Prospective observational study of mechanical cardiopulmonary resuscitation, extracorporeal membrane oxygenation and early reperfusion for refractory cardiac arrest in Sydney: the 2CHEER study

Mark Dennis, Hergen Buscher, David Gattas, Brian Burns, Karel Habig, Paul Bannon, Sanjay Patel, Heidi Buhr, Claire Reynolds, Sean Scott, Priya Nair, Jon Hayman, Emily Granger, Ryan Lovett, Paul Forrest, Jennifer Coles and David A Lowe; on behalf of the Sydney ECMO Research Interest Group

ABSTRACT

Background: Patients with prolonged cardiac arrest that is not responsive to conventional cardiopulmonary resuscitation have poor outcomes. The use of extracorporeal membrane oxygenation (ECMO) in refractory cardiac arrest has shown promising results in carefully selected cases. We sought to validate the results from an earlier extracorporeal cardiopulmonary resuscitation (ECPR) study (the CHEER trial·

Methods: Prospective, consecutive patients with refractory in-hospital (IHCA) or out-of-hospital cardiac arrest (OHCA) who met predefined inclusion criteria received protocolised care, including mechanical cardiopulmonary resuscitation, initiation of ECMO, and early coronary angiography (if an acute coronary syndrome was suspected).

Results: Twenty-five patients were enrolled in the study (11 OHCA, 14 IHCA); the median age was 57 years (interquartile range [IQR], 39–65 years), and 17 patients (68%) were male. ECMO was established in all patients, with a median time from arrest to ECMO support of 57 minutes (IQR, 38–73 min). Percutaneous coronary intervention was performed on 18 patients (72%). The median duration of ECMO support was 52 hours (IQR, 24–108 h). Survival to hospital discharge with favourable neurological recovery occurred in 11/25 patients (44%, of which 72% had IHCA and 27% had OHCA). When adjusting for lactate, arrest to ECMO flow time was predictive of survival (odds ratio, 0.904; $P = 0.035$).

Conclusion: ECMO for refractory cardiac arrest shows promising survival rates if protocolised care is applied in conjunction with predefined selection criteria.

Crit Care Resusc 2020; 22 (1): 26-34

Survival from refractory out-of-hospital (OHCA) and in-hospital cardiac arrest (IHCA) with favourable neurological outcome using conventional cardiopulmonary resuscitation (CCPR) remains poor[1,2] The use of extracorporeal membrane oxygenation (ECMO) for refractory cardiac arrest has increased substantially, and may provide improved survival rates over CCPR.[3,4] The prospective CHEER (ECPR, Hypothermia, ECMO and Early Revascularisation) trial[5] reported neurologically intact survival to discharge in 54% of patients. Herein, we report our experience using a similar protocol, but without the use of therapeutic hypothermia. We aimed to evaluate that protocol in our setting and to establish its external validity.

Methods

Study design

We conducted a prospective cohort study of patients with refractory cardiac arrest within the New South Wales Ambulance Service network for the Royal Prince Alfred Hospital and St Vincent's Hospital, Sydney, Australia, and within these two participating hospitals. The study protocol conforms with the ethics guidelines of the 1975 Declaration of Helsinki and was approved by the Human Research and Ethics Review Committee of Sydney Local Health District (reference X14-0337 and HREC/14/RPAH/453).

Study population

The Royal Prince Alfred and St Vincent's hospitals are ECMO referral centres that provide ECMO retrieval support for NSW. St Vincent's Hospital is the designated heart and lung transplant centre for NSW. Initial management of cardiac arrests was performed as per NSW Ambulance and Australian Resuscitation Council Guidelines.[6,7]

Inclusion criteria

Patients with OHCA refractory to CCPR were eligible for ECPR if they were aged 12–70 years, and met all the following criteria:

- the cardiac arrest was likely to be of primary cardiac or respiratory cause (including myocardial depression secondary to hypothermia or drug effects);
- the cardiac arrest was witnessed;
- chest compressions commenced within 10 minutes;
- initial cardiac rhythm of ventricular fibrillation or ventricular tachycardia;
- immediate availability of a mechanical cardiopulmonary resuscitation (CPR) device with paramedic staff; and
- the cardiac arrest duration (collapse to arrival at the emergency department [ED]) has been less than 60 minutes.

The above inclusion criteria were applicable for IHCA patients, with the exception that non-shockable rhythms were eligible for ECPR if senior clinicians considered it to be potentially reversible, and when all necessary personnel and equipment were available to commence ECMO cannulation within 60 minutes from the time of arrest.

Exclusion criteria

Patients were excluded if there was active bleeding, if it was known that the patient did not want to receive invasive resuscitation, or if the patient had a pre-existing comorbidity and/or functional limitation such that it would prevent a future return to independent life.

Intervention

Consecutive patients with refractory IHCA or OHCA who met the inclusion and exclusion criteria were enrolled. Mechanical CPR (MCPR) was provided with a LUCAS 2 device (Jolife AB; Stryker) and advanced life support was continued throughout the arrest.[6,7]

Potential patients with OHCA were identified by the ambulance paramedics, who notified the ED before hospital arrival. Potential IHCA patients were identified by the hospital's intensive care or medical emergency teams. After identification of a potential ECPR patient, the hospital's ECPR team was activated.

For ECPR patients, peripheral venoarterial ECMO was established via the femoral artery and vein, using a percutaneous, ultrasound-guided Seldinger technique. A 15 or 17 Fr cannula was used for arterial cannulation and a 23 or 25 Fr cannula for venous cannulation. Cannulae positioning was confirmed by transoesophageal echocardiography or fluoroscopy. A distal limb perfusion cannula (7–9 Fr) was placed after ECMO flow was established.

MCPR continued throughout cannulation, with brief cessation permitted for vascular access with guide wires. Defibrillation was paused during cannulation and restarted after, if required.

During cannulation, 5000 units of unfractionated heparin were administered intravenously. CARDIOHELP ECMO pumps (Getinge Group) were used with Quadrox-D oxygenators (Getinge Group) and heparin-bonded circuits. In the absence of contraindications, on admission to the intensive care unit (ICU), heparin was infused to a target activated partial thromboplastin time of 50–70 seconds.

Patients with presumed acute coronary syndrome underwent immediate coronary angiography with or without angioplasty. Pulmonary embolism was confirmed on computer tomography pulmonary angiography before thrombolysis or thrombectomy, where possible.

On admission to the ICU, post-arrest care was implemented, including targeted temperature management to a core temperature of 36°C for 24 hours, in line with established protocol[8] and outlined in the online Appendix (available at cicm.org.au/Resources/Publications/Journal).

Sample size

This trial was intended as a pilot study without any a priori sample size calculation based on a primary end point. A sample size of 25 patients was considered feasible for completion within a 2-year study period.

Definitions

"Arrest to ECMO flow time" refers to the time from the phone call to emergency services (OHCA) or from the call to the medical emergency response team (IHCA) to commencement of ECMO flow.

Outcomes

The primary outcome was survival to hospital discharge. The secondary outcomes included length of stay, neurological status at hospital discharge, bleeding, thrombotic events, and vascular complications. The neurological status was assessed according to the Cerebral Performance Category (CPC) at hospital discharge.[9] A favourable neurological outcome was defined as a CPC score of 1 or 2.

Bleeding was classified according to the Bleeding Academic Research Consortium (BARC) consensus report.[10] Bleeding events were then subdivided further into minor and major bleeding — minor bleeding events being BARC Types 0–2, and major bleeding events being BARC Types 3–5.

Statistical analysis

Categorical variables were summarised using number and percentages and a P value for the Pearson χ^2 test for the general association between the two groups and the corresponding levels of the variables.

Table 1. Baseline characteristics and cardiac arrest details

Variable	Total (*n* = 25)	Survivors (*n* = 11)	Non-survivors (*n* = 14)	*P*
Demographics				
Age (years), median (IQR)	57 (39–65)	57 (37–65)	54 (42–64)	0.809
Male	17 (68%)	6 (55%)	11 (79%)	0.201
Body mass index (kg/m^2), median (IQR)	26 (24–31)	25 (24–33)	26 (25–31)	0.531
Type 2 diabetes	2 (8%)	2 (18%)	0	0.067
Hypertension	6 (24%)	2 (14%)	4 (67%)	0.296
History of ischaemic heart disease	7 (28%)	5 (46%)	2 (14%)	0.101
Arrest data				
In-hospital cardiac arrest (IHCA)	14 (56%)	8 (72%)	6 (43%)	0.135
Out-of-hospital cardiac arrest (OHCA)	11 (44%)	3 (27%)	8 (57%)	
Arrest/call to patient contact (min), median (IQR)	9 (6–13)	9 (6–NA)	9 (6–14)	0.889
On scene time (min), median (IQR)	23 (21–35)	26.5 (23–NA)	22 (19–39)	1.000
Arrest to loaded ambulance (min), median (IQR)	37 (28–44)	35 (28–NA	33 (27–49)	1.000
Arrest to ED time (min), median (IQR)	44 (35–60)	35 (35–48)	52 (40–63)	0.283
Adrenaline dose (mg), median (IQR)	5 (4–6)	4 (4–4)	5 (3–6)	NA
Number of defibrillator shocks, median (IQR)	7 (4–11)	12 (12–12)	5 (4–9)	NA
Cannulation to flow time (min), median (IQR)	16 (11–30)	17 (11–22)	16 (11–35)	0.970
Arrest to ECMO flow time (min), median (IQR)	57 (38–73)	41 (33–58)	69 (52–77)	0.011
Time on LUCAS 2 device* (min), median (IQR)	38 (25–52)	34 (15–41)	48 (29–58)	0.089
IHCA arrest to ECMO (min), median (IQR)	40 (31–53)	39 (29–48)	48 (31–63)	0.524
OHCA arrest to ECMO (min), median (IQR)	74 (59–77)	58 (49–NA)	76 (68–84)	0.012
Initial rhythm				
Ventricular tachycardia	2 (8%)	1 (9%)	1 (7%)	0.672
Ventricular fibrillation	16 (64%)	6 (54%)	10 (71%)	
Pulseless electrical activity	7 (28%)	4 (36%)	3 (21%)	
Cannulation details				
Emergency location	14 (56%)	6 (55%)	8 (57%)	0.563
Intensive care unit	8 (32%)	4 (36%)	4 (29%)	
Angiogram suite	1 (4%)	0	1 (7%)	
Operating room	1 (4%)	1 (9%)	0	
Ward/other	1 (4%)	0	1 (7%)	
Backflow cannula inserted	17 (68%)	8 (73%)	9 (64%)	0.653
Arrest aetiology				
Acute coronary syndrome	12 (48%)	8 (73%)	4 (29%)	0.119
Pulmonary embolism	2 (8%)	0	2 (14%)	
Primary arrhythmia	3 (12%)	0	3 (21%)	
Myocarditis	1 (4%)	0	1 (7%)	
Coronary vasospasm	1 (4%)	1 (9%)	0	
Congenital heart disease	2 (8%)	0	2 (14%)	
Unclear	3 (8%)	2 (14%)	1 (9%)	
Anaphylaxis	1 (4%)	1 (9%)	0	

(*Continues*)

Table 1. Baseline characteristics and cardiac arrest details (*Continued*)

Variable	Total (*n* = 25)	Survivors (*n* = 11)	Non-survivors (*n* = 14)	*P*
Angiography data				
Received angiogram	18 (72%)	9 (82%)	9 (64%)	0.332
Received stent	12 (48%)	7 (64%)	5 (36%)	0.376
Lactate				
First lactate after cannulation, median (IQR)	10.4 (8–13)	8.5 (7.7–14)	11.2 (9.6–12)	0.557
6-hour lactate, median (IQR)	5.25 (4–9)	4.4 (3.4–7.2)	6.6 (4–12)	0.295
24-hour lactate, median (IQR)	1.9 (2–4)	1.6 (1–2)	3.9 (3–13)	< 0.001
APACHE score, median (IQR)	26 (18–34)	24 (19–33)	26 (18–34)	0.820

APACHE = Acute Physiology and Chronic Health Evaluation; ECMO = extracorporeal membrane oxygenation; IQR = interquartile range. * Jolife AB; Stryker.

Numeric variables were summarised using the summary statistics *n* and median and interquartile range (IQR). The non-parametric Mann–Whitney U test was performed for comparison of two groups, with $P < 0.05$ considered significant.

Logistic regression analyses were performed to determine the predictors of mortality. The selection of the variables for logistic regression is based on known clinical relevance to mortality before development of logistic modelling. These included: arrest location (ie, IHCA or OHCA), gender, shockable or non-shockable rhythm, arrest to ECMO flow time, age, and first lactate level taken at time of ECPR. The first lactate level was chosen (as opposed to a lactate level at 24 h) as it is most likely to influence decision making at time of ECPR cannulation.

The statistics produced were odds ratio (OR) and 95% confidence interval (CI) and the overall *P* value. All tests were completed with SPSS Statistics 25 (IBM).

Results

From February 2016 to August 2018, 25 patients (14 IHCA, 11 OHCA) were enrolled, with a median age of 57 years (IQR, 39–65 years). The baseline characteristics and cardiac arrest details are shown in Table 1. All patients were successfully established on peripheral venoarterial ECMO.

Arrest details

All arrests were witnessed and received bystander CPR. Eighteen patients (72%) had an initial shockable rhythm, with seven of these (39%) surviving to discharge. Seven IHCA patients had pulseless electrical activity (PEA) as an initial rhythm, with four surviving to hospital discharge. One IHCA patient died in hospital 120 days after cessation of ECPR.

For OHCA patients, the median time from arrest call to patient contact was 9 minutes (IQR, 6–13 min), and the median time spent on scene was 23 minutes (IQR, 21–35 min), with a median adrenaline dose 5 mg (IQR, 4–6 mg) and a median number of shocks administered of 7 (IQR, 4–11).

The median time from arrest to establishing ECMO flow was 57 minutes (IQR, 38–73 min), with a time from commencement of cannulation to commencement of ECMO flows 16 minutes (IQR, 11–30 min). Survivors had a significantly lower arrest to ECMO flow time than non-survivors (median, 41 min [IQR, 33–58] *v* 69 min [IQR, 52–77]; $P = 0.011$). Arrest to ECMO flow time was significantly shorter in IHCA patients than in OHCA patients (median, 40 min [IQR, 31–53] *v* 74 min [IQR, 59–77]; $P < 0.001$). The median arrest to ECMO flow time was 62 minutes (IQR, 45–76 min), for ventricular tachycardia and/or ventricular fibrillation arrests, versus 40 minutes (IQR, 30–50 min) in PEA arrests ($P = 0.028$) (online Appendix, supplementary tables 1 and 2).

Hospital stay and outcomes

Eleven patients (44%) — eight IHCA (72%) and three (27%) OHCA — survived to hospital discharge, all with favourable neurological outcome (CPC 1 or 2) at discharge. Nine patients (36%) had a CPC of 1 and two patients (8%) a CPC of 2.

The median time on ECMO was 52 hours (median time for survivors, 72 h [IQR, 25–140]; and median time for non-survivors, 32 h [IQR, 2–84]; $P = 0.004$) (Table 2). The duration of ECMO support was significantly shorter in OHCA than in IHCA patients (median, 24 h [IQR, 22–55) *v* 70 h [IQR, 33–153], respectively; $P = 0.015$).

Thirty-six per cent ($n = 5$) of deaths were due to hypoxic brain injury and five (36%) due to multi-organ failure. There were three deaths from bleeding, two

Table 2. Hospital stay and outcomes

	Total (*n* = 25)	Survivors (*n* = 11)	Non-survivors (*n* = 14)	*P*
Hospital stay data				
ECMO run (h), median (IQR)	52 (24–108)	72 (25–140)	32 (2–84)	0.004
Mechanical ventilation (days), median (IQR)	3 (1–8)	6 (4–12)	2 (1–4)	0.003
Total ICU LOS (days), median (IQR)	5 (1–17)	12 (5–19)	2 (1–4)	0.004
Total hospital LOS (days), median (IQR)	7.5 (1–26)	26 (16–77)	2 (1–6)	< 0.001
Required RRT, median (IQR)	11 (44%)	4 (36%)	7 (50%)	0.495
CPC of survivors				
CPC 1		9 (82%)		
CPC 2		2 (18%)		
Cause of death				
Cardiac failure and MODS			5 (36%)	
Hypoxic brain injury			5 (36%)	
Embolic cerebrovascular event			1 (7%)	
Intracranial haemorrhage			2 (14%)	
Abdominal compartment syndrome/haemorrhage			1 (7%)	

CPC = Cerebral Performance Category; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; IQR = interquartile range; LOS = length of stay; MODS = multiple organ dysfunction syndrome; RRT = renal replacement therapy.

from intracranial haemorrhage and one from abdominal compartment syndrome. Two patients became organ donors. Acute Physiology and Chronic Health Evaluation (APACHE) scores were not significantly different between survivors and non-survivors.

Complications

Complications are presented in Table 3. Leg ischaemia requiring intervention occurred in six patients (24%), of whom four had a distal perfusion cannula in situ and five survived to discharge. All ischaemic complications were managed surgically. No patient required amputation or died as a result of leg ischaemia. Vascular surgical repair was performed in eight patients (32%). Twelve major bleeding events occurred in ten (40%) patients. One patient experienced a spinal cord infarction and survived, with residual deficits in the lower limbs.

Predictors of outcome

Regression analysis of survival predictors at cannulation are presented in Table 4. None of these were significantly associated with survival. On sensitivity analysis, when lactate was removed as a variable, arrest to ECMO flow time became significant (OR, 0.904; 95% CI, 0.823–0.993; $P = 0.035$).

Discussion

In response to encouraging survival rates, the use of ECPR for refractory cardiac arrest has increased significantly in recent years.[11] We have previously reported our retrospective experience with ECPR, with a survival rate of 33% of IHCA and 37% of OHCA patients, all with favourable neurological outcomes (CPC 1 or 2).[12] We now report our two-centre, prospective experience in 25 patients, with a survival rate of 57% in IHCA and 27% in OHCA patients, all with favourable neurological outcome.

Our IHCA results were similar to the CHEER trial[5] (57% *v* 60%), although our OHCA survival rate was lower (27% *v* 45%). While we had similar inclusion criteria to the CHEER trial, we did not use intra-arrest therapeutic hypothermia in our patients, as recent data have shown that this does not improve survival.[13] Moreover, when analysing the outcomes of the CHEER OHCA patients that received ECPR (three of nine patients, 33%), the survival rates are similar. The time from arrest to ECMO flow (median 56 min [IQR, 40–85] for CHEER *v* 57 min [IQR, 38–73] for 2CHEER) was also similar despite different geographies and health care services. Our survival rates for IHCA and OHCA are in line with contemporary ECPR studies[14-16] and large registry data.[17] Importantly, excellent neurological outcomes in survivors remain, which is consistent across a number of studies.[18,19]

These results appear promising when compared with overall survival rates for cardiac arrest using CCPR, where overall survival rate is reported at 15–31%[20-23] for IHCA patients and 8–14% for OHCA patients.[24,25] However, direct comparison with CCPR outcomes is difficult and prone to multiple confounding variables. Recent systematic reviews and a meta-analysis of ECPR versus CCPR have failed to show a clear benefit of ECPR over CCPR, which, in large part, is likely due to the poor quality and heterogenous nature of the current available data.[26-28]

Table 3. Vascular, bleeding, and central nervous system complications

	Total (*n* = 25)	Survivors (*n* = 11)	Non-survivors (*n* = 14)	*P*
Vascular complications				
Surgery repair after cannulation	8 (32%)	5 (46%)	3 (21%)	0.201
Ischaemic leg	7 (28%)	5 (46%)	2 (14%)	0.085
Ischaemic leg requiring intervention	6 (24%)	5 (46%)	1 (7%)	0.084
Bleeding complications				
BARC bleeding criteria*				
Type 0 — no bleeding	10 (40%)	2 (18%)	8 (57%)	
Type 1 — bleeding not actionable	5 (20%)	4 (36%)	1 (7%)	
Type 2	1 (4%)	0	1 (7%)	
Type 3a	6 (24%)	4 (36%)	2 (14%)	
Type 3b	3 (12%)	1 (9%)	2 (14%)	
Type 5	3 (12%)		3 (21%)	
Packed red blood cells during run, median (IQR)	2 (0–8)	3 (1–8)	1 (0–8)	0.501
Central nervous system complications	4 (16%)			
Ischaemic stroke	2 (8%)		2 (14%)	
Cerebral bleeding	2 (8%)		2 (14%)	
Spinal cord infarction	1 (4%)	1 (9%)		

BARC = Bleeding Academic Research Consortium; IQR = interquartile range. * Mehran et al.[10]

Table 4. Regression analysis of predictors of survival

		95% CI		
Variable	**Odds ratio**	**Lower**	**Upper**	*P*
Male gender	5.47	0.190	158.200	0.316
Age (years)	1.05	0.960	1.140	0.297
Arrest location	0.64	0.021	19.687	0.800
Shockable rhythm (VT/VF)	1.03	0.102	10.430	0.980
Arrest to ECMO flow time (min)	0.91	0.822	1.015	0.094
First lactate at cannulation	1.047	0.750	1.462	0.787

ECMO = extracorporeal membrane oxygenation; VF = ventricular fibrillation; VT = ventricular tachycardia.

The components of the ECPR inclusion criteria (ie, witnessed arrests, shockable rhythm, bystander CPR, and young age) inherently select a more favourable cardiac arrest cohort, and the overall survival rate of patients with these variables in OHCA treated with CCPR is reported in up to 28% of patients.[29-35] However, even in the presence of these variables, survival rapidly declines with prolonged resuscitation efforts — survival has been reported at about 2% after 15 minutes of CCPR for OHCA[34] and at 8% at 30 minutes after IHCA.[22] Not all studies of refractory cardiac arrests treated with CCPR have shown such poor outcomes. A recent OHCA study reported survival rates of 20% in patients with a median time to return of spontaneous circulation of 27 minutes (IQR, 20–41 min).[36] In our experience, few patients (in particular OHCA patients) can be established on extracorporeal support within 40 minutes, and it is likely that patients with very prolonged cardiac arrests would have poor outcomes.[37]

Seven patients with an initial PEA rhythm were included in our study, of whom four survived. They were all IHCA patients and may have been subject to selection bias by clinicians. There is a potential substantial variability in PEA survival, depending on prognostic factors not uniformly collected or reported in this and other cardiac arrest studies. For example, transient signs of life, brief periods of return of spontaneous circulation, and end-tidal carbon dioxide are likely to predict better outcomes.[14] It is possible that the identification and validation of these and other prognostic markers may refine patient selection, regardless of the initial rhythm. Furthermore, identification of these factors may allow for broader inclusion criteria for OHCA patients (eg, PEA arrests) without compromising clinical outcomes. Larger, more detailed, multicentre cohort and randomised controlled studies are required to inform clinicians.

Our data support the importance of arrest to ECMO flow and therefore suggest that low-flow duration as an independent predictor of outcomes in patients with cardiac arrest, when reviewed independently from lactate, a confounding variable. Longer low-flow duration is likely to be a major contributing factor to the

lower rate of survival in our OHCA patients compared with IHCA. Although the overall survival rates between our IHCA and OHCA patients were not statistically significant, this is most likely due the small sample size and a type 2 error. IHCA patients are more likely to have shorter arrest to CPR times, better quality CPR, and shorter time to mechanical CPR and commencement of ECMO support. The importance of low-flow on outcomes has been confirmed elsewhere.[38] Minimising delays from arrest to commencement of extracorporeal support is crucial.

We did not find a significant difference in the initial lactate level between survivors and non-survivors, although this has been demonstrated in other ECPR studies[39,40] Lactate level is used as an exclusion criterion for ECPR in some centres,[19] although there are limited data to support an upper threshold limit above which ECPR is not instituted. It is possible that the timing of lactate was different in our study, as timing of arterial blood gas sampling is often only possible after establishment of ECMO.

The duration of ECMO support was short in both survivors and non-survivors and is consistent with contemporary studies.[5] Despite the short duration of ECMO support, vascular and bleeding complications were common. Vascular complications are associated with worse outcomes[41] and continued training and technological advances are required to minimise these complications. Forty per cent of patients in our study had a major bleeding event, with three deaths occurring as a direct result (one with gastrointestinal haemorrhage and two with intracranial haemorrhage). The cause of intracranial bleeding seen after arrest on ECMO is yet to be elucidated. Anticoagulation management on ECMO and after ECPR has yet to be standardised and it should be subject to rigorous randomised controlled studies. Rapid reduction of carbon dioxide, often seen after establishment of ECMO, has been associated with worse outcomes[42] but is unlikely to be the sole factor. Severe coagulopathy and initiation under time pressure while CPR is ongoing is likely to contribute and serves to show the difficulty and complexity of these patients. Continual training and research are required in this area.

Other centres have reported increased organ donor rates with the application of an ECPR program.[43] In our study, two non-survivors became organ donors. Given the small denominator, limited conclusions can be made regarding the likely impact that the wider application of ECPR would have on organ donation rates.

Between two ECMO centres, only 25 eligible patients were enrolled over 2.5 years. There are several reasons for this slow recruitment. Firstly, only a small fraction of cardiac arrests are likely to qualify for ECPR. Reynolds and colleagues[44] found as few as 4% of refractory (> 20 min) OHCA cases would meet ECPR criteria. Secondly, only six MCPR devices were available for use in OHCA patients, which was likely to have restricted recruitment. Although MCPR has not been shown to improve survival compared with CCPR, it provides effective CPR, with less risk to ambulance personnel during rapid patient transfer.[45] Ongoing training of ambulance personnel is required to facilitate appropriate recognition and expedited management of potential ECPR patients. System level changes to improve all parts of the cardiac arrest survival chain are required for an optimal cardiac arrest program that includes ECPR.

Finally, the provision of ECPR was mostly limited to normal working hours due to the availability of appropriately trained staff.

Limitations

Our study is limited by small sample size and absence of a control arm. CPC at discharge is a relative insensitive assessment of neurological function, and longer term quality of life and functional studies are required. However, CPC at discharge is a commonly used metric in cardiac arrest studies. Alternate prognostic variables, such as signs of life during arrest, were not captured. The limitation of the provision of ECPR to normal working hours limited recruitment and generalisability to 24-hour services.

Conclusion

In our prospective study of ECPR for refractory cardiac arrest, we found encouraging survival rates for both IHCA and OHCA, and that duration of arrest was predictive of outcome. Further well designed, large multicentre prospective cohort studies and randomised control trials are required to test efficacy over CCPR, refine patient inclusion criteria and confirm prognostic markers, and should be a priority moving forward. Two randomised controlled trials — INCEPTION (Early Initiation of Extracorporeal Life Support in Refractory OHCA) (ClinicalTrials.gov identifier: NCT03101787) and EROCA (ECPR for Refractory OHCA) (ClinicalTrials.gov identifier: NCT03065647) — are currently recruiting and may provide some answers to these questions.

Acknowledgements: The following collaborators of the Sydney ECMO Research Interest Group have been integral to the completion of this study: Suhel Al Soufi, Damien Boyd, Jeff Breeding, Mark Daley, Michael Dinh, Kumud Dhital, Carmen Frost, Nicky Gleinster, Mani Gopal, Anthony Grabs, Christopher Hayward, Debra J Hutch, Andrew Jackson, Paul Jansz, Heike Koelzow, Eugene Kotlyar, Mark Lucey, Peter MacDonald, Kevin Maruno, Matthew Morgan, Mark Nicholls, Michael O'Leary, Matthew Oliver, Paul Phipps, Roger Pye, Nayyera N Rashid, Claire Richmond, Sam Rudham, Desiree Robson, David Roy, Máté Rudas, Claudio Soto, Timothy Southwood, Sanjay Tarvade, Richard J Totaro, Phillip Spratt, Susan Whittam, Clive Woolfe, Lap-Wah James Wun. All authors take responsibility for

all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Competing interests

Getinge (Germany) provided the ECMO disposables and Stryker (Australia) provided the LUCAS 2 devices used in this study. No other support was provided and vendors had no influence on study design, data collection or manuscript preparation.

Author details

Mark Dennis[1,2]
Hergen Buscher[3,4,5]
David Gattas[1,6]
Brian Burns[1,7]
Karel Habig[7]
Paul Bannon[1,8,9]
Sanjay Patel[1,2]
Heidi Buhr[6]
Claire Reynolds[3]
Sean Scott[3,4]
Priya Nair[3,4,5]
Jon Hayman[1,10]
Emily Granger[11]
Ryan Lovett[12]
Paul Forrest[1,13]
Jennifer Coles[6]
David A Lowe[3,4]
on behalf of the Sydney ECMO Research Interest Group*

1 Sydney Medical School, University of Sydney, Sydney, NSW, Australia.
2 Department of Cardiology, Royal Prince Alfred Hospital, Sydney, NSW, Australia.
3 Department of Intensive Care, St Vincent's Hospital, Sydney, NSW, Australia.
4 Centre of Applied Medical Research, St Vincent's Hospital Sydney, NSW, Australia.
5 University of New South Wales, Sydney, NSW, Australia.
6 Intensive Care Service, Royal Prince Alfred Hospital, Sydney, NSW, Australia.
7 Greater Sydney Area Helicopter Emergency Medical Service, New South Wales Ambulance Service, Sydney, NSW, Australia.
8 Institute of Academic Surgery, Royal Prince Alfred Hospital, Sydney, NSW, Australia.
9 Department of Cardiothoracic Surgery, Royal Prince Alfred Hospital, Sydney, NSW, Australia.
10 Department of Emergency Medicine, Royal Prince Alfred Hospital, Sydney, NSW, Australia.
11 Department of Cardiothoracic Surgery St Vincent's Hospital, Sydney, NSW, Australia.
12 New South Wales Ambulance Service, Sydney, NSW, Australia.
13 Department of Anaesthetics, Royal Prince Alfred Hospital, Sydney, NSW, Australia.

***Correspondence*:** mark.dennis@sydney.edu.au

* The full list of collaborating authors of the Sydney ECMO Research Interest Group is provided in the online Appendix.

References

1 Nagao K, Nonogi H, Yonemoto N, et al. Duration of prehospital resuscitation efforts after out-of-hospital cardiac arrest. *Circulation* 2016; 133: 1386-96.
2 Goldberger ZD, Chan PS, Berg RA, et al. Duration of resuscitation efforts and survival after in-hospital cardiac arrest: an observational study. *Lancet* 2012; 380: 1473.
3 Shin TG, Choi JH, Jo IJ, et al. Extracorporeal cardiopulmonary resuscitation in patients with inhospital cardiac arrest: a comparison with conventional cardiopulmonary resuscitation. *Crit Care Med* 2011; 39: 1-7.
4 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.
5 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.
6 Australian Resuscitation Council, New Zealand Resuscitation Council. Cardiopulmonary resuscitation for advanced life support providers. ARC and NZRC guideline 2010. *Emerg Med Australas* 2011; 23: 264-70.
7 Australian Resuscitation Council, New Zealand Resuscitation Council. Basic life support: cardiopulmonary resuscitation. ARC and NZRC guideline 2010. *Emerg Med Australas* 2011; 23: 259-60.
8 Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. *N Engl J Med* 2013; 369: 2197-206.
9 A randomized clinical trial of calcium entry blocker administration to comatose survivors of cardiac arrest. Design, methods, and patient characteristics. The Brain Resuscitation Clinical Trial II Study Group. *Control Clin Trials* 1991; 12: 525-45.
10 Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation* 2011; 123: 2736-47.
11 Hutin A, Abu-Habsa M, Burns B, et al. Early ECPR for out-of-hospital cardiac arrest: best practice in 2018. *Resuscitation* 2018; 130: 44-8.
12 Dennis M, McCanny P, D'Souza M, et al. Extracorporeal cardiopulmonary resuscitation for refractory cardiac arrest: a multicentre experience. *Int J Cardiol* 2017; 231: 131-6.
13 Bernard SA, Smith K, Finn J, et al. Induction of therapeutic hypothermia during out-of-hospital cardiac arrest using a rapid infusion of cold saline: the RINSE trial (Rapid Infusion of Cold Normal Saline). *Circulation* 2016; 134: 797-805.
14 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.

15 Pozzi M, Koffel C, Armoiry X, et al. Extracorporeal life support for refractory out-of-hospital cardiac arrest: should we still fight for? A single-centre, 5-year experience. *Int J Cardiol* 2016; 204: 70-6.

16 Fagnoul D, Taccone FS, Belhaj A, et al. Extracorporeal life support associated with hypothermia and normoxemia in refractory cardiac arrest. *Resuscitation* 2013; 84: 1519-24.

17 Richardson AS, Schmidt M, Bailey M, et al. ECMO cardio-pulmonary resuscitation (ECPR), trends in survival from an international multicentre cohort study over 12-years. *Resuscitation* 2017; 112: 34-40.

18 Patricio D, Peluso L, Brasseur A, et al. Comparison of extracorporeal and conventional cardiopulmonary resuscitation: a retrospective propensity score matched study. *Crit Care* 2019; 23: 27.

19 Bartos JA, Carlson K, Carlson C, et al. Surviving refractory out-of-hospital ventricular fibrillation cardiac arrest: Critical care and extracorporeal membrane oxygenation management. *Resuscitation* 2018; 132: 47-55.

20 Girotra S, Chan PS. Trends in survival after in-hospital cardiac arrest. *N Engl J Med* 2013; 368: 680-1.

21 Bradley SM, Kaboli P, Kamphuis LA, et al. Temporal trends and hospital-level variation of inhospital cardiac arrest incidence and outcomes in the Veterans Health Administration. *Am Heart J* 2017; 193: 117-23.

22 Goldberger ZD, Chan PS, Berg RA, et al. Duration of resuscitation efforts and survival after in-hospital cardiac arrest: an observational study. *Lancet* 2012; 380: 1473-81.

23 Fennessy G, Hilton A, Radford S, et al. The epidemiology of in-hospital cardiac arrests in Australia and New Zealand. *Intern Med J* 2016; 46: 1172-81.

24 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.

25 Wong MK, Morrison LJ, Qiu F, et al. Trends in short- and long-term survival among out-of-hospital cardiac arrest patients alive at hospital arrival. *Circulation* 2014; 130: 1883-90.

26 Holmberg MJ, Geri G, Wiberg S, et al. Extracorporeal cardiopulmonary resuscitation for cardiac arrest: a systematic review. *Resuscitation* 2018; 131: 91-100.

27 Beyea MM, Tillmann BW, Iansavichene AE, et al. Neurologic outcomes after extracorporeal membrane oxygenation assisted CPR for resuscitation of out-of-hospital cardiac arrest patients: a systematic review. *Resuscitation* 2018; 130: 146-58.

28 Twohig CJ, Singer B, Grier G, Finney SJ. A systematic literature review and meta-analysis of the effectiveness of extracorporeal-CPR versus conventional-CPR for adult patients in cardiac arrest. *J Intensive Care Soc* 2019; 20: 347-57.

29 Rea TD, Eisenberg MS, Becker LJ, et al. Temporal trends in sudden cardiac arrest: a 25-year emergency medical services perspective. *Circulation* 2003; 107: 2780-5.

30 van Diepen S, Girotra S, Abella BS, et al. Multistate 5-year initiative to improve care for out-of-hospital cardiac arrest: primary results from the HeartRescue project. *J Am Heart Assoc* 2017; 6: e005716.

31 Daya MR, Schmicker RH, Zive DM, et al. Out-of-hospital cardiac arrest survival improving over time: results from the Resuscitation Outcomes Consortium (ROC). *Resuscitation* 2015; 91: 108-15.

32 Kitamura T, Kiyohara K, Sakai T, et al. Public-access defibrillation and out-of-hospital cardiac arrest in Japan. *N Engl J Med* 2016; 375: 1649-59.

33 Rajan S, Folke F, Hansen SM, et al. Incidence and survival outcome according to heart rhythm during resuscitation attempt in out-of-hospital cardiac arrest patients with presumed cardiac etiology. *Resuscitation* 2017; 114: 157-63.

34 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: 2488-94.

35 Wang HE, Prince DK, Drennan IR, et al. Post-resuscitation arterial oxygen and carbon dioxide and outcomes after out-of-hospital cardiac arrest. *Resuscitation* 2017; 120: 113-8.

36 Gregers E, Kjaergaard J, Lippert F, et al. Refractory out-of-hospital cardiac arrest with ongoing cardiopulmonary resuscitation at hospital arrival — survival and neurological outcome without extracorporeal cardiopulmonary resuscitation. *Crit Care* 2018; 22: 242.

37 Rajan S, Folke F, Kragholm K, et al. Prolonged cardiopulmonary resuscitation and outcomes after out-of-hospital cardiac arrest. *Resuscitation* 2016; 105: 45-51.

38 Wengenmayer T, Rombach S, Ramshorn F, et al. Influence of low-flow time on survival after extracorporeal cardiopulmonary resuscitation (eCPR). *Crit Care* 2017; 21: 157.

39 Mizutani T, Umemoto N, Taniguchi T, et al. The lactate clearance calculated using serum lactate level 6 h after is an important prognostic predictor after extracorporeal cardiopulmonary resuscitation: a single-center retrospective observational study. *J Intensive Care* 2018; 6: 33.

40 D'Arrigo S, Cacciola S, Dennis M, et al. Predictors of favourable outcome after in-hospital cardiac arrest treated with extracorporeal cardiopulmonary resuscitation: a systematic review and meta-analysis. *Resuscitation* 2017; 121: 62-70.

41 Tanaka D, Hirose H, Cavarocchi N, Entwistle JW. The impact of vascular complications on survival of patients on venoarterial extracorporeal membrane oxygenation. *Ann Thorac Surg* 2016; 101: 1729-34.

42 Bembea MM, Lee R, Masten D, et al. Magnitude of arterial carbon dioxide change at initiation of extracorporeal membrane oxygenation support is associated with survival. *J Extra Corpor Technol* 2013; 45: 26-32.

43 Magliocca JF, Magee JC, Rowe SA, et al. Extracorporeal support for organ donation after cardiac death effectively expands the donor pool. *J Trauma* 2005; 58: 1095-101; discussion 1101-2.

44 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.

45 Wang PL, Brooks SC. Mechanical versus manual chest compressions for cardiac arrest. *Cochrane Database Syst Rev* 2018; (8): CD007260.