes— whereas non-surviving study subjects favored earlier transport in our analysis as they had "nothing to lose" (and had potential gain from ECPR), this is not true for those who survived with unfavorable neurological outcomes for whom

management decisions have the potential to further worsen the outcomes.

Limitations

This study was performed in the metropolitan regions within one province in Canada which demonstrate a high rate of survival from OHCA[1]; population characteristics, medical management, and outcomes of OHCA may vary in different settings. Namely, a standardized protocol for early termination of resuscitation was not utilized[35] and the majority of patients in whom ROSC was not achieved were treated exclusively the prehospital setting without transport to hospital. Whereas prehospital resuscitation and protocolized hospital care followed AHA guidelines, we cannot account for individual patient treatment. Unstructured withdrawal of care (in the prehospital and hospital setting including those pre-ROSC and post-arrest) is a limitation, as providers' perception of poor predicted outcome leading to cessation of efforts thereby confers a poor outcome. Our survival curve illustrating the proportion of survivors among those who remained pulseless at increasing time junctures included patients who were no longer receiving resuscitation; although it is likely that these patients would not have survived with longer attempts this may have resulted in an underestimation of survival. Our ECPR criteria, although based on existing data, may not be the optimal criteria to identify patients who would most likely benefit with ECPR. In particular, it is likely appropriate to expand the eligibility of those who have OHCA secondary to hypothermia.[41] Furthermore, there may have been patients included in our cohort with certain characteristics that made them inappropriate for ECPR therapies. We used the start of professional CPR as the time at which to compare the time of ROSC; while duration from the arrest to ROSC may be of interest, reliable data on actual arrest times are unavailable. When developing a prehospital protocol, however, the duration of on-scene resuscitative efforts is likely the most pragmatic time period to use, rather than requiring personnel to estimate and calculate the duration of arrest. Finally, there were 21 (1.7%) patients within our ECPR group for whom data on the initial rhythm were unavailable, precluding inclusion in the rhythm subgroup analysis.

CONCLUSION

Our data suggest that transport to hospital for ECPR should be considered between 8 to 24 min of elapsed conventional on-scene resuscitation, with 16 min balancing the risks and benefits of early and later transport equally. Earlier transport in this window may be preferred if high quality CPR can be maintained during transport and for those with initial non-shockable rhythms.

References

1. Nichol G, Thomas E, Callaway CW, et al. Regional variation in out-of-hospital cardiac arrest incidence and outcome. JAMA. 2008;300(12):1423–31. doi:10.1001/jama.300.12.1423.
2. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics–2014 update: a report from the American Heart Association. Circulation. 2014;129(3):e28–292. doi:10.1161/01.cir.0000441139.02102.80.
3. Kahn CA, Pirrallo RG, Kuhn EM. Characteristics of fatal ambulance crashes in the United States: an 11-year retrospective analysis. Prehosp Emerg Care. 1997;5(3):261–9.
4. Zive D, Koprowicz K, Schmidt T, et al. Variation in out-of-hospital cardiac arrest resuscitation and transport practices in the Resuscitation Outcomes Consortium: ROC Epistry-Cardiac Arrest. Resuscitation. 2011;82(3):277–84. doi:10.1016/j.resuscitation.2010.10.022.
5. Kennedy JH. The role of assisted circulation in cardiac resuscitation. JAMA. 1966;197(8):615–8.
6. Morimura N, Sakamoto T, Nagao K, et al. Extracorporeal cardiopulmonary resuscitation for out-of-hospital cardiac arrest: A review of the Japanese literature. Resuscitation. 2011;82(1):10–14. doi:10.1016/j.resuscitation.2010.08.032.
7. Wang C-H, Chou N-K, Becker LB, et al. Improved outcome of extracorporeal cardiopulmonary resuscitation for out-of-hospital cardiac arrest - A comparison with that for extracorporeal rescue for in-hospital cardiac arrest. Resuscitation. 2014;85(9):1219–24. doi:10.1016/j.resuscitation.2014.06.022.
8. Leick J, Liebetrau C, Szardien S, et al. Door-to-implantation time of extracorporeal life support systems predicts mortality in patients with out-of-hospital cardiac arrest. Clin Res Cardiol. 2013;102(9):661–9. doi:10.1007/s00392-013-0580-3.
9. Stub D, Bernard S, Pellegrino V, et al. Refractory cardiac arrest treated with mechanical CPR, hypothermia, ECMO and early reperfusion (the CHEER Trial). Resuscitation. September 2014:1–7. doi:10.1016/j.resuscitation.2014.09.010.
10. Krarup NH, Terkelsen CJ, Johnsen SP, et al. Quality of cardiopulmonary resuscitation in out-of-hospital cardiac arrest is hampered by interruptions in chest compressions—a nationwide prospective feasibility study. Resuscitation. 2011;82(3):263–9. doi:10.1016/j.resuscitation.2010.11.003.
11. Christenson J, Andrusiek D, Everson-Stewart S, et al. Chest compression fraction determines survival in patients with out-of-hospital ventricular fibrillation. Circulation. 2009;120(13):1241–7. doi:10.1161/CIRCULATIONAHA.109.852202.
12. Sakamoto T, Morimura N, Nagao K, et al. Extracorporeal cardiopulmonary resuscitation versus conventional cardiopulmonary resuscitation in adults with out-of-hospital cardiac arrest: A prospective observational study. Resuscitation. February 2014:1–7. doi:10.1016/j.resuscitation.2014.01.031.
13. Haneya A, Philipp A, Diez C, et al. A 5-year experience with cardiopulmonary resuscitation using extracorporeal life support in non-postcardiotomy patients with cardiac arrest. Resuscitation. 2012;83(11):1331–7. doi:10.1016/j.resuscitation.2012.07.009.
14. Avalli L, Maggioni E, Formica F, et al. Favourable survival of in-hospital compared to out-of-hospital refractory cardiac arrest patients treated with extracorporeal membrane oxygenation: an Italian tertiary care centre experience. Resuscitation. 2012;83(5):579–83. doi:10.1016/j.resuscitation.2011.10.013.
15. Le Guen M, Nicolas-Robin A, Carreira S, et al. Extracorporeal life support following out-of-hospital refractory cardiac arrest. Crit Care. 2011;15(1):R29. doi:10.1186/cc9976.

16. Maekawa K, Tanno K, Hase M, Mori K, Asai Y. Extracorporeal cardiopulmonary resuscitation for patients with out-of-hospital cardiac arrest of cardiac origin: a propensity-matched study and predictor analysis. Crit Care Med. 2013;41(5):1186–96. doi:10.1097/CCM.0b013e31827ca4c8.
17. Nagao K, Kikushima K, Watanabe K, et al. Early induction of hypothermia during cardiac arrest improves neurological outcomes in patients with out-of-hospital cardiac arrest who undergo emergency cardiopulmonary bypass and percutaneous coronary intervention. Circ J. 2010;74(1):77–85. doi:10.1253/circj.CJ-09-0502.
18. Kim S, Jung J, Park J, Park J, Hong Y, Lee S. An optimal transition time to extracorporeal cardiopulmonary resuscitation for predicting good neurological outcome in patients with out-of-hospital cardiac arrest: a propensity-matched study. Crit Care. 2014;18(5):535. doi:10.1186/s13054-014-0535-8.
19. Statistics Canada. Focus on Geography Series, Analytical products, 2011 Census. Ottawa, Ontario: 2012.
20. Berg RA, Hemphill R, Abella BS, et al. Part 5: adult basic life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2010;122(18 Suppl 3):S685–705. doi:10.1161/CIRCULATIONAHA.110.970939.
21. BC Ambulance Service Policy. Resuscitation of Critically Ill Patients. Vancouver: B.C. Emergency Health Services, 2010.
22. Morrison LJ, Nichol G, Rea TD, et al. Rationale, development and implementation of the resuscitation outcomes consortium epistry-cardiac arrest. Resuscitation. 2008;78(2):161–9. doi:10.1016/j.resuscitation.2008.02.020.
23. Fagnoul D, Taccone FS, Belhaj A, et al. Extracorporeal life support associated with hypothermia and normoxemia in refractory cardiac arrest. Resuscitation. 2013;84(11):1519–24. doi:10.1016/j.resuscitation.2013.06.016.
24. Johnson NJ, Acker M, Hsu CH, et al. Extracorporeal life support as rescue strategy for out-of-hospital and emergency department cardiac arrest. Resuscitation. 2014;85(11):1527–32. doi:10.1016/j.resuscitation.2014.08.028.
25. Anderson LW, Bivens MJ, Giberson T, et al. The relationship between age and outcome in out-of-hospital cardiac arrest patients. Resuscitation. 2015; 94:49–54. http://dx.doi:http://dx.doi.org/doi:10.1016/j.resuscitation.2015.05.015.
26. Hasselqvist-Ax I, Riva G, Herlitz J, et al. Early cardiopulmonary resuscitation in out-of-hospital cardiac arrest. N Engl J Med. 2015;372(24):2307–15. doi:10.1056/NEJMoa1405796.
27. Jacobs I, Nadkarni V, Bahr J, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries. A statement for healthcare professionals from a task force of the international liaison committee on resusci. Resuscitation. 2004;63(3):233–49. doi:10.1016/j.resuscitation.2004.09.008.
28. Reynolds JC, Frisch A, Rittenberger JC, Callaway CW. Duration of resuscitation efforts and functional outcome after out-of-hospital cardiac arrest: when should we change to novel therapies?. Circulation. 2013;128(23):2488–94. doi:10.1161/CIRCULATIONAHA.113.002408.
29. Stiell IG, Wells GA, DeMaio VJ, et al. Modifiable factors associated with improved cardiac arrest survival in a multicenter basic life support/defibrillation system: OPALS Study Phase I results. Ontario Prehospital Advanced Life Support. Ann Emerg Med. 1999;33(1):44–50.
30. Stiell IG, Brown SP, Nichol G, et al. What is the optimal chest compression depth during out-of-hospital cardiac arrest resuscitation of adult patients?. Circulation. 2014;130(22):1962–70. doi:10.1161/CIRCULATIONAHA.114.008671.
31. Cheskes S, Schmicker RH, Verbeek PR, et al. The impact of peri-shock pause on survival from out-of-hospital shockable cardiac arrest during the Resuscitation Outcomes Consortium PRIMED trial. Resuscitation. 2014;85(3):336–42. doi:10.1016/j.resuscitation.2013.10.014.
32. Fox J, Fiechter R, Gerstl P, et al. Mechanical versus manual chest compression CPR under ground ambulance transport conditions. Acute Card Care. 2013;15(1):1–6. doi:10.3109/17482941.2012.735675.
33. Hallstrom A, Rea TD, Sayre MR, et al. Manual chest compression vs use of an automated chest compression device during resuscitation following out-of-hospital cardiac arrest: a randomized trial. JAMA. 2006;295(22):2620–8. doi:10.1001/jama.295.22.2620.
34. Zeiner S, Sulzgruber P, Datler P, et al. Mechanical chest compression does not seem to improve outcome after out-of hospital cardiac arrest. A single center observational trial. Resuscitation. Nov 2015;96:220–5. doi:10.1016/j.resuscitation.2015.07.051.
35. Perkins GD, Lall R, Quinn T, et al.; PARAMEDIC trial collaborators. Mechanical versus manual chest compression for out-of-hospital cardiac arrest (PARAMEDIC): a pragmatic, cluster randomised controlled trial. Lancet (London, England). 2015;385(9972):947–55. doi:10.1016/S0140-6736(14)61886-9.
36. Rubertsson S, Lindgren E, Smekal D, et al. Mechanical chest compressions and simultaneous defibrillation vs conventional cardiopulmonary resuscitation in out-of-hospital cardiac arrest: the LINC randomized trial. JAMA. 2014;311(1):53–61. doi:10.1001/jama.2013.282538.
37. Brooks SC, Bigham BL, Morrison LJ. Mechanical chest compressions versus manual chest compressions for cardiac arrest. Cochrane Database Syst Rev. 2014 Feb; 2:CD007260. doi:10.1002/14651858.CD007260.
38. Bosson N, Kaji AH, Niemann JT, et al. The Utility of Prehospital ECG Transmission in a Large EMS System. Prehosp Emerg Care. 2015;19(4):496–503. doi:10.3109/10903127.2015.1005260.
39. Choi SW, Shin SD, Ro YS, Song KJ, Lee YJ, Lee EJ. Effect of emergency medical service use and inter-hospital transfer on time to percutaneous coronary intervention in patients with st elevation myocardial infarction: a multicenter observational study. Prehosp Emerg Care. 20(1):66–75. doi:10.3109/10903127.2015.1056892.
40. Ross G, Alsayed T, Turner L, Olynyk C, Thurston A, Verbeek PR. Assessment of the safety and effectiveness of emergency department STEMI bypass by defibrillation-only emergency medical technicians/primary care paramedics. Prehosp Emerg Care. 19(2):191–201. doi:10.3109/10903127.2014.959226.
41. Nordberg P, Ivert T, Dalén M, Forsberg S HA. Surviving two hours of ventricular fibrillation in accidental hypothermia. 2014;18(3):446–9. doi:10.3109/10903127.2014.891066.

APPENDIX 1

BCAS policy indicates that all patients must be provided resuscitative treatments for cardiac arrest except in the following circumstances:

"(1)"Obvious Death" defined as rigor mortis, decapitation, post-mortem levity, tissue decomposition, thoracic or abdominal transection, incineration of the torso or head, or complete destruction or removal of vital organ;
(2)The patient has been unresponsive and without respirations and no CPR performed for > 15 minutes (excluding those with hypothermia);
(3)There is a "No CPR" order in effect; or,
(4)Underwater submersion for > 60 minutes."[1]