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 ≤ 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

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%. 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.

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. 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 On 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,5–9 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 pre-hospital emergency medical care through a 9-1-1 emergency service. All fire department personnel are trained in basic cardiopulmonary life-support20 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 Consortium22 cardiac arrest registry between 2007 and 2011 inclusive. Based on previous ECPR protocols9,12,23,24 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

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

<table>
<thead>
<tr>
<th>Table 1. Characteristics of study population</th>
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<tbody>
<tr>
<td><strong>Full Cohort</strong></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Number</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Male sex</td>
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<tr>
<td>Public Location</td>
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<td>Bystander Witnessed</td>
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<td>Bystander CPR</td>
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<tr>
<td>9-1-1 Call to EMS arrival, min</td>
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<tr>
<td>ALS Involvement</td>
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<tr>
<td>Advanced Airway</td>
</tr>
<tr>
<td>Initial Shockable Rhythm</td>
</tr>
<tr>
<td>Epinephrine Administered</td>
</tr>
<tr>
<td>Epinephrine Dose, mg</td>
</tr>
</tbody>
</table>

*Patients with missing data on initial rhythm were excluded from the subgroups based on initial rhythm.
1EMS-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.
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 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

<table>
<thead>
<tr>
<th>Variable (referent)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Gender (female)</td>
<td>1.60(1.14–2.26)</td>
<td>1.43(0.95–2.17)</td>
</tr>
<tr>
<td>Age in years (per year increase)</td>
<td>1.00(0.98–1.02)</td>
<td>0.99(0.97–1.01)</td>
</tr>
<tr>
<td>Public location</td>
<td>1.88(1.39–2.55)</td>
<td>1.08(0.75–1.57)</td>
</tr>
<tr>
<td>Bystander CPR⁠*</td>
<td>1.42(1.02–1.98)</td>
<td>1.25(0.83–1.89)</td>
</tr>
<tr>
<td>Witnessed by EMS</td>
<td>1.29(0.89–1.85)</td>
<td>1.52(0.91–2.51)</td>
</tr>
<tr>
<td>Time from 9-1-1 call to EMS arrival (per minute increase)</td>
<td>0.94(0.89–0.99)</td>
<td>0.94(0.88–0.99)</td>
</tr>
<tr>
<td>Initial Shockable rhythm</td>
<td>5.35(3.83–7.46)</td>
<td>5.75(3.89–8.49)</td>
</tr>
<tr>
<td>Time to ROSC (per minute increase)</td>
<td>0.91(0.89–0.93)</td>
<td>0.91(0.89–0.93)</td>
</tr>
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</table>

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

**Table 3.** Logistic regression models for survival to hospital discharge

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

![Figure 2](image2.png)

**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](image3.png)

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

![Figure 4](image4.png)

**Figure 4.** ROC curve for No Pulse as a positive test to predict non-survival at increasing time junctures from commencement of resuscitation.
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 suggesting that ECPR may be a viable option 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%. 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. 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.

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; 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, 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 sub-
Projects 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


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.”

(2)The patient has been unresponsive and without respirations and no CPR performed for > 15 minutes (excluding those with hypothermia);