Extracorporeal Cardiopulmonary Resuscitation for Patients With Out-of-Hospital Cardiac Arrest of Cardiac Origin: A Propensity-Matched Study and Predictor Analysis*

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Objective: Encouraging results of extracorporeal cardiopulmonary resuscitation for patients with refractory cardiac arrest have been shown. However, the independent impact on the neurologic outcome remains unknown in the out-of-hospital population. Our objective was to compare the neurologic outcome following extracorporeal cardiopulmonary resuscitation and conventional cardiopulmonary resuscitation and determine potential predictors that can identify candidates for extracorporeal cardiopulmonary resuscitation among patients with out-of-hospital cardiac arrest of cardiac origin.

Design: Post hoc analysis of data from a prospective observational cohort.

Setting: A tertiary care university hospital in Sapporo, Japan (January 2000 to September 2004).

Patients: A total of 162 adult patients with witnessed cardiac arrest of cardiac origin who had undergone cardiopulmonary resuscitation for longer than 20 minutes (53 in the extracorporeal cardiopulmonary resuscitation group and 109 in the conventional cardiopulmonary resuscitation group).

Interventions: None.

Measurements and Main Results: The primary endpoint was neurologically intact survival at three months after cardiac arrest. We used propensity score matching to reduce selection bias and balance the baseline characteristics and clinical variables that could potentially affect outcome. This matching process selected 24 patients from each group. The impact of extracorporeal cardiopulmonary resuscitation was estimated in matched patients. Intact survival rate was higher in the matched extracorporeal cardiopulmonary resuscitation group than in the matched conventional cardiopulmonary resuscitation group (29.2% [7/24] vs. 8.3% [2/24], log-rank $p = 0.018$). According to the predictor analysis, only pupil diameter on hospital arrival was associated with neurologic outcome (adjusted hazard ratio, 1.39 per 1-mm increase; 95% confidence interval, 1.09–1.78; $p = 0.008$).

Conclusions: Extracorporeal cardiopulmonary resuscitation can improve neurologic outcome after out-of-hospital cardiac arrest of cardiac origin; furthermore, pupil diameter on hospital arrival may be a key predictor to identify extracorporeal cardiopulmonary resuscitation candidates. (*Crit Care Med* 2013; 41:1186–1196)

Key Words: cardiopulmonary arrest; cardiopulmonary bypass; cardiopulmonary resuscitation; extracorporeal circulation; extracorporeal membrane oxygenation; out-of-hospital cardiac arrest

Cardiac arrest patients can only tolerate a short period of absence of circulation and the chances of survival decline rapidly if cardiopulmonary resuscitation (CPR) duration lasts longer than 15–30 minutes (1, 2). Chest compression generates, at best, 25% of normal cardiac output; this limited blood flow decreases as CPR duration is prolonged (3).

It was suggested in 1966 as a principle that extracorporeal cardiopulmonary resuscitation (ECPR) using extracorporeal membrane oxygenation (ECMO) can restore blood flow in patients with prolonged cardiac arrest (4, 5). Recent advances in technology have enabled such treatment to be applied rapidly (6), and several studies have shown encouraging results for the resuscitation of patients with refractory cardiac arrest (7–9).

ECPR has been assigned a Class 2b recommendation in recent guidelines for reversible cardiac arrest (10, 11). The only evidence in the out-of-hospital population was derived from our nonrandomized observational study (12), which

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contained unbalanced possible confounders such as age, location of arrest, witness status, bystander CPR, initial cardiac rhythm, and cardiac arrest time and CPR duration.

Many cases with a favorable outcome after ECPR were reported in Japanese journals, and ECPR has already been a standard of care in Japan (13). Nonetheless, the reliability of predictors that can identify ECPR candidates remains unknown.

Our objective was to estimate survival with good neurologic outcome following ECPR and conventional cardiopulmonary resuscitation (CCPR) and compare for differences between well-balanced groups, based on a propensity score matching method. In addition, we investigated potential clinical variables that could predict the neurologic outcome of ECPR patients; these variables were obtained before patients underwent ECPR.

MATERIALS AND METHODS

We performed post hoc analysis of the previously published, prospective observational study (12). The present study received approval from our institutional review board. Informed consent was waived because of the life-threatening emergency situation and the absence of any therapeutic alternative. Information was delivered to the patient's relatives after inclusion as appropriate in a life-threatening context.

Setting

The study was undertaken at Sapporo Medical University Hospital, a tertiary care center approved by the Ministry of Health, Labour and Welfare and located in the city of Sapporo, which covers 1121 km^2 with a population of approximately 1.9 million. The city is served by a single emergency ambulance service provided under government contract by the Sapporo Fire Bureau (SFB). All calls for ambulances throughout Sapporo are received centrally by the ambulance command center. On receipt of a call by the command center, emergency medical services personnel request mobilization of a physician-staffed ambulance from Sapporo City General Hospital according to the regional protocol. All ambulances are staffed by three paramedics, including at least one emergency life-saving technician whose scope of clinical care is governed by specific SFB clinical practice guidelines. During the study period, defibrillation with automated external defibrillators, securing of the airway with a laryngeal mask airway or esophageal obturator airway, and establishment of venous access by emergency life-saving technicians were permitted. However, drug administration by emergency life-saving technicians and automated external defibrillator use by citizens was not legally permitted in everyday situations. In the present study, approximately 60% of cases were transported by a physician-staffed ambulance, and all cases were treated by emergency physicians according to Advanced Cardiac Life Support guidelines in the emergency department and only cases successfully resuscitated were admitted to the hospital ward.

Patients

We included all consecutive patients with out-of-hospital cardiac arrest of presumed cardiac origin, aged 16 years or older, who were referred to our hospital between January 1, 2000 and September 30, 2004.

As compared with our previous study, we restricted this analysis to patients who had received CPR for longer than 20 minutes after witnessed arrest of presumed cardiac origin.

Cardiac arrest was presumed to be of cardiac origin unless it was known or likely to have been caused by trauma, submersion, hypothermia, drug overdose, asphyxia, exsanguination, or any other noncardiac cause including intracranial hemorrhage, acute aortic dissection, and terminal malignancy as evident by the case record.

We excluded patients who had previously signed "do-not-resuscitate" orders and who were pronounced dead before hospital arrival.

The patients were divided into an ECPR group and a CCPR group on the basis of treatment received.

ECMO Management and Postresuscitation Care

The decision to initiate ECPR was dependent on the attending physicians. ECMO was implanted by the ECPR team, which comprised well-trained emergency physicians and clinical engineers. However, the ECPR team was not available at all times because all physicians were not equally prepared to implant ECMO.

In general, ECPR was initiated if the return of spontaneous circulation did not occur or could not be maintained during transportation, if the patient was assessed to have good activities of daily life before cardiac arrest by interview of the patient's relatives, and if the cardiac arrest was clinically presumed as cardiac in origin by the patient's information reported by paramedics and rapid echocardiographic examination. Emergency physicians tended to initiate ECPR in nonelderly patients with refractory ventricular fibrillation under standard CPR, based on experience. We usually established a percutaneous cannulation in the femoral vein and artery. Femoral cut down procedures were not performed for any of the patients in our study. Chest compression was continued until the start of ECMO.

All aspects of postresuscitation care after the start of ECMO (the ECPR group) or return of spontaneous circulation without ECMO (the CCPR group) were at the discretion of the attending physicians. Postresuscitation care included adequate oxygenation, vasopressors, and fluids administered to maintain systolic arterial pressure at 90 mm Hg, therapeutic hypothermia (target body temperature, 34°C; duration, 2–3 days), and cardiac catheterization and revascularization when indicated. Anticoagulation was essentially accomplished in the ECPR group through a bolus injection of unfractionated heparin, followed by continuous intravenous infusion; meanwhile, in the CCPR group, anticoagulation was accomplished only after cardiac revascularization and implantation of intra-aortic balloon pumping.

The principal component of the ECMO circuit was a heparin-bonded surface circuit, including a centrifugal pump and hollow-fiber oxygenator (Capiox; Terumo Corp., Tokyo, Japan).

The circuit was preorganized and primed with approximately 590 mL of saline. The ECMO circuit was connected to a heat exchanger to induce hypothermia. However, normothermia was maintained in hemodynamically unstable patients failing to maintain systolic arterial pressure at 90 mm Hg with the maximum dose of vasopressors (20 μg/kg/min for dopamine or 0.2 μg/kg/min for norepinephrine). Cannulae of sizes 15–17 F were used for the femoral artery, whereas those of sizes 19–21 F were used for the femoral vein. To avoid limb ischemia, an anterograde reperfusion catheter for distal limb perfusion was inserted as necessary. The flow rate was initially set at 50 to 60 mL/min/kg. Transthoracic echocardiography was frequently performed by cardiologists to monitor left ventricular function and potential intraventricular thrombus formation. Weaning of ECMO was considered when the patient was hemodynamically stable and adequately oxygenated with the ECMO flow of 1,500 mL/min, and/or when the left ventricular ejection time examined using echocardiography surpassed 200 ms. Withdrawal of ECMO was considered when there was irreversible multiple organ failure or severe neurologic damage equivalent to brain death, but only after obtaining consent from the patient's relatives.

Data Collection

We collected data on patient demographics and prehospital variables from the registry of the SFB and data on in-hospital variables from the medical registry of our department. The registry of the SFB contained Utstein-style information (14) for all out-of-hospital cardiac arrests in Sapporo, collected by paramedics in charge of each patient. The medical registry of our department contained summaries of subsequent interventions after admission and hospital courses, collected by attending physicians. Data collection points were standardized and subject to quality control. Paramedics of SFB and attending physicians of our department were not aware of this study at the time of data collection and data entry.

Cardiac arrest time was defined as the interval from arrest to basic life support. CPR duration was defined as the interval from start to finish of chest compression (7).

Outcome Measures

The primary endpoint was a favorable neurologic status at three months after cardiac arrest, defined as a Cerebral Performance Categories (CPC) score of 1 or 2 (15). We assessed neurologic outcome with telephone and mail survey to the patient's general practitioner. Answers to questions given during the telephone interview or on the written questionnaire were used to determine CPC scores.

Analysis

The propensity score matching method was used to reduce the effects of selection bias and possible confounding factors and to simulate a randomized trial (8, 9, 16). The propensity score was derived using a nonparsimonious logistic regression model (8). All baseline prehospital characteristics that varied between the ECPR and CCPR groups at a p value less than 0.10, and which were potentially related to outcome, were included in the propensity score model. Because the objective of this study was to evaluate the independent therapeutic impact of ECPR, proven interventions, including therapeutic hypothermia (17, 18) and primary percutaneous coronary intervention (PCI) (19, 20), were added to the model. Model discrimination was assessed with c statistics. Each patient was assigned a propensity score that reflected the probability of receiving ECPR. Using a caliper and a radius matching algorithm (maximum caliper of 0.03), ECPR and CCPR cases were matched by their propensity score in blocks of 1:1, 2:2, 3:3, or 4:4 (8). The selected patients formed well-matched 1:1 pairs in both groups.

Continuous variables were expressed as medians with interquartile ranges. Continuous variables were compared using Student t test. Categorical variables were compared with the chi-square test or Fisher's exact test. Primary endpoints were compared between the matched ECPR and matched CCPR groups by the log-rank test. Survival time was defined as the duration from CPR to death in cases that did not survive, and as the duration from CPR to recovery at three months after cardiac arrest in cases that survived. Median survival time was defined as the time point at which the Kaplan-Meier survival curves crossed 50%. The Cox regression model was used to generate the hazard ratios (HRs), which were reported along with 95% confidence intervals (CI) and p values. Variables with a p value less than 0.10 by Cox regression univariate analysis were considered as candidates for multivariate analysis. Independent predictors for favorable neurologic outcome were identified as those with a p value less than 0.05 by Cox regression multivariate analysis. Receiver operating characteristic (ROC) curve analysis was used to assess the discriminative power of predictive factors and identify the optimum value of a continuous variable to differentiate between favorable and unfavorable neurologic outcomes.

All analyses were carried out using StatView 5.0 (SAS Institute Inc., Cary, NC) and SPSS version 19.0 (SPSS, Chicago, IL). All reported p values were two-tailed, and values less than 0.05 were considered statistically significant.

RESULTS

Patient Characteristics

A total of 398 patients with out-of-hospital cardiac arrest of presumed cardiac origin were registered during the study period; of these, 53 were enrolled in the ECPR group and 109 were enrolled in the CCPR group according to the selection criteria (**Fig. 1**). ECMO implantation was successful in 98.1% of cases (52/53) in the ECPR group, except for one case of cannulation failure. This patient was analyzed within the ECPR group. No patient in the CCPR group received ECMO later in the course of their hospitalization. All patients either completed follow up or died at three months after cardiac arrest, which was considered the study endpoint.

Baseline characteristics and prehospital variables of both groups are shown in **Table 1** along with the subsequent interventions.

Patients in the ECPR group were significantly younger than those in the CCPR group, more likely to have satisfactory

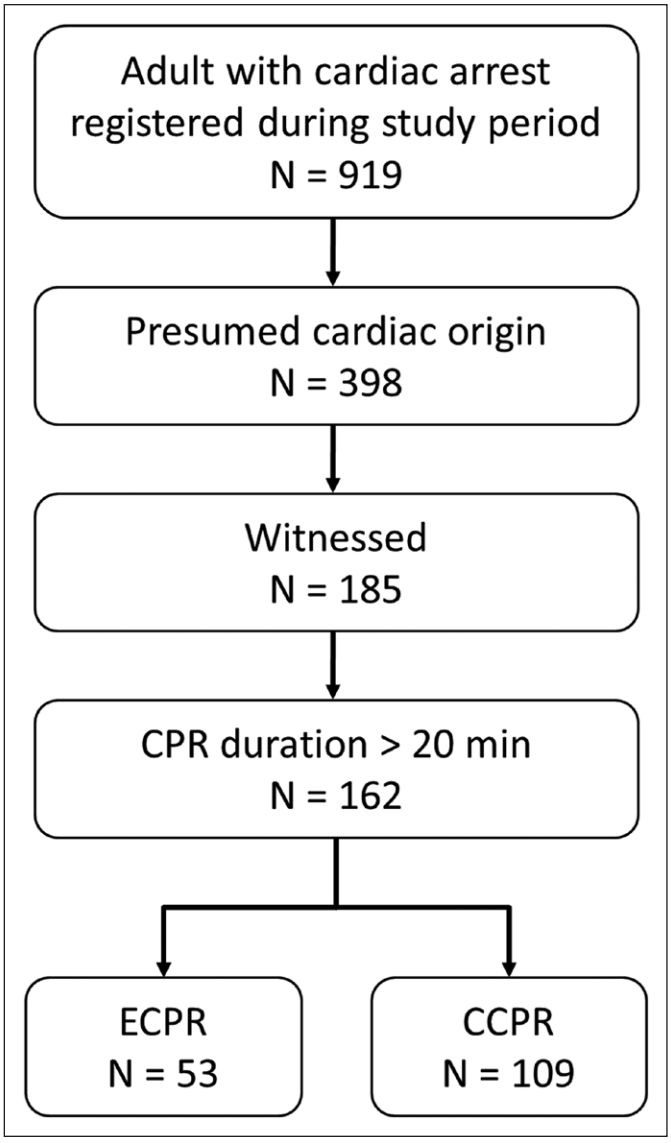

Figure 1. Study subject enrollment. Adult patients (≥ 16 yrs) who suffered witnessed arrest and cardiopulmonary resuscitation (CPR) duration (defined as the interval from beginning to termination of chest compression) for > 20 min were recruited in this cohort. ECPR = extracorporeal CPR; CCPR = conventional CPR.

activities of daily living before cardiac arrest, have been administered CPR by a bystander, have initially presented with shockable rhythm (ventricular fibrillation or ventricular tachycardia), and have received further countershocks during transportation. Time interval from arrest to advanced life support and CPR duration were both significantly shorter in the ECPR group than in the CCPR group; however, time interval from arrest to hospital arrival was similar between both groups.

Because patients successfully resuscitated with ECMO became possible candidates for receiving definitive treatments without return of spontaneous circulation, the rates of subsequent interventions, including therapeutic hypothermia and primary PCI, were significantly higher in the ECPR group than in the CCPR group.

Propensity Score-Matched Groups and Outcome Analysis

The c statistic for the propensity score model was 0.88. The propensity score matching process selected 24 patients from each group for further analysis (the matched ECPR group and the matched CCPR group). The matched ECPR group included one unsuccessful ECMO case. Covariate balance was improved after propensity score matching; however, time interval from arrest to first defibrillation was longer in the matched ECPR group than in the matched CCPR group. Median propensity score was 0.47 (range, 0.22–0.69) in the matched ECPR group and 0.47 (0.23–0.67) in the matched CCPR group ($p = 0.99$) (**Table 2**).

A favorable outcome was observed in seven patients (29.2%) in the matched ECPR group and two patients (8.3%) in the matched CCPR group. The absolute difference of 20.9% (95% CI, −1.2 to 32.6) translated into a number needed to treat of 4.8 to achieve one favorable outcome. Survival analysis with Kaplan-Meier plot showed a better neurologic outcome in the matched ECPR group at the end of three months (log-rank $p = 0.018$; **Fig. 2**); meanwhile, estimated median survival time did not differ between the matched ECPR group (1 day, 95% CI, 0–2) and the matched CCPR group (0 day, 95% CI, 0–0).

Independent Predictors Associated With a Favorable Outcome of ECPR

Of the 53 patients in the ECPR group, 52 with successful ECMO implantation were included in the predictor analyses. Favorable neurologic outcomes were achieved in eight patients (15.4%), whereas unfavorable neurologic outcomes were achieved in 44 patients (84.6%). Baseline characteristics, prehospital variables, clinical variables on hospital arrival, and complications related to ECPR were shown in **Table 3** along with the subsequent interventions.

In univariate analysis, the following pre-ECPR variables were associated with unfavorable neurologic outcome: preexisting arrhythmia including treated and untreated ones (HR, 0.33), atropine administration (HR, 1.55 per 1-mg increase), CPR duration (HR, 1.18 per 10-min increase), pupil diameter on hospital arrival (HR, 1.56 per 1-mm increase), shockable rhythm on hospital arrival (HR, 0.39), spontaneous breathing on hospital arrival (HR, 0.28), and serum lactate levels (HR, 1.05 per 1-mmol/L increase; **Table 4**). In multivariate analysis, pupil diameter emerged as the most powerful independent predictor of neurologic outcome (adjusted HR, 1.39 per 1-mm increase; 95% CI, 1.09–1.78; Table 4).

ROC analysis showed that the area under the curve was 0.87 (95% CI, 0.75–0.98); it identified a pupil diameter of <6 mm as the optimal cut-off point, with a sensitivity and specificity of 100% and 59%, respectively, and positive and negative predictive values of 31% and 100%, respectively, for predicting favorable outcomes (**Table 5**).

DISCUSSION

In the present study of patients with out-of-hospital cardiac arrest, we observed that ECPR was associated with a 20.9%

TABLE 1. Baseline and Clinical Characteristics and Outcomes of the Extracorporeal Cardiopulmonary Resuscitation Group and the Conventional Cardiopulmonary Resuscitation Group (Unmatched)

	Overall (*n* = 162)	ECPR (*n* = 53)	CCPR (*n* = 109)	*P*
Propensity score	0.18 (0.03–0.58)	0.64 (0.45–0.90)	0.08 (0.02–0.24)	<0.0001
Baseline characteristics				
Age, yr	64 (54–74)	54 (47–60)	71 (59–80)	<0.0001
Gender; male, *n* (%)	123 (75.9)	44 (83.0)	79 (72.5)	0.14
Activities of daily living, *n* (%)				
No disability	133 (82.1)	49 (92.5)	84 (77.1)	0.097
Mild disability	9 (5.6)	2 (3.8)	7 (6.4)	
Severe disability	3 (1.9)	0 (0)	3 (2.8)	
Unknown	17 (10.4)	2 (3.8)	15 (13.8)	
Pre-hospital variables				
Location of arrest, *n* (%)				
Home	69 (42.6)	20 (37.7)	49 (45.0)	0.58
Public place	87 (53.7)	31 (58.5)	56 (51.4)	
Other	6 (3.7)	2 (3.8)	4 (3.7)	
CPR by witness, *n* (%)	71 (43.8)	29 (54.7)	42 (38.5)	0.051
Initial rhythm; ventricular fibrillation/ventricular tachycardia, *n* (%)	56 (34.6)	32 (60.4)	24 (22.0)	<0.0001
Countershock, number	0 (0–3)	2 (1–5)	0 (0–1)	<0.0001
Definitive airway insertion, *n* (%)	143 (88.3)	45 (84.9)	98 (89.9)	0.35
Venous access, *n* (%)	121 (74.7)	43 (81.1)	78 (71.6)	0.19
Physician-staffed ambulance, *n* (%)	93 (57.4)	34 (64.2)	60 (55.0)	0.27
Return of spontaneous circulation during transportation, *n* (%)	12 (7.4)	2 (3.8)	10 (9.2)	0.34
Time courses				
Arrest to EMS, min	6 (3–10)	6 (2–9)	7 (3–10)	0.44
EMS to hospital, min	26 (19–33)	25 (20–32)	26 (19–34)	0.73
Arrest to hospital, min	33 (25–42)	33 (25–41)	33 (26–43)	0.53
Arrest to basic life support (cardiac arrest time), min	4 (0–9)	2 (0–8)	5 (0–9)	0.13
Arrest to first defibrillation, min	10 (6–16)	10 (7–17)	8 (6–16)	0.40
Arrest to advanced life support, min	23 (17–31)	21 (15–25)	26 (18–32)	0.011
Basic life support to CPR termination (CPR duration), min	52 (43–65)	49 (41–59)	56 (47–66)	0.042
Subsequent interventions				
Therapeutic hypothermia, *n* (%)	33 (20.4)	26 (49.1)	7 (6.4)	<0.0001
Intra-aortic balloon pumping, *n* (%)	37 (22.8)	27 (50.9)	10 (9.2)	<0.0001
Primary percutaneous coronary intervention, *n* (%)	27 (16.7)	21 (39.6)	6 (5.5)	<0.0001
Outcome				
Mortality in the emergency room, *n* (%)	84 (51.9)	2 (3.8)	82 (75.2)	<0.0001
Survival to discharge, *n* (%)	24 (14.8)	17 (32.1)	7 (6.4)	<0.0001
Survival at 3 mo, *n* (%)	20 (12.3)	15 (28.3)	5 (4.6)	<0.0001
Cerebral Performance Category status 1 or 2 at 3 mo, *n* (%)	11 (6.8)	8 (15.1)	3 (2.8)	0.006

CPR = cardiopulmonary resuscitation; ECPR = extracorporeal CPR; CCPR = conventional CPR; EMS = emergency medical service.
Continuous variables were expressed as medians with interquartile ranges.

TABLE 2. Baseline and Clinical Characteristics and Outcomes of the Extracorporeal Cardiopulmonary Resuscitation Group and the Conventional Cardiopulmonary Resuscitation Group (Matched)

	ECPR matched (*n* = 24)	CCPR matched (*n* = 24)	*p*
Propensity score	0.47 (0.22–0.69)	0.47 (0.23–0.67)	0.98
Baseline characteristics			
Age, yr	57 (48–63)	57 (50–68)	0.51
Gender; male *n* (%)	19 (79.2)	19 (79.2)	0.99
Activities of daily living, *n* (%)			
No disability	23 (95.8)	22 (91.7)	0.22
Mild disability	1 (4.2)	0 (0)	
Severe disability	0 (0)	0 (0)	
Unknown	0 (0)	2 (8.3)	
Pre-hospital variables			
Location of arrest, *n* (%)			
Home	9 (37.5)	7 (29.2)	0.83
Public place	14 (58.3)	16 (66.7)	
Other	1 (4.2)	1 (4.2)	
CPR by witness, *n* (%)	13 (54.2)	14 (58.3)	0.77
Initial rhythm; ventricular fibrillation/ventricular tachycardia, *n* (%)	13 (54.2)	14 (58.3)	0.77
Countershock, number	2 (1–8)	1 (0–4)	0.56
Definitive airway insertion, *n* (%)	22 (91.7)	21 (87.5)	0.99
Venous access, *n* (%)	20 (83.3)	18 (75.0)	0.72
Physician-staffed ambulance, *n* (%)	12 (50.0)	13 (54.2)	0.77
Return of spontaneous circulation, *n* (%)	1 (4.2)	3 (12.5)	0.61
Time courses			
Arrest to EMS, min	5 (2–10)	4 (0–8)	0.33
EMS to hospital, min	25 (21–30)	24 (17–31)	0.56
Arrest to hospital, min	31 (25–37)	28 (23–34)	0.31
Arrest to basic life support (cardiac arrest time), min	2 (0–8)	0 (0–5)	0.30
Arrest to first defibrillation, min	11 (7–17)	8 (5–9)	0.035
Arrest to advanced life support, min	23 (14–27)	20 (16–27)	0.99
Basic life support to CPR termination (CPR duration), min	49 (43–66)	52 (43–65)	0.98
Subsequent interventions			
Therapeutic hypothermia, *n* (%)	9 (37.5)	7 (29.2)	0.54
Intra-aortic balloon pumping, *n* (%)	9 (37.5)	7 (29.2)	0.54
Percutaneous coronary intervention, *n* (%)	5 (20.8)	6 (25.0)	0.99
Outcome			
Mortality in the emergency room, *n* (%)	23 (95.8)	9 (37.5)	<0.0001
Survival to discharge, *n* (%)	9 (37.5)	3 (12.5)	0.093
Survival at 3 mo, *n* (%)	9 (37.5)	2 (8.3)	0.036
Cerebral Performance Category status 1 or 2 at 3 mo, *n* (%)	7 (29.2)	2 (8.3)	0.14

CPR = cardiopulmonary resuscitation; ECPR = extracorporeal CPR; CCPR = conventional CPR; EMS = emergency medical service.
Continuous variables were expressed as medians with interquartile ranges.

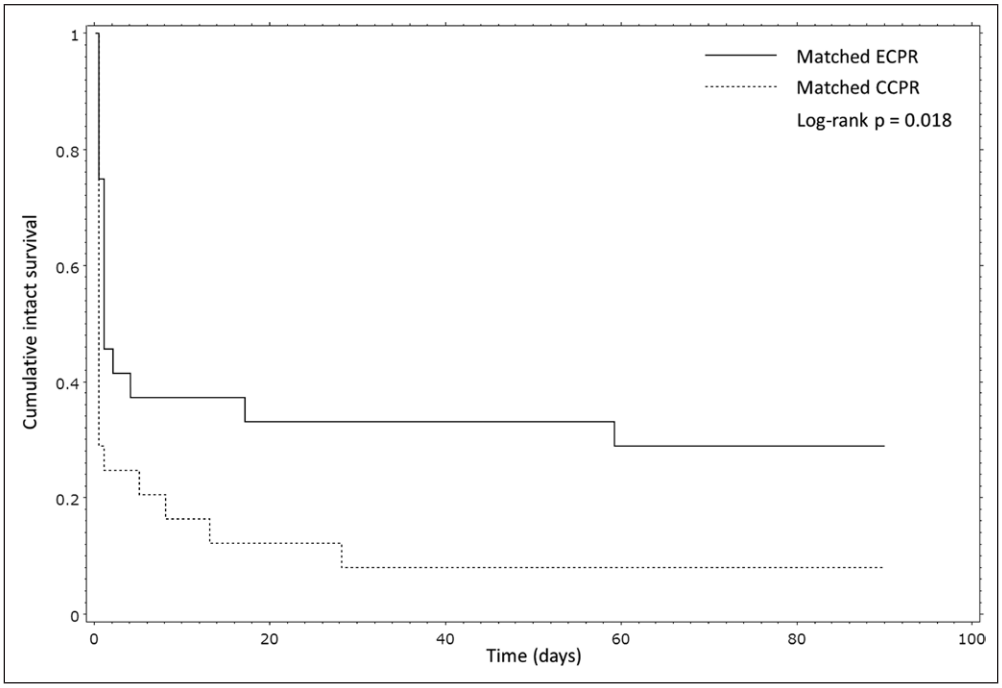

Figure 2. Kaplan-Meier plot of the neurologically intact survival curves in the matched extracorporeal cardiopulmonary resuscitaion (ECPR) group and the matched conventional cardiopulmonary resuscitation (CCPR) group for three months.

absolute reduction of a poor neurologic outcome at three months after cardiac arrest. Given the low intact survival rates among these patients, this suggests that approximately five patients with cardiac arrest similar to those in the matched cohort would need to receive ECPR to achieve a favorable neurologic outcome. As shown in Figure 2, ECPR prevented early mortality, and this mortality gap accounted for the differences of neurologic outcome.

In one observational study, Chen et al reported the use of a propensity score matching method to balance potential confounding factors, and they suggested that ECPR had a survival benefit over CCPR in patients with in-hospital cardiac arrest of cardiac origin and who received CPR for more than 10 minutes (8). The median duration of CPR (49 vs. 53 min) and the rate of survival at discharge (37.5% vs. 32.6%) reported in the present study were consistent with those reported by Chen et al.

Another recent study reported by Shin et al suggested that ECPR improved survival at discharge with minimal neurologic impairment in patients with in-hospital cardiac arrest (9). They performed an observational study in a cohort of matched patients, who were selected using a propensity score matching method. However, they did not adjust for the differences in subsequent interventions, such as primary PCI that could affect outcomes. In the present study, ECPR improved neurologic outcome after adjustment for differences in subsequent interventions, including primary PCI and therapeutic hypothermia. Our findings promote the use of ECMO for patients with prolonged cardiac arrest of cardiac origin in the out-of-hospital population.

In their 2010 CPR guidelines, the American Heart Association recommended the consideration of ECPR for patients with short-duration CPR and a reversible cause of cardiac arrest at institutions where ECPR is readily available (11). However, it is very difficult to prospectively identify patients who have suffered irreversible cerebral anoxia before ECPR initiation. Many factors influence neurologic outcome after cardiac arrest. The severity of cerebral dysfunction is generally associated with the time of cardiac arrest and the duration of CPR (21–24). In the present study, all patients suffered a witnessed cardiac arrest of short duration. Le Guen et al performed an observational study of adult patients who received ECPR following out-of-hospital cardiac arrest and showed a lower intact survival rate than that shown in our study (3.9% vs. 15.1%) (25). This difference in outcome may reflect the much longer CPR duration (120 vs. 49 min) in their study. In the present study, CPR duration was not associated with neurologic outcome after ECPR, and the ROC curve analysis revealed a small discriminative power for this variable. Although it is clear that delayed ECMO implantation worsens outcome, the relationship between CPR duration and outcome may not necessarily be linear. In another case series of adults with in-hospital cardiac arrest, Chen et al suggested that the time window of effective resuscitation could be extended up to 60 minutes with the use of ECMO (7). With regard to our neurologically intact survivors who received ECPR, the longest CPR duration was 65 minutes. However, the upper limit of CPR duration before ECPR, which results in an acceptable neurologic outcome, remains unknown.

In the present study, intact survivors who had received ECPR showed contracted pupils before ECMO implantation. The pupils often dilate following cardiac arrest; however, the mechanism is not completely understood. It is commonly presumed that, during CPR, the functions of pupilloconstrictor cells and the sympathetic nervous system would be impaired because of inadequate tissue perfusion in critical midbrain sites (26). Dilation of pupils may also be linked to ineffective chest compression. Steen–Hansen et al observed that resuscitation efforts were invariably futile if the pupils were initially dilated and subsequently remained dilated (27). Pupil diameter may be affected by several pharmacologic agents including adrenaline and atropine. However, human investigations into the pupillary effects of these drugs during CPR are lacking. In the present study, there were no correlations between the dosage of these drugs and pupil diameter (data not shown). Based on our observations, a pupil diameter of ≥ 6 mm

TABLE 3. Baseline and Clinical Characteristics of ECPR Patients

	Overall, ECPR (*n* = 52)	Favorable Outcome (*n* = 8)	Unfavorable Outcome (*n* = 44)	*p*
Baseline characteristics				
Age, yr	54 (47–60)	50 (47–57)	55 (47–60)	0.65
Gender; male, *n* (%)	44 (84.6)	5 (62.5)	39 (88.6)	0.095
Preexisting comorbidity, *n* (%)				
Diabetes	13 (25.0)	1 (12.5)	12 (27.3)	0.66
Hypertension	18 (34.6)	4 (50.0)	14 (31.8)	0.42
Dyslipidaemia	3 (5.8)	0 (0.0)	3 (6.8)	0.99
Malignancy	0 (0)	0 (0.0)	0 (0.0)	1.0
Lung insufficiency	2 (3.8)	1 (12.5)	1 (2.3)	0.29
Stroke	2 (3.8)	0 (0.0)	2 (4.5)	0.99
Chronic renal disease	2 (3.8)	0 (0.0)	2 (4.5)	0.99
Cardiac disease	15 (28.8)	2 (25.0)	13 (29.5)	0.99
Arrhythmia	6 (11.5)	3 (37.5)	3 (6.8)	0.04
Vascular disease	3 (5.8)	0 (0.0)	3 (6.8)	0.99
Chronic hepatitis	2 (3.8)	1 (12.5)	1 (2.3)	0.29
Pre-hospital variables				
Location of arrest, *n* (%)				
Home	20 (38.5)	2 (25.0)	18 (40.9)	0.52
Public place	30 (57.7)	6 (75.0)	24 (54.5)	
Other	2 (3.8)	0 (0.0)	2 (4.5)	
CPR by witness, *n* (%)	28 (53.8)	5 (62.5)	23 (52.3)	0.71
Initial rhythm; ventricular fibrillation/ ventricular tachycardia, *n* (%)	31 (59.6)	6 (75.0)	25 (56.8)	0.45
Countershock, number	2 (1–5)	5 (3–7)	2 (1–4)	0.066
Definitive airway insertion, *n* (%)	44 (84.6)	6 (75.0)	38 (86.4)	0.59
Venous access, *n* (%)	43 (82.7)	6 (75.0)	37 (84.1)	0.61
Physician-staffed ambulance, *n* (%)	34 (65.4)	4 (50.0)	30 (68.2)	0.42
Return of spontaneous circulation during transportation, *n* (%)	2 (3.8)	1 (12.5)	1 (2.3)	0.29
Drug administration				
Adrenaline, mg	1 (0–3)	1 (0–3)	2 (0–3)	0.64
Atropine, mg	0 (0–2)	0 (0-0)	1 (0–2)	0.026

(*Continued*)

TABLE 3. (*Continued*). Baseline and Clinical Characteristics of ECPR Patients

	Overall, ECPR (*n* = 52)	Favorable Outcome (*n* = 8)	Unfavorable Outcome = 44)	*p*
Time courses				
Time period; A (0900–1700), *n* (%)	24 (46.2)	3 (37.5)	21 (47.7)	0.71
Arrest to EMS, min	6 (3–9)	4 (2–10)	6 (3–9)	0.67
EMS to hospital, min	26 (21–32)	23 (18–30)	27 (21–33)	0.41
Arrest to hospital, min	33 (25–41)	29 (24–33)	34 (25–41)	0.31
Hospital to extracorporeal membrane oxygenation start, min	19 (14–29)	24 (18–30)	18 (13–28)	0.30
Arrest to basic life support (cardiac arrest time), min	3 (0–8)	3 (0–4)	3 (0–8)	0.55
Arrest to first defibrillation, min	10 (8–17)	10 (7–12)	11 (8–17)	0.30
Arrest to advance life support, min	22 (15–26)	17 (12–23)	22 (15–27)	0.17
Basic life support to CPR termination (CPR duration), min	48 (41–58)	49 (41–54)	48 (41–59)	0.73
Clinical variables on hospital arrival				
Pupils diameter, mm	6 (5–6)	4 (3–5)	6 (5–7)	0.0011
Positive pupillary reflex, *n* (%)	0 (0.0)	0 (0.0)	0 (0)	1.0
Spontaneous breathing, *n* (%)	11 (21.2)	6 (75.0)	5 (11.4)	0.0005
Cardiac rhythm; ventricular fibrillation/ ventricular tachycardia, *n* (%)	19 (36.5)	7 (87.5)	12 (27.3)	0.0023
Temperature, Celsius	33.9 (33.6–34.6)	34.6 (34.4–34.8)	33.9 (33.5–34.5)	0.14
Blood gas analysis				
pH	7.00 (6.94–7.09)	7.01 (6.98–7.08)	7.00 (6.92–7.09)	0.41
Base deficit, mmol/L	21.2 (16.5–24.8)	20.2 (19.0–21.4)	21.2 (16.5–25.1)	0.45
Lactate, mmol/L	17.2 (12.6–18.6)	12.6 (12.3–13.2)	17.3 (13.8–19.8)	0.039
Subsequent interventions				
Therapeutic hypothermia, *n* (%)	26 (50.0)	8 (100.0)	18 (40.9)	0.0042
Intra-aortic balloon pumping, *n* (%)	27 (51.9)	7 (87.5)	20 (45.5)	0.051
Percutaneous coronary intervention, *n* (%)	21 (40.4)	4 (50.0)	17 (38.6)	0.70
Complications related to extracorporeal membrane oxygenation				
Cannulation site bleeding, *n* (%)	17 (32.7)	1 (12.5)	16 (36.4)	0.24
Cannulation site infection, *n* (%)	4 (7.7)	0 (0)	4 (9.1)	0.99
Leg ischemia requiring reperfusion, *n* (%)	8 (15.4)	2 (25.0)	6 (13.6)	0.59
Compartment syndrome requiring fasciotomy, *n* (%)	1 (1.9)	0 (0)	1 (2.3)	0.99

CPR = cardiopulmonary resuscitation; ECPR = extracorporeal CPR; CCPR = conventional CPR; EMS = emergency medical service.

on hospital arrival appears to be an absolute contraindication for ECPR in patients with out-of-hospital cardiac arrest.

This assessment of the impact of ECPR and of the predictive variables for ECPR candidates must be viewed from the perspective of the study limitations. First, in terms of the impact on improved neurologic outcome after cardiac arrest, only patients with witnessed arrest in an out-of-hospital population were included. During the study period, 58.3% (232/398) of patients with cardiac arrest were not witnessed. Second, although the Utstein data, hospital course, and neurologic outcome were collected prospectively, the observations and conclusions of these historical data should be interpreted from the perspective of the

TABLE 4. Predictors of a Neurologic Outcome in Extracorporeal Cardiopulmonary Resuscitation Patients Using Cox Regression Model

	Hazard Ratio (95% Confidence Interval)	Adjusted Hazard Ratio (95% Confidence Interval)	*p*
Preexisting arrhythmia	0.33 (0.10–1.06)	0.59 (0.16–2.13)	0.42
Atropine administration (+1 mg)	1.55 (1.16–2.07)	1.28 (0.92–1.77)	0.14
Duration of cardiopulmonary resuscitation (+10 min)	1.18 (0.98–1.42)	1.08 (0.86–1.34)	0.52
Pupils diameter on hospital arrival (+1 mm)	1.56 (1.26–1.93)	1.39 (1.09–1.78)	0.0075
Breathing spontaneously on hospital arrival	0.28 (0.11–0.71)	0.42 (0.14–1.28)	0.13
Shockable rhythm on hospital arrival	0.39 (0.20–0.77)	0.84 (0.36–1.99)	0.69
Initial lactate level (+1 mmol/L)	1.05 (0.99–1.12)	1.03 (0.96–1.10)	0.40

Hazard ratios were adjusted by all variables listed here.

TABLE 5. Discriminative Powers and Optimum Values of Continuous Variables to Predict a Favorable Neurologic Outcome in Extracorporeal Cardiopulmonary Resuscitation Patients

Prognostic Variables	Area Under the Curve (95% CI)	Cut-off	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)
Atropine administration	0.75 (0.61–0.89)	< 1 mg	100% (71–100%)	50% (45–50%)	27% (19–27%)	100% (89–100%)
Duration of cardiopulmonary resuscitation	0.54 (0.34–0.73)	< 66 min	100% (72–100%)	23% (18–23%)	19% (14–19%)	100% (78–100%)
Pupils diameter on hospital arrival	0.87 (0.75–0.98)	< 6 mm	100% (71–100%)	59% (53–59%)	31% (22–31%)	100% (91–100%)
Initial lactate level	0.73 (0.57–0.90)	< 13.0 mmol/L	75% (44–93%)	78% (72–81%)	38% (22–46%)	94% (88–98%)

CI = confidence interval.

limitations imposed by a retrospective study design. Third, ECPR was initiated not by randomization but on the basis of the attending physicians' decision, only at the time when ECPR team was available. The propensity score approach could reduce selection bias; however, bias can still remain because of the small group size ($n = 24$) of the matched groups and the possible confounders including nonstandardized postresuscitation care. Fourth, the quality of CPR and the defibrillation time interval were not controlled between comparison groups because of their nature. Fifth, the impact of ECPR may be attributed, to some extent, to observer bias rather than extracorporeal support. Because ECMO use cannot be blinded, observer bias may confound the interpretation of results. Sixth, subsequent interventions after ECPR were not included in the predictor analyses. Multiple interventions, such as primary PCI and therapeutic hypothermia, could affect neurologic outcomes. However, this was precisely the reason for the analyses, i.e., to identify appropriate ECPR candidates by determining pre-ECPR variables in patients with cardiac arrest.

As compared with our previous study, we restricted this analysis to patients who had received CPR for more than 20 minutes after witnessed arrest of presumed cardiac origin in the out-of-hospital population. The present study suggests that ECPR could improve neurologic outcome better than CCPR in this population. Based on our results, pupil diameter on hospital arrival may be a key predictor of neurologic outcome in patients who receive ECPR. However, further studies are required to identify the most appropriate candidates for ECPR.

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