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- Resuscitative extracorporeal membrane oxygenation for in hospital
- cardiac arrest: A Canadian observational experience
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ABSTRACT

Background: Among patients with reversible conditions who sustain cardiac arrest, extracorporeal membrane oxygenation (ECMO) may support end organ perfusion while bridging to definitive therapy. *Methods*: A single center retrospective review (February 2008–September 2013) of adults receiving ECMO for cardiac arrest ≥15 min duration refractory to conventional management (E-CPR) or profound cardiogenic shock following IHCA (E-CS) was conducted. The primary outcome was 30-day survival with good neurologic function defined as a cerebral performance category (CPC) of 1–2. Secondary outcomes included intensive care unit (ICU) and hospital length of say, duration of mechanical ventilation, and univariate predictors of 30-day survival with favorable neurologic function.

Results: Thirty-two patients (55 ± 11 years, 66% male) were included of which 22 (69%) received E-CPR and 10 (31%) received E-CS following return of spontaneous circulation (ROSC). Cardiac arrest duration was 48.8 ± 21 min for those receiving E-CPR and 25 ± 23 min for the E-CS group. Patients received ECMO support for 70.7 ± 47.6 h. Death on ECMO support occurred in 7 (21.9%) patients, while 7 (21.9%) were bridged to another form of mechanical circulatory support, and 18 (56.3%) were successfully decannulated. ICU length of stay was 7.5 [3.3-14] days and ICU survival occurred in 16 (50%) of patients. 30-Day survival was 5 (50%) in the E-CS group, 10 (45.4%) in the E-CPR group, and 15 (47%) overall. All survivors had CPC 1–2 neurologic status.

Conclusion: In this single center experience, the use of resuscitative ECMO was associated with neurologically favorable 30-day survival in 47% of patients with prolonged IHCA (H2012:172).

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1. Introduction

Outcomes of in-hospital cardiac arrest (IHCA) have changed modestly in recent decades despite modern approaches to

hospital discharge remain unfavorable, varying from 7 to 18% among adults with IHCA.^{4,5} Resuscitative extracorporeal membrane oxygenation (ECMO) was first applied to IHCA in 1976 among a population of patients with pulmonary emboli and cardiothoracic trauma,⁶ but early attempts had high rates of complications. Technological advances including low resistance, rapidly primed centrifugal pumps and heparin-coated circuits have since reduced

bleeding complications, 7 and ultrasound has increased the safety of

cardiopulmonary resuscitation (CPR).¹⁻³ Estimates of survival to

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percutaneous access.⁸ The portability of ECMO units has improved dramatically, allowing broader use in diverse hospital settings and the pre-hospital environment.^{9,10}

Recently ECMO has gained popularity in the resuscitation of patients with severe cardiopulmonary compromise. When applied to select patients with reversible conditions who sustain cardiac arrest (E-CPR)¹¹ or develop profound cardiogenic shock (E-CS),¹² ECMO may support end organ perfusion while bridging to definitive therapy. Reports of survival following E-CPR for IHCA range from 28 to 42% in retrospective series, ^{13–17} to 40% in a 135 patient meta-analysis.¹⁸ Despite these encouraging reports, two recent trials of E-CPR with propensity matched control groups reached conflicting conclusions regarding therapeutic benefit.^{19,20} Younger age¹⁸ and shorter low – flow duration^{16,18,21} have been associated with greater likelihood of survival, however knowledge of other predictors of outcome among recipients of resuscitative ECMO is evolving.

Although international consensus recommendations cite growing evidence for resuscitative ECMO at capable centers, ²² requirements for specialized equipment and timely access to rapid response ECMO teams have limited its broad application. Outside of Eurasia, resuscitative ECMO for adult IHCA has been performed at limited sites in North America, ^{23,24} but has not yet been reported in Canada. We sought to determine 30-day mortality and neurologic outcome among a broad population of non-cardiotomy patients receiving ECMO following IHCA at a tertiary care Canadian center. Second, we examined univariate predictors of 30-day survival.

2. Methods

2.1. Study design

We performed a retrospective cohort study examining the clinical records of consecutive adult patients who received veno-arterial ECMO following witnessed IHCA at a single academic tertiary-care center (St. Boniface Hospital, Winnipeg, Canada) between February 2008 and September 2013. Informed consent was waived for this retrospective chart review. The study protocol received approval from the University of Manitoba and St. Boniface Hospital research ethics review boards.

2.2. Data collection

A list of variables including demographics, comorbidities, ECMO-related variables, laboratory data, and in-hospital clinical course was generated during interdisciplinary focus group meetings based on results of published ECMO literature and consensus of biologic plausibility. Thereafter, pre-specified variables were obtained from the medical record. Patients were categorized as E-CPR if ECMO cannulation occurred during ongoing cardiopulmonary resuscitation and as E-CS if ECMO was initiated for refractory cardiogenic shock following return of spontaneous circulation (ROSC) post-cardiac arrest. Low flow time was defined as the total duration of cardiopulmonary resuscitation that occurred prior to ECMO cannulation. Patients who received ECMO for profound hypothermia or drug overdose were excluded from this analysis. The primary outcome was 30-day survival with good neurologic function defined as a cerebral performance category (CPC) of 1–2.²⁵ CPC status was ascertained by review of the medical record. Data abstractors were not blinded to patient management details. Secondary outcomes included intensive care unit (ICU) and hospital length of say, duration of mechanical ventilation, and univariate predictors of 30-day survival with favorable neurologic function.

2.3. Patient selection

Candidates for resuscitative ECMO (E-CPR or E-CS) were evaluated by the mechanical circulatory support surgeon on call. Inclusion criteria for E-CPR were (i) witnessed cardiac arrest ≥15 min with immediate CPR, (ii) an identifiable, reversible cause, and (iii) no apparent contraindication to aggressive medical care such as an advanced directive. Inclusion criteria for E-CS were refractory cardiogenic shock following IHCA defined by hypotension (systolic blood pressure < 90 mmHg) and insufficient systemic oxygen delivery despite inotropic/vasopressor support and/or intra-aortic balloon counterpulsation. Insufficient systemic oxygen delivery was defined as clinical or biochemical evidence of tissue hypoxia as evidenced by progressive metabolic acidosis, urine output <0.5 cc/kg/h, or central venous oxygen saturation <70%.

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Relative exclusion criteria for resuscitative ECMO included septic shock, uncontrolled infection, active traumatic hemorrhage, multi-system organ failure, advanced malignancy, heparin induced thrombocytopenia, peripheral arterial disease with lower extremity ischemia, morbid obesity (body mass index > 40), and aortic dissection.

2.4. ECMO conduct

ECMO cannulation was established with 15-19F arterial and 24/29-30/33 two-stage venous cannulas using a percutaneous approach whenever possible. The ECMO circuit was comprised of a femoral venous line connected to a BioMedicus 540 centrifugal pump (Medtronic, Minneapolis, MN, USA) that propelled blood through a Medtronic Affinity NT oxygenator/heat exchanger into the common femoral arterial cannula. Circuits were primed with 600 mL of room temperature lactated ringers solution. Following ECMO initiation, unresponsive patients (Glasgow Coma Score ≤ 8) received therapeutic hypothermia with temperature targets of 33-34°C for 24h. An infusion of intravenous heparin was maintained to achieve a target activated clotting time of 160–200 s. The etiology of cardiac arrest was confirmed using coronary angiography, echocardiography, and computed tomography where applicable. Aggressive therapeutic intervention was undertaken to correct the underlying pathology including percutaneous coronary intervention, catheter ablation, coronary artery bypass grafting and valve repair or replacement.

After 24 h of support patients were considered for initiation of the weaning protocol if signs of end-organ recovery were evident on moderate pulmonary and inotropic support. This was accomplished by gradually reducing ECMO flow while observing for signs of myocardial recovery via echocardiography and clinical assessment of adequacy of systemic oxygen delivery. If weaning was unsuccessful after 7–10 days of support but end-organ function was improving and transplant candidacy was confirmed, the patient was transitioned to a long-term ventricular assist device. However, if weaning was unsuccessful and the patient was not deemed to be a transplant candidate, life-sustaining care was withdrawn following multidisciplinary discussion with the patient's family and treatment team.

2.5. Statistical analysis

Normally distributed continuous variables were reported as mean ± standard deviation (SD) and compared using Student's *t*-test. Non-normally distributed variables were reported as median and interquartile range (IQR) and compared using the Mann–Whitney U test. Categorical variables were expressed as frequencies and were compared using the chi-squared or Fisher's exact test. Univariate predictors of 30-day survival with good neurologic function (CPC 1–2) were determined. Variables with a *p*

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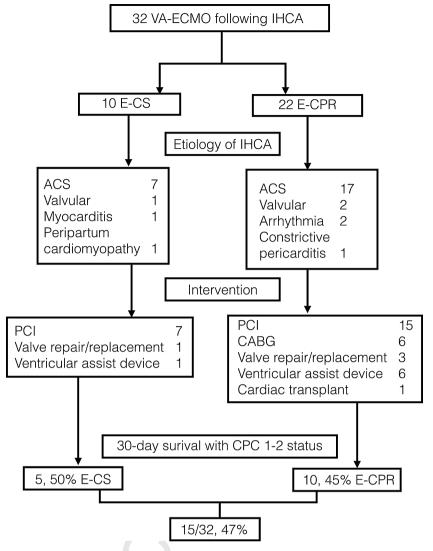


Fig. 1. Summary of patient flow among adults treated with extracorporeal membrane oxygenation (ECMO) for in hospital cardiac arrest (IHCA). E-CS, ECMO-cardiogenic shock; E-CPR, ECMO-cardiopulmonary resuscitation; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CPC, cerebral performance category. Data for short-term ventricular assist devices are shown.

value less than 0.05 were considered statistically significant. The Kaplan–Meier method was used to calculate 30-day survival with good neurologic function, with censoring for death or hospital discharge. Analyses were performed with GraphPad Prism V6.0c (GraphPad Software Inc., La Jolla, USA) and SAS V9.2 (SAS Institute Inc.).

3. Results

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3.1. Patient characteristics

Thirty-two patients received resuscitative ECMO following cardiac arrest, with 22 patients receiving E-CPR and 10 patients receiving E-CS following ROSC (Fig. 1). Baseline characteristics and univariable analysis for 30-day survival are displayed in Table 1. Respective etiologies of cardiac arrest included acute coronary syndrome (n = 24), critical valvular pathology (n = 3), primary arrhythmia (n = 2), myocarditis (n = 1), peripartum cardiomyopathy (n = 1), and constrictive pericarditis (n = 1). The underlying cause of cardiac arrest was not significantly associated with 30-day survival (p = 0.42 - 1.00). Among patient comorbidities recorded, survivors were less likely to have diabetes mellitus (13.3% vs 58.8%, p = 0.01).

The presence of an initial cardiac rhythm amenable to defibrillation/cardioversion was 7 (46.7%) in survivors and 7 (41.2%) in non-survivors, respectively (p = 0.76). No significant differences in age, Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, or initial cardiac rhythm were present in survivors compared to non-survivors (p = 0.17–0.61).

ECMO cannulation occurred most frequently in the cardiac catheterization suite (n = 17), followed by the intensive care unit (n=12), operating room (n=2), and emergency room (n=1). Mean low flow duration was $38.3 \pm 27.9 \, \text{min}$ in survivors and 45.5 ± 21.6 min in non-survivors (p = 0.36). Mean ECMO duration was 66.6 and 74.3 h in survivors and non-survivors respectively (p = 0.63). Nine survivors were treated with the rapeutic hypothermia, while 13 non-survivors were cooled (p = 0.45). Percutaneous coronary intervention was undertaken in 22 patients, while six patients underwent coronary artery bypass grafting, and four received cardiac valve replacement/repair. Two patients received long-term ventricular assist-devices and one patient was bridged to cardiac transplant. Overall, interventions were similar in survivors and non-survivors (Table 2). However, continuous venovenous hemodiafiltration (CVVHDF) was required less frequently among survivors (4 vs 11, p = 0.03). Median lactate levels were significantly

Table 1

04 Baseline characteristics for patients treated with extracorporeal membrane oxygenation for in-hospital cardiac arrest.

Non-survivors $(n = 17)$	<i>p</i> -Value
56.12 ± 8.9	0.61
12(70.6)	0.53
32.0 (25.1–34.0)	0.51
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9(52.9)	0.06
4(23.5)	0.66
3(17.7)	1.00
9(52.9)	0.46
13(76.5)	0.17
10(58.8)	0.01
8(47.1)	0.46
1(5.9)	1.00
0	0.21
Ü	0.21
23.5 ± 8.9	0.17
26.75 ± 2.8	0.53
31 ± 1.9	0.10
9.7 (7–11.8)	0.99
9.7 (7-11.8)	0.55
4(23.5)	1.00
4(23.5)	1.00
7(41.2)	0.95
2(11.8)	1.00
45.5 + 24.6	0.26
45.5 ± 21.6	0.36
52.1 ± 4.6	0.61
29.6 ± 12.0	0.56
6(35.3)	0.34
6.73 ± 5.3	0.08
14(82.4)	0.42
1(5.9)	0.59
1(5.9)	1.00
0	0.47
1(5.9)	1.00
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0	0.47
10(58.8)	0.49
6(35.3)	0.78
1(5.9)	1.00
1(0.0)	1.00
74.3 ± 53.6	0.81
	0.77
	0.32
	0.45
	74.3 ± 53.6 69.6 ± 14.6 85.5 ± 29 $13(76.5)$

a BMI, body mass index; CVA, cerebrovascular accident; APACHE II, acute physiology and chronic health evaluation II; ECMO, extracorporeal membrane oxygenation; mmol, millimoles; mg, milligrams,

higher among non-survivors during hours 6-48 of ECMO support (p < 0.05 for each time point) (Fig. 2). Ten patients developed extremity malperfusion requiring cannula revision or thrombectomy, and one patient required fasciotomy for compartment syndrome.

3.2. Patient outcomes

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Primary and secondary outcomes are listed in Table 3. Eighteen patients were alive following ECMO decannulation. 30-Day survival was 5 (50%) in the E-CS group, 10 (45.4%) in the E-CPR group, and 15 (47%) overall. Survival was independent of extracorporeal support category (E-CPR n = 10, E-CS n = 5, p = 1.00). All survivors had favorable neurologic outcome at 30 days defined by CPC status of 1 or 2. Non-survivors died most frequently due to anoxic brain injury or cerebral infarction (5 (29.4%)), withdrawal of care (4 (23.5%)), and multi-system organ failure (3 (17.7%)). Two patients (11.8%) died due to refractory heart failure despite available mechanical support. Two patients (11.8%) died from refractory bleeding due to retroperitoneal and intra-thoracic hemorrhage, respectively. Last, one patient (5.9%) died due to septic shock. A Kaplan–Meier 30-day survival curve is depicted in Fig. 3.

4. Discussion

This case series demonstrates the successful application of resuscitative ECMO to a group of patients with prolonged IHCA with a high proportion of neurologically intact survivors at 30 days. Our promising short-term outcomes are at least consistent with recent reports of E-CPR in IHCA, 13-15 and exceed the 27% survival reported in the ELSO registry of 408 entries of adult E-CPR as of 2010.⁷ Several factors must be considered when interpreting our patient outcomes. We studied a population for which the majority received E-CPR, but several patients received resuscitative ECMO just after or in between recurrent cardiac arrests with evidence of severe refractory shock. For the purposes of consistent data reporting and registry input - we strictly defined E-CPR patients as those who were percutaneously cannulated for ECMO with CPR ongoing. Both E-CPR and E-CS groups defined in this report represent a patient population with dismal prognosis without emergent

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b Low-flow duration refers to time from cardiac arrest to cannulation or return of spontaneous circulation.

Table 2Interventions, complications, and transfusion requirements among patients receiving extracorporeal membrane oxygenation for in-hospital cardiac arrest.

	All patients (n = 32)	Survivors (n = 15)	Non-survivors (n = 17)	<i>p</i> -Value
Interventions				
Percutaneous coronary intervention, $n(\%)$	22(68.8)	9(60)	13 (76.5)	0.45
IABP, a n (%)	19(59.4)	8 (53.3)	11 (64.7)	0.51
Coronary artery bypass grafting, $n(\%)$	6(18.8)	3(20)	3(17.7)	1.00
Valvular replacement/repair, n (%)	4(12.5)	2(13.3)	2(11.8)	1.00
Ventricular assist device (short term), n (%)	7(21.9)	3(20)	4(23.5)	1.00
Ventricular assist device (long term), n (%)	2(6.3)	2(13.3)	0	0.21
Cardiac transplantation, $n(\%)$	1(3.1)	1 (6.7)	0	0.47
Complications				
Transfusion				
Red blood cells – units (IQR)	7.5 (2.25-14.8)	6(0-10)	12 (3-16)	0.10
Platelets-adult doses ^b (IQR)	1(0-3)	1(0-1)	2(0-3)	0.24
Fresh frozen plasma – units ^c (IQR)	2(0-7.5)	0 (0-4)	4(0-8)	0.16
Continuous venovenous hemodiafiltration, n (%)	15(46.9)	4(26.7)	11 (64.7)	0.03
Cerebral ischemia, d n (%)	5(15.6)	0	5 (29.4)	0.05
Mesenteric ischemia, n (%)	1(3.1)	0	1 (5.9)	1.00
Malperfusion of extremity requiring revision/repair, n (%)	10(31.3)	5(33.3)	5 (29.4)	1.00
ECMO site bleeding requiring revision/repair, n (%)	6(18.8)	2(13.3)	4(23.5)	0.66
Sepsis, n (%)	9(28.1)	5(33.3)	4(23.5)	0.70

- ^a IABP: intra-aortic balloon counterpulsation, IQR: inter-quartile range, ECMO: extracorporeal membrane oxygenation
- ^b One adult dose is a pool of six whole blood derived platelets.
- ^c One unit of fresh frozen plasma is equivalent to 500 cc.
- ^d Cerebral ischemia was defined as cerebrovascular accident or diffuse anoxic injury.

salvage therapy and may warrant similar consideration. However, because of the unique situational urgency and technical challenges of E-CPR, we have also reported outcomes in this group separately. Next, we did not include patients with out of hospital cardiac arrest – a population in which active research is attempting to clarify the therapeutic benefit of E-CPR. ^{14,16,26} Finally, in addition to the therapeutic benefit of resuscitative ECMO, the favorable results in our review also reflect the longitudinal care imparted by an expert multi-disciplinary heart failure, critical care, and transplant cardiology team.

Our study has several strengths and implications. First, our site is a 554 bed acute care facility which sees 25,000 admissions annually – which is small in comparison to the 2000 bed

facilities performing E-CPR in Taiwan and Korea. ^{19,27} These findings support the generalizability of E-CPR delivery at smaller centers than those that popularized the technique, provided advanced cardiothoracic surgical capabilities and expertise are available. Second, we examined a population that is most relevant to clinicians attempting to determine which cardiac arrest patients encountered in daily practice might benefit from resuscitative ECMO by excluding post-cardiotomy patients and those with generally accepted indications for E-CPR (cardio-toxic drug overdose and environmental hypothermia). Third, all survivors in our study demonstrated favorable neurologic status at 30 days, a finding that would be unexpected in survivors of prolonged cardiac arrest (mean low flow duration, 41.4 min) who received conventional cardiopulmonary

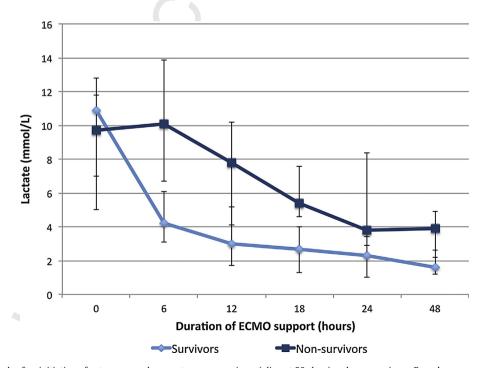


Fig. 2. Median lactate levels after initiation of extracorporeal support among survivors (alive at 30-days) and non-survivors. Error bars represent limits of inter-quartile range (IQR).

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Table 3Primary and secondary outcomes among patients receiving ECMO for in-hospital cardiac arrest.

	n	Survivors	Non-survivors	<i>p</i> -Value			
30 day survival, <i>n</i> (%)							
Total	32	15(46.9)	17(53.1)	-			
E-CPR ^a	22	10(45.4)	12(54.5)	-			
E-CS	10	5(50)	5(50)	-			
CPC 1-2 status, n (%)	32	15(46.9)	0	-			
Intensive care unit LOS, days, median (IQR)							
Total	32	14(6-27)	5(2-9)	0.003			
E-CPR	22	15.5 (9.5-43.5)	4.5 (2-6.8)	< 0.001			
E-CS	10	6(4-12.5)	8(3.5-12)	0.90			
Hospital length of stay, days, me	dian (IQR)						
Total	32	29(17-45)	7(2.8-10)	< 0.001			
E-CPR	22	34(29-61)	6.5 (1–11)	< 0.001			
E-CS	10	17(13-23)	7(3.5–12)	0.01			
Duration of mechanical ventilation, days, median (IQR)							
Total	32	9(5–14)	5(2-11)	0.15			
E-CPR	22	12(5-35)	5(2-7)	0.01			
E-CS	10	10(4–16)	5(3-7)	0.22			

^a E-CPR, ECMO initiated during cardiopulmonary resuscitation; E-CS, ECMO initiated for cardiogenic shock following cardiopulmonary resuscitation; CPC, cerebral performance category, CPC 1, good cerebral performance; CPC 2, moderate cerebral disability; CPC 3, severe cerebral disability; CPC 4, coma/vegetative state; CPC 5, brain death ²⁵

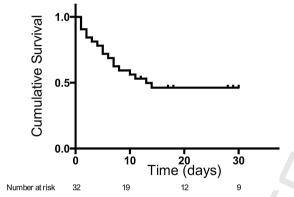


Fig. 3. Kaplan-Meier survival characteristics among patients treated with extracorporeal membrane oxygenation for in hospital cardiac arrest at 30-days, censoring for hospital discharge or death.

resuscitation.²⁸ This finding should be interpreted with some caution due to survivor bias and the inherent limitations of CPC scoring in assessing neurologic outcome.²⁹ Anoxic encephalopathy did occur in our patient population and was the primary contributor to mortality

After univariate analysis, lactate clearance in the immediate post-resuscitative phase was associated with 30-day survival. Although Haneya et al. 16 noted higher initial lactate values in non-survivors of cardiac arrest treated with ECMO, we believe this is the first report to suggest the significance of a lactate trend in the first 48 h of ECMO support. Given our small sample size multivariate analysis was not possible, making this finding only hypothesis generating. If confirmed in future research, lactate clearance together with markers such as pre-circuit peripheral venous oxygen saturation³⁰ may aid clinicians making decisions to limit established extracorporeal support due to futility, or conversely escalate or modify therapy in the post resuscitative phase. Contrary to previous efforts to elucidate predictors of success in E-CPR recipients, we did not find age or duration of resuscitation to be significant predictors of survival. Without the power of a larger sample size, we are unable to ascertain whether low flow duration or age are indeed predictors of survival, or whether by virtue of our inclusion and exclusion criteria these variables are less important. Further study is warranted before adopting protocols that advise rigid cutoffs for age or low flow duration when determining E-CPR candidacy.

Our experience highlights that despite the potential therapeutic benefit of E-CPR, this invasive therapy is frequently complicated by extremity malperfusion, life threatening hemorrhage, and acute renal failure. These risks are acceptable given the lack of alternative therapy for patients with refractory cardiac arrest. Prolonged cardiac resuscitation is associated with reduced chance of return of spontaneous circulation and greater likelihood of undesirable neurologic outcome.^{31,32} Accordingly, a review of a large national IHCA registry confirmed most unsuccessful resuscitation efforts are terminated prior to 30 min,³³ far shorter than the mean duration of cardiac arrest in our study. Broader questions regarding the impact of E-CPR on scarce perfusion resources, elective surgery slates, cardiac intensive care unit occupancy, and costs of hospital stay warrant careful consideration and ethical debate. This study adds to the growing body of E-CPR literature that challenges our understanding of cardiac arrest as a terminal manifestation of a disease process with treatment options fraught with futility. Rather, for selected patients, cardiac arrest may be better considered an exacerbating symptom of underlying disease with a therapeutic window to effectively restore perfusing circulation while providing definitive therapy. It is conceivable that ECMO will play an important role in the resuscitation of such patients in the future.

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This study is subject to the limitations of retrospective patient series and lacks both a control group and randomization. In addition, our report by nature is highly susceptible to selection bias. We were unable to report data on patients referred for ECMO consultation, but not cannulated based on exclusion criteria, though these cases are exceedingly rare. Given the limited sample size the results of our univariate analysis are hypothesis generating. We were unable to report long-term functional outcomes, however, by establishing a follow-up clinic for IHCA survivors we hope to report this data in depth in the future. Finally, we did not have access to detailed data regarding temperature trends amongst our cohort, an important factor in assessing interventions and outcomes in cardiac arrest.²

5. Conclusions

Resuscitative ECMO was associated with neurologically favorable short-term survival among a population of patients with prolonged IHCA. Further inquiry is required to investigate the prognostic significance of lactate clearance following extracorporeal support.

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Conflict of interest statement

The authors have no financial or other conflicts of interest to disclose. No funding was utilized in this retrospective review

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