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Descriptive analysis of extracorporeal cardiopulmonary resuscitation following out-of-hospital cardiac arrest—An ELSO registry study'☆

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ABSTRACT

Aim: Extracorporeal cardiopulmonary resuscitation (ECPR) is an emerging therapy for refractory cardiac arrest. The purpose of this study was to analyze and report characteristics and outcomes of adult patients treated with ECPR after out-of-hospital cardiac arrest (OHCA) in a large international registry.
Methods: The Extracorporeal Life Support Organization's Extracorporeal Life Support Registry was queried for adult cardiac arrests with arrest location of "EMT Transport" or "Outside Hospital."
Results: From 2010–2016, 217 cases of ECPR following OHCA were reported in Europe (47%), Asia-Pacific (29%), and North America (24%). The median age was 52 years (IQR 45–62, range 18–87); 73% were male. The median duration of ECPR was 47 h (IQR 17–94, range 0–711). Reported complications included hemorrhage (31.3%), limb complications (11.1%), circuit complications (8.8%), infection (7.4%), and seizures (5.5%). The rate of percutaneous coronary intervention (PCI) was higher in Europe (35.6%) and Asia-Pacific (25.8%) than North America (9.4%; $p < 0.01$). Survival to hospital discharge was 27.6% (95% CI 22.1–34.0%), and male gender was independently associated with mortality (adjusted odds ratio 2.1 [95% CI 1.1–4.2], $p < 0.05$). Survival did not differ by region, race, age, or year. Brain death was reported in 16.6% [95% CI 12.2–22.1%]; organ donation rate was not reported.
Conclusion: This international analysis of ECPR for refractory OHCA reveals a survival rate of 27.6%, demonstrates association of male gender with mortality, and highlights regional differences in PCI utilization. These results will help inform implementation and research of this potentially life-saving strategy for refractory OHCA.

Introduction

Extracorporeal cardiopulmonary resuscitation (ECPR) for refractory cardiac arrest involves the addition of percutaneous veno-arterial extracorporeal membrane oxygenation (ECMO) to standard resuscitative efforts. This technique provides temporary circulatory support and maintains vital organ perfusion while clinicians identify and reverse the underlying cause of arrest. ECPR is emerging as a feasible and effective resuscitation strategy for patients who fail standard resuscitative efforts. The overall survival to hospital discharge rate for EMS treated out-of-hospital cardiac arrest (OHCA) in the United States is 11.4% [1], while utilization of ECPR for OHCA refractory to standard therapy has reported survival rates ranging from 4 to 55% in select populations from single institutions, local regions, or single countries [2–15].

The utilization of ECPR for refractory OHCA has increased in recent years [16]. As more centers begin to perform ECPR following OHCA, accurate reporting of techniques, equipment, process variables, outcomes, and complications is essential in guiding clinical implementation and future research. However, the majority

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of published ECPR data involves in-hospital cardiac arrest (IHCA), which is a different patient population than those with refractory OHCA. Therefore, reporting ECPR data specific to OHCA is essential, as patient demographics, pathology, arrest etiology, and outcomes differ significantly from IHCA. Furthermore, generalization of results from single centers or regions can be limited, as patient demographics and process variables may vary based on country or region.

The Extracorporeal Life Support Organization (ELSO) is an international consortium of health care institutions dedicated to the development and evaluation of novel therapies for support of failing organ systems, and maintains the largest international registry of patients receiving ECMO, including ECPR. By collecting data from self-reporting centers in six continents and over 50 countries, regional commonalities and differences can be identified. Our aim was to perform a descriptive analysis of patient demographics, process variables, outcomes, and complications of ECPR for refractory OHCA from the ELSO database. We hypothesized that survival to hospital discharge, complications, and process variables related to ECPR for OHCA differed across geographic regions.

Methods

Study design

This was a retrospective review of data from the ELSO Registry that was approved by ELSO and the Institutional Review Board at the University of Michigan.

Study population and inclusion criteria

The ELSO registry contains data on patients from self-reporting centers in six continents and over 50 countries. We queried the ELSO Extracorporeal Life Support Registry for all adult (≥18 years of age) OHCA cases defined as a documented arrest location of "EMT Transport" or "Outside Hospital." Patient demographics (age, gender, weight, race, geographic region, year), process variables (duration of ECPR, diameter and location of cannulas, pump used, membrane lung used, heat exchanger used), and patient outcome data (survival to hospital discharge, complications) were extracted and analyzed.

Statistical analysis

We performed bivariate comparisons between survivors and non-survivors. The 95% confidence intervals for survival rates across levels of different variables were estimated [17]. Independent samples *t*-tests were used to analyze continuous variables, and chi-squared and z-tests for comparison of independent proportions were used to analyze categorical variables. Multiple logistic regression analysis was used to test for associations between predictor variables (i.e., gender and ECPR duration) and the odds of mortality [18]. A relatively large subsample of patients (n = 19) had missing data on the weight variable, and this subsample consisted of mostly male non-survivors with lower than average duration of ECPR. We therefore excluded the weight variable from the multiple logistic regression analysis. All analyses were conducted with SAS software version 9.4 (SAS Institute, 2013).

Results

Patient demographics

From 2010–2016, 217 cases of adult ECPR following OHCA were reported in Europe (47%), Asia-Pacific (29%), and North America (24%) (Table 1). The location of one case was unknown. The median age was 52 years (IQR 45–62, range 18–87). Seventy-three percent of patients were male, 25% were female, and the gender of five patients (2%) was unknown. The majority of patients were White (69%), followed by Asian (19%), Black (5%), Hispanic (1%), and the race of 13 patients (6%) was listed as other or unknown. The median weight was 80 kg (IQR 70–90, range 50–182); the weight of 19 patients (8.8%) was unknown. Of the patients with unknown weight (n = 19), 84% were male, compared to 74% of those with complete data on weight (n = 198) ($p > 0.05$). The median weight of males was significantly greater than that of females (80.5 kg vs 70 g, $p < 0.01$). Survival for those with unknown weight (n = 19) was 11%, as compared to 29% for those with complete data on weight (n = 198, $p > 0.05$).

Temporal trends

The reported number of cases of ECPR for OHCA increased each year from 2010 (2) to 2015 (83), while data is not yet available for the entirety of 2016. No significant difference was observed in survival between years, with minimum of 0% [95% CI 0–63.1%] in 2010 and maximum of 40.0% [95% CI 24.6–57.7%] in 2013 (Table 1).

Process variables

Most patients (88.9%) had two cannulas placed, while 10.1% of patients had three cannulas placed (Table 1). Most were placed percutaneously (71.0%), and the most common locations were the femoral artery (98.6%) and femoral vein (95.7%). Additional cannula locations reported included the aorta, common carotid artery, right atrium, and internal jugular vein. The most common arterial cannula diameters were 17 Fr (22.3%) and 19 Fr (14.9%), and the most common venous cannula diameters were 21 Fr (21.7%) and 25 Fr (14.0%) (Supplemental Table 1). The most commonly used cannula diameters (17 Fr arterial and 21 Fr venous) did not differ by gender. The most commonly used pumps were the Jostra Rotaflow (35.0%) and Cardiohelp (29.0%) (Supplemental Table 2). The Jostra Quadrox (47.0%) and Cardiohelp (25.8%) were the most commonly used membrane lungs. The most commonly used heat exchangers were the Quadrox Integrated (34.1%) and Jostra (10.1%).

ECPR duration

The overall median duration of ECPR was 47 h (IQR 17–94, range 0–711) (Table 2). The duration of ECPR for survivors was significantly longer than that of non-survivors (78 vs 37 h, $p < 0.05$). ECPR was discontinued due to patient recovery (34.6%), organ failure (35.5%), diagnoses incompatible with life (24%), family request (2.3%), hemorrhage (1.4%), and unknown reason (2.3%). All cases of hemorrhage requiring discontinuation of ECPR occurred within 72 h of initiation. Among non-survivors, ECPR was discontinued within 24 h of initiation in greater than one third of patients. ECPR was discontinued due to family request less frequently in Europe (0%) than Asia-Pacific (3.2%) or North America (5.8%; $p < 0.05$), although the sample sizes were small (Table 3). ECPR was discontinued due to diagnoses incompatible with life less frequently in Europe (13.9%) than in Asia-Pacific (33.9%) or North America (32.7%, $p < 0.05$). ECPR was discontinued due to organ failure more frequently in Europe (47.5%) than Asia-Pacific (24.2%) or North America (26.9%, $p < 0.05$).

Survival

Overall survival to hospital discharge was 27.6% [95% CI 22.1–34.0%] (Table 4). Brain death was reported in 16.6% [95% CI 12.2–22.1%] of cases; organ donation rate was not available.

Table 1
Patient demographics, temporal trends, and process variables.

	Overall n = 217	Survivors n = 60	Non-survivors n = 157	Survival Rate, % (95% CI)	*p*
Gender, n					<0.05
Male	158	38	120	24.1 (18.0–31.3)	
Female	54	21	33	38.9 (27.0–52.2)	
Unknown	5	1	4	20.0 (2.0–64.0)	
Median age, years (IQR)	52 (45–62)	51 (45–60)	53 (45–62)		
Median weight, kg (IQR)	80 (70–90)	75 (67–90)	80 (70–91)		
Unknown weight, n (%)	19 (8.8)	2 (3.3)	17 (10.8)		
Race, n					>0.05
White	150	44	106	29.3 (22.6–37.1)	
Asian	42	12	30	28.6 (17.1–43.7)	
Black	10	3	7	30.0 (10.3–60.8)	
Unknown	8	0	8	0.0 (0.0–29.3)	
Other	5	1	4	20.0 (2.0–64.0)	
Hispanic	2	0	2	0.0 (0.0–63.1)	
Region, n					>0.05
Europe	101	31	70	30.7 (22.5–40.3)	
Asia-Pacific	62	16	46	25.8 (16.5–38.0)	
North America	53	13	40	24.5 (14.8–37.7)	
Unknown	1	0	1	0.0 (0.0–77.7)	
Year, n					>0.05
2010	2	0	2	0.0 (0.0–63.1)	
2011	11	2	9	18.2 (4.0–48.9)	
2012	23	7	16	30.4 (15.4–51.1)	
2013	30	12	18	40.0 (24.6–57.7)	
2014	43	14	29	32.6 (20.4–47.6)	
2015	83	17	66	20.5 (13.1–30.5)	
2016 (Jan–July)	25	8	17	32.0 (17.1–51.7)	
Total number of cannulas placed, n (%)	428	118	310		>0.05
Patients with 2 cannulas placed	193 (88.9)	54 (90)	139 (88.5)	28.0 (22.1–34.7)	
Patients with 3 cannulas placed	22 (10.1)	6 (10)	16 (10.2)	27.3 (12.9–48.4)	
Other	2 (0.9)	0	2 (1.3)		
Cannulation Technique, n (%)					<0.05
Percutaneous	304 (71.0)	74 (62.7)	230 (74.2)	24.3 (19.8–29.5)	
Other/Unknown	124 (29.0)	44 (37.3)	80 (25.8)	35.5 (27.6–44.2)	
Arterial Cannula Location, n (%)	215	60	155		>0.05
Femoral Artery	212 (98.6)	59 (98.3)	153 (98.7)		
Right	124 (57.7)	36 (60)	88 (56.8)	29.0 (21.7–37.6)	
Left	88 (40.9)	23 (38.3)	65 (41.9)	26.1 (18.0–36.2)	
Aorta	2 (0.9)	1 (1.7)	1 (0.6)	50.0 (9.4–90.6)	
Common Carotid Artery	1 (0.5)	0	1 (0.6)	0.0 (0.0–83.2)	
Venous Cannula Location, n (%)	207	56	151		>0.05
Femoral Vein	198 (95.7)	52 (92.9)	146 (96.7)		
Right	136 (65.7)	32 (57.1)	104 (68.9)	23.5 (17.1–31.4)	
Left	62 (30)	20 (35.7)	42 (27.8)	32.3 (21.9–44.7)	
Right Atrium	3 (1.4)	2 (3.6)	1 (0.7)	66.7 (20.2–94.4)	
Internal Jugular Vein	6 (2.9)	2 (3.6)	4 (2.6)	33.3 (9.2–70.4)	
Cannula Site Listed as “Other,ï	6	2	4		

CI = confidence interval, IQR = interquartile range, kg = kilograms.

Table 2
ECPR duration and discontinuation.

	Overall n = 217	Survivors n = 60	Non-survivors n = 157	*p*
Duration of ECPR				
Median duration of ECPR, hours (IQR)	47 (17–94)	78 (45–122)	37 (11–78)	<0.05
Duration of ECPR, n (%)				<0.01
<12 h	43 (19.8)	3 (5)	40 (25.5)	
12–24 h	20 (9.2)	3 (5)	17 (10.8)	
25–72 h	77 (35.5)	21 (35)	56 (35.7)	
3–7 days	51 (23.5)	23 (38.3)	28 (17.8)	
>7 days	20 (9.2)	7 (11.7)	13 (8.3)	
Unknown	6 (2.8)	3 (5)	3 (1.9)	
Reason for discontinuation of ECPR, n (%)				<0.001
Recovery	75 (34.6)	58 (96.7)	17 (10.8)	
Family Request	5 (2.3)	0	5 (3.2)	
Hemorrhage	3 (1.4)	0	3 (1.9)	
Diagnoses incompatible with life	52 (24)	0	52 (33.1)	
Organ failure	77 (35.5)	0	77 (49)	
Other/unknown	5 (2.3)	2 (3.3)	3 (1.9)	

ECPR = extracorporeal cardiopulmonary resuscitation, IQR = interquartile range.

Table 3
Regional trends.

	Asia-Pacific (n = 62)	Europe (n = 101)	North America (n = 53)	*p*
Reason for discontinuation of ECPR, n (%)				<0.05
Recovery	22 (35.5)	37 (36.6)	16 (30.8)	
Family Request	2 (3.2)	0	3 (5.8)	
Hemorrhage	1 (1.6)	1 (1.0)	1 (1.9)	
Diagnoses incompatible with life	21 (33.9)	14 (13.9)	17 (32.7)	
Organ failure	15 (24.2)	48 (47.5)	14 (26.9)	
Other/unknown	1 (1.6)	1 (1.0)	1 (1.9)	
Survival to hospital discharge, % (95% CI)	25.8 (16.5–38.0)	30.7 (22.5–40.3)	24.5 (14.8–37.7)	>0.05
Rate of percutaneous coronary intervention, % (95% CI)	25.8 (16.5–38.0)	35.6 (27.0–45.4)	9.4 (3.7–20.7)	<0.01

ECPR = extracorporeal cardiopulmonary resuscitation, CI = confidence interval.

Table 4
Survival and ancillary interventions.

	Overall n = 217	Survivors n = 60	Non-survivors n = 157	Survival Rate, % (95% CI)	*p*
Survival to hospital discharge, n	217	60	157	27.6 (22.1–34.0)	
Discharge location, n (%)					
Home		14 (23.3)			
Referring hospital		20 (33.3)			
Other service/other facility		24 (40)			
Unknown		2 (3.3)			
Survival to hospital discharge by age (years), n					>0.05
18–29	25	6	19	24.0 (11.2–43.8)	
30–39	15	5	10	33.3 (15.0–58.5)	
40–49	45	13	32	28.9 (17.6–43.5)	
50–59	65	21	44	32.3 (22.2–44.4)	
60–69	49	10	39	20.4 (11.3–33.8)	
≥70	18	5	13	27.8 (12.2–51.2)	
Survival to hospital discharge by weight (kg), n					>0.05
≤60	12	4	8	33.3 (13.6–61.2)	
61–70	53	21	32	39.6 (27.6–53.1)	
71–80	47	14	33	29.8 (18.6–44.1)	
81–90	37	5	32	13.5 (5.4–28.5)	
91–100	24	10	14	41.7 (24.4–61.2)	
101–110	13	2	11	15.4 (3.1–43.5)	
>110	12	2	10	16.7 (3.5–46.0)	
Unknown	19	2	17	10.5 (1.7–32.6)	
Ancillary interventions performed, n (%)					>0.05
Percutaneous coronary intervention	57 (26.3)	16 (26.7)	41 (26.1)	28.1 (18.0–40.9)	
Coronary artery bypass graft	5 (2.3)	3 (5)	2 (1.3)	60.0 (22.8–88.4)	
Intra-aortic balloon pump	16 (7.4)	6 (10)	10 (6.4)	37.5 (18.4–61.5)	
Aortic valvuloplasty or replacement	3 (1.4)	1 (1.7)	2 (1.3)	33.3 (5.6–79.8)	
Ventricular assist device	1 (0.5)	1 (1.7)	0	100.0 (16.8–100.0)	

CI = confidence interval, kg = kilograms.

Survival was significantly greater for females compared to males (38.9% [95% CI 27.0–52.2%] vs 24.1% [95% CI 18.0–31.3%], p < 0.05). Results from bivariate and multiple logistic regression analyses (Table 5) demonstrated that male gender was individually predictive of mortality (odds ratio [OR] 2.0 [95%CI 1.0-3.9], p < 0.05; adjusted odds ratio [AOR] 2.1 [95% CI 1.1–4.2], p < 0.05). Longer duration of ECPR was statistically significantly associated with lower odds of mortality (OR 0.95 [95%CI 0.91-0.99], p < 0.05; AOR 0.95 [95% CI 0.91–0.99], p < 0.05). The weight of survivors was significantly less than that of non-survivors (median 75 kg vs 80 kg, p < 0.05), although the weight of 17 (10.8%) non-survivors was unknown. Bivariate logistic regression demonstrated that weight was significantly associated with higher odds of mortality (OR 1.02 [95% CI 1.01–1.04], p < 0.05). No regional difference in survival existed between Europe, Asia-Pacific, or North America (p > 0.05, Table 1), and survival did not differ by race (p > 0.05, Table 1). Survival did not significantly differ by year (p > 0.05, Table 1) or age (p > 0.05, Table 4). The age of the oldest survivor was 87 years, for whom duration of ECPR was 16 h.

Table 5
Bivariate and Multiple Logistic Regression Analysis of Predictors of Mortality.

	Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Gender		
Male	2.0* (1.0–3.9)	2.1* (1.1–4.2)
Female	–	–
Weight	1.02* (1.01–1.04)	NA
Duration of ECPR	0.95* (0.91–0.99)	0.95* (0.91–0.99)

CI = confidence interval, ECPR = extracorporeal cardiopulmonary resuscitation
* p < 0.05.

Ancillary interventions

Additional interventions (Table 4) included percutaneous coronary intervention (PCI) (26.3%), intra-aortic balloon pump (7.4%), and coronary artery bypass graft (2.3%). Rates of ancillary procedures performed did not differ significantly between survivors and non-survivors. The rate of PCI was lower in North America (9.4%) than Asia-Pacific (25.8%) and Europe (35.6%, p < 0.01) (Table 3).

Complications

Cardiovascular complications were the most frequent complications, occurring in 53% of patients (Table 6). The most common cardiovascular complications were inotrope use (48.8%),

Table 6
Complications: number of patients with ≥1 (%).

	Overall n = 217	Survivors n = 60	Non-survivors n = 157	*p*
Cardiovascular complications	115 (53.0)	35 (58.3)	80 (51)	>0.05
Inotropes required	106 (48.8)	33 (55)	73 (46.5)	
Myocardial stunning	22 (10.1)	7 (11.7)	15 (9.6)	
Arrhythmia	20 (9.2)	4 (6.7)	16 (10.2)	
CPR required	11 (5.1)	2 (3.3)	9 (5.7)	
Hypertension requiring vasodilators	2 (0.9)	2 (3.3)	0	
Tamponade	2 (0.9)	1 (1.7)	1 (0.6)	
Renal complications	60 (27.7)	16 (26.7)	57 (36.3)	>0.05
Hemofiltration required	34 (15.7)	6 (10)	28 (17.8)	
CAVHD required	15 (6.9)	6 (10)	9 (5.7)	
Dialysis required	11 (5.1)	4 (6.7)	7 (4.5)	
Neurologic complications	52 (24.0)	6 (10)	46 (29.3)	<0.01
Brain death	36 (16.6)	0	36 (22.9)	
Seizures	12 (5.5)	5 (8.3)	7 (4.5)	
Central nervous system infarction	6 (2.8)	1 (1.7)	5 (3.2)	
Hemorrhagic complications	68 (31.3)	21 (35)	47 (29.9)	>0.05
Canulation site bleeding	40 (18.4)	15 (25)	25 (15.9)	
Gastrointestinal hemorrhage	21 (9.7)	6 (10)	15 (9.6)	
Disseminated intravascular coagulation	8 (3.7)	0	8 (5.1)	
Surgical site bleeding	8 (3.7)	3 (5)	5 (3.2)	
Central nervous system hemorrhage	5 (2.3)	1 (1.7)	4 (2.5)	
Pulmonary hemorrhage	5 (2.3)	1 (1.7)	4 (2.5)	
Pulmonary complications	6 (2.8)	2 (3.3)	4 (2.5)	>0.05
Pneumothorax requiring treatment	6 (2.8)	2 (3.3)	4 (2.5)	
Mechanical/ECMO circuit complications	19 (8.8)	6 (10)	13 (8.3)	>0.05
Clots in oxygenator	7 (3.2)	0	7 (4.5)	
Cannula problems	7 (3.2)	2 (3.3)	5 (3.2)	
Oxygenator failure	5 (2.3)	2 (3.3)	3 (1.9)	
Hemolysis	4 (1.8)	1 (1.7)	3 (1.9)	
Air in circuit	4 (1.8)	2 (3.3)	2 (1.3)	
Clots in hemofilter	3 (1.4)	2 (3.3)	1 (0.6)	
Clots in other location	2 (0.9)	2 (3.3)	0	
Tubing rupture	1 (0.5)	1 (1.7)	0	
Cracks in pigtail connectors	1 (0.5)	0	1 (0.6)	
Limb complications	24 (11.1)	7 (11.7)	17 (10.8)	>0.05
Ischemia	20 (9.2)	6 (10)	14 (8.9)	
Fasciotomy required	4 (1.8)	1 (1.7)	3 (1.9)	
Compartment syndrome	2 (0.9)	2 (3.3)	0	
Infectious complications	33 (15.2)	18 (30)	16 (10)	<0.01
Culture location:				
Respiratory	28 (12.9)	14 (23.3)	14 (8.9)	
Blood	15 (6.9)	6 (10)	9 (5.7)	
Surgical wound	6 (2.8)	3 (5)	3 (1.9)	
Urine	4 (1.8)	1 (1.7)	3 (1.9)	
Other	3 (1.4)	3 (5)	0	
Stool	1 (0.5)	1 (1.7)	0	
Skin and soft tissue	1 (0.5)	1 (1.7)	0	
Timing of infection:				
On ECPR	16 (7.4)	7 (11.7)	9 (5.7)	
Other	23 (10.6)	12 (20)	9 (5.7)	
Organism:				
Gram negative	25 (11.5)	12 (20)	13 (8.3)	
Gram positive	16 (7.4)	9 (15)	7 (4.5)	
Fungus	7 (3.2)	5 (8.3)	2 (1.3)	
Virus	2 (0.9)	0	2 (1.3)	

CPR = cardiopulmonary resuscitation, CAVHD = continuous arterio-venous hemodialysis, ECMO = extracorporeal membrane oxygenation, ECPR = extracorporeal cardiopulmonary resuscitation.

myocardial stunning (10.1%), and arrhythmia (9.2%). Hemorrhagic complications occurred in 31.3% of patients, including cannulation site bleeding (18.4%) and gastrointestinal hemorrhage (9.7%). Rates of neurologic complications observed included seizures (5.5%), central nervous system (CNS) infarction (2.8%), and CNS hemorrhage (2.3%). Neurologic complications occurred more frequently in non-survivors than survivors (29.3% vs 10%, $p < 0.01$). Limb complications occurred in 11.1% of patients, including ischemia (9.2%) and need for fasciotomy (1.8%). ECMO circuit and mechanical complications occurred in 8.8% of patients. Culture proven infection was observed in 7.4% of patients while on ECPR, and the most common sources were respiratory and bloodstream. Infectious complications occurred more frequently in survivors than non-survivors (30% vs 10%, $p < 0.01$).

Discussion

This retrospective analysis of 217 ECPR cases for refractory OHCA from the ELSO registry revealed an overall survival to hospital discharge rate of 27.6% (95% CI 22.1–34.0%). Male gender was independently associated with mortality (AOR 2.1 [95% CI 1.1–4.2], $p < 0.05$), while age was not, despite an age range of 18–87 years. Increasing weight was associated with mortality (OR 1.02 [95% CI 1.01–1.04], $p < 0.05$). ECMO circuit and mechanical complications occurred in 8.8% of patients. Regional differences in the rate of PCI (lower in North America than Asia-Pacific and Europe) and reasons for discontinuation of ECPR were observed.

The observed survival to hospital discharge rate of 27.6% (95%CI 22.1-34.0%) is consistent with previously published case series of

ECPR for OHCA (4–55% [2–15]), and significantly higher than the overall survival to hospital discharge rate for EMS treated OHCA in the United States (11.4% [1]). Inclusion and exclusion criteria for this potentially life-saving therapy continue to be an area of uncertainty and active research. While ECPR may provide survival benefits to select patient populations, it is a resource intensive therapy, and inappropriate patient selection may lead to significant increases in resource utilization without change in outcome. We observed male gender (AOR 2.1 [95% CI 1.1–4.2], $p < 0.05$) and weight (OR 1.02 [95% CI 1.01–1.04], $p < 0.05$) to be associated with mortality, with a trend towards lower survival in patients weighing greater than 100 kg. Contrarily, no associations between mortality and age, race, or region were observed. These findings are similar to a recent meta-analysis [26] of ECPR for refractory OHCA that also observed no significant association between age and mortality, but observed a trend towards female gender with increased odds of survival. While prior exclusion criteria for ECPR have included age greater than 70 or 75 [2,8,13,15,20], this study observed a similar survival rate in patients greater than and less than 70 years old, and the oldest reported survivor was 87 years old. This result brings into question rigid exclusion criteria based on age alone. As inclusion and exclusion criteria continue to differ by center and evolve with time, these findings may aid in patient selection for both future research and clinical implementation of ECPR for OHCA.

To our knowledge, this is the largest analysis of an international population undergoing ECPR for OHCA to date. While similar descriptive analyses of ECPR process variables and complication rates exist for cardiac arrests of all locations (being comprised of mostly IHCA patients) [16], this is the first ELSO registry-based descriptive analysis of ECPR for strictly OHCA. The vessels cannulated and cannula diameter used from this large international registry-based study are similar to prior reports of such process variables from smaller case series or single regions [8–15,21]. The observed overall median duration of ECPR of 47 h, with a significantly longer duration in survivors than non-survivors (78 vs 37 h, $p < 0.05$), is within range of prior widely varying reports of ECPR duration following OHCA (10–156 h [2,3,8,9,12,14,15,19]). Accurate reporting of duration of ECPR may help avoid both premature withdrawal of therapy and unnecessary prolonged resource utilization. Reporting of process variables associated with ECPR for OHCA can potentially influence practice patterns at sites currently performing this rescue therapy and guide decision making for those developing new ECPR programs.

For patients undergoing ECPR following OHCA, the observed overall rate of PCI (26.3%) was lower than that previously reported by Kagawa [22] (88%), Yannopoulos [15] (67%), Avalli [2] (61%), Sakamoto [13] (54.8%), Stub [14] (42%), Bellezzo [3] (40%), Maekawa [11] (39.6%), Kagawa [9] (38%), and Choi [4] (31%). While the retrospective nature of this study cannot assess causation, there was no significant difference in survival between patients who underwent PCI (28.1%) and those who did not (27.5%). Regional differences in the rate of PCI were observed, with a lower rate in North America than Asia-Pacific or Europe. The underlying reasons for this apparent discrepancy cannot be determined based on the available data, but is an important topic for further investigation.

Regional differences also existed in reasons for discontinuing ECPR, including a lower rate of discontinuation due to family request in Europe than North America or Asia-Pacific. This may be reflective of cultural beliefs and values dictated by region, but may also reflect regional differences in prognostication and physician-family communication. Additional regional differences existed in rates of discontinuation due to organ failure and diagnoses incompatible with life, although these terms were not defined and thus overlap may have existed.

Extensive reporting of complication rates for ECPR following OHCA is essential to ensure appropriate evaluations of risks and benefits as this therapy continues to expand in use. While robust reporting of similar complication rates exists for ECPR used for IHCA or IHCA and OHCA combined [7,14,16,23–25], less is available for comparison for strictly OHCA [6,8,9,11,12,15]. This robust reporting of international complication rates associated with ECPR following OHCA can provide centers wishing to monitor institutional complication rates a benchmark for comparison, and can guide decision making around risk-benefit decisions associated with this relatively complex and resource-intensive therapy.

Limitations

This study has several important limitations. Data was collected from a volunteer registry, and thus the compliance and accuracy of reporting are unknown. The retrospective data utilized in this analysis precludes assessment of causation. No short-term or long-term functional outcomes (ie, Modified Rankin, Cerebral Performance Category) were available for review, and thus patient outcome data is limited to survival to hospital discharge. Specific data around circumstances of the arrest, resuscitation, and post-arrest care previously associated with outcomes, including the majority of Utstein data, were not available. These include presence of witnessed arrest, presence of bystander CPR, total anoxic time, initial arrest rhythm, duration of CPR, intra-arrest medications/management, time from arrest to on ECMO, and utilization of targeted temperature management. The location of cannulation and specialty of the cannulator were unknown, and no data on neuroprognostication was provided. Since only OHCA patients who had received ECPR were included, the impact of ECPR on survival cannot be evaluated in the absence of a control group. Finally, while this is the largest international cohort of ECPR for refractory OHCA reported to date, the sample size remained too small to detect outcome differences based on cannulation technique, ECMO devices, or ancillary procedures.

Conclusions

This international analysis of ECPR for refractory OHCA, which is the largest such international report to date, revealed an overall survival to hospital discharge rate of 27.6% (95%CI 22.1-34.0%). It demonstrated association of male gender and weight with increased mortality but observed no detectable association of age with mortality. Procedural preferences, common complications, and adjunctive therapies utilized were highlighted, and regional differences in reasons for ECPR discontinuation and the rate of PCI were observed. The generalizability of these results will help inform clinical implementation and future research to optimize this potentially life-saving strategy for refractory OHCA, and regional commonalities observed support a standardized approach to implementation.

Conflicts of interest

Authors NLH, RAC, CHH, and JAC have no conflicts of interest to disclose. Author RWN receives support from NIH-R01HL133129: ECPR After Prolonged Cardiac Arrest: Targeting Mechanisms of the No-Reflow and NIH-R44HL091606: Commercialization of a Simple Automatic Perfusion System for ECPR. He also receives equipment support for clinical and laboratory research from PhysioControl.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.resuscitation.2017.08.003.

References

[1]. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, et al. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. Circulation 2017.
[2]. Avalli L, Maggioni E, Formica F, Redaelli G, Migliari M, Scanziani M, 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.
[3]. Bellezzo JM, Shinar Z, Davis DP, Jaski BE, Chillcott S, Stahovich M, et al. Emergency physician-initiated extracorporeal cardiopulmonary resuscitation. Resuscitation 2012;83:966–70.
[4]. Choi DS, Kim T, Ro YS, Ahn KO, Lee EJ, Hwang SS, 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.
[5]. Fagnoul D, Combes A, De Backer D. Extracorporeal cardiopulmonary resuscitation. Curr Opin Crit Care 2014;20:259–65.
[6]. Fagnoul D, Taccone FS, Belhaj A, Rondelet B, Argacha JF, Vincent JL, et al. Extracorporeal life support associated with hypothermia and normoxemia in refractory cardiac arrest. Resuscitation 2013;84:1519–24.
[7]. Haneya A, Philipp A, Diez C, Schopka S, Bein T, Zimmermann M, 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.
[8]. Johnson NJ, Acker M, Hsu CH, Desai N, Vallabhajosyula P, Lazar S, et al. Extracorporeal life support as rescue strategy for out-of-hospital and emergency department cardiac arrest. Resuscitation 2014;85:1527–32.
[9]. Kagawa E, Inoue I, Kawagoe T, Ishihara M, Shimatani Y, Kurisu S, 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.
[10]. Le Guen M, Nicolas-Robin A, Carreira S, Raux M, Leprince P, Riou B, et al. Extracorporeal life support following out-of-hospital refractory cardiac arrest. Crit Care 2011;15:R29.
[11]. 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.
[12]. Leick J, Liebetrau C, Szardien S, Fischer-Rasokat U, Willmer M, van Linden A, 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.
[13]. Sakamoto T, Morimura N, Nagao K, Asai Y, Yokota H, Nara S, 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.
[14]. Stub D, Bernard S, Pellegrino V, Smith K, Walker T, Sheldrake J, et al. Refractory cardiac arrest treated with mechanical CPR, hypothermia, ECMO and early reperfusion (the CHEER trial). Resuscitation 2015;86:88–94.
[15]. Yannopoulos D, Bartos JA, Martin C, Raveendran G, Missov E, Conterato M, et al. Minnesota resuscitation consortium's advanced perfusion and reperfusion cardiac life support strategy for out-of-hospital refractory ventricular fibrillation. J Am Heart Assoc 2016:5.
[16]. Richardson AS, Schmidt M, Bailey M, Pellegrino VA, Rycus PT, Pilcher DV. ECMO Cardio-Pulmonary Resuscitation (ECPR), trends in survival from an international multicentre cohort study over 12-years. Resuscitation 2017;112:34–40.
[17]. Agresti A, Coull B. Approximate is better than exact for interval estimation of binomial proportions. Am Stat 1998;52(2):119.
[18]. Agresti Alan. Categorical data analysis. Hobocken, NJ: Wiley-interscience; 2013. Print.
[19]. Morimura N, Sakamoto T, Nagao K, Asai Y, Yokota H, Tahara Y, et al. Extracorporeal cardiopulmonary resuscitation for out-of-hospital cardiac arrest: a review of the Japanese literature. Resuscitation 2011;82:10–4.
[20]. Chen YS, Lin JW, Yu HY, Ko WJ, Jerng JS, Chang WT, et al. Cardiopulmonary resuscitation with assisted extracorporeal life-support versus conventional cardiopulmonary resuscitation in adults with in-hospital cardiac arrest: an observational study and propensity analysis. Lancet 2008;372:554–61.
[21]. Tonna JE, Johnson NJ, Greenwood J, Gaieski DF, Shinar Z, Bellezo JM, et al. Practice characteristics of Emergency Department extracorporeal cardiopulmonary resuscitation (eCPR) programs in the United States: the current state of the art of Emergency Department extracorporeal membrane oxygenation (ED ECMO). Resuscitation 2016;107:38–46.
[22]. Kagawa E, Dote K, Kato M, Sasaki S, Nakano Y, Kajikawa M, et al. Should we emergently revascularize occluded coronaries for cardiac arrest? rapid-response extracorporeal membrane oxygenation and intra-arrest percutaneous coronary intervention. Circulation 2012;126:1605–13.
[23]. Cheng R, Hachamovitch R, Kittleson M, Patel J, Arabia F, Moriguchi J, 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.
[24]. Thiagarajan RR, Brogan TV, Scheurer MA, Laussen PC, Rycus PT, Bratton SL. Extracorporeal membrane oxygenation to support cardiopulmonary resuscitation in adults. Ann Thorac Surg 2009;87:778–85.
[25]. Belle L, Mangin L, Bonnet H, Fol S, Santre C, Delavenat L, et al. Emergency extracorporeal membrane oxygenation in a hospital without on-site cardiac surgical facilities. EuroIntervention 2012;8:375–82.
[26]. Debaty G, Babaz V, Durand M, Gaide-Chevronnay L, Fournel E, Blancher 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.