

Out-of-hospital cardiac arrest patients with an initial non-shockable rhythm could be candidates for extracorporeal cardiopulmonary resuscitation: a retrospective study.

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Abstract

Background Extracorporeal cardiopulmonary resuscitation (ECPR) is a promising treatment for refractory out-of-hospital cardiac arrest (OHCA). Most studies evaluating the effectiveness of ECPR include patients with an initial shockable rhythm. However, the effectiveness of ECPR for patients with an initial non-shockable rhythm remains unknown. This retrospective single-center study aimed to evaluate the effectiveness of ECPR for patients with an initial non-shockable rhythm, with reference to the outcomes of OHCA patients with an initial shockable rhythm. **Methods** Adult OHCA patients treated with ECPR at our center during 2011–2018 were included in the study. Patients were classified into the initial shockable rhythm group and the non-shockable rhythm group. The primary outcome was the cerebral performance category (CPC) scale score at hospital discharge. A CPC score of 1 or 2 was defined as a good outcome. **Results** In total, 186 patients were eligible. Among them, 124 had an initial shockable rhythm and 62 had an initial non-shockable rhythm. Among all patients, 158 (85%) were male, with a median age of 59 (interquartile range [IQR], 48–65) years, and the median low flow time was 41 (IQR, 33–48) min. Collapse was witnessed in 169 (91%) patients, and 36 (19%) achieved return of spontaneous circulation (ROSC) transiently. Proportion of female patients, presence of bystander cardiopulmonary resuscitation, and collapse after the arrival of emergency medical service personnel were significantly higher in the non-shockable rhythm group. The rate of good outcomes at hospital discharge was not significantly different between the shockable and non-shockable groups (19% vs. 16%, $p=0.69$). Initial shockable rhythm was not significantly associated with good outcome after controlling for potential confounders (adjusted odds ratio 1.58, 95% confidence interval: 0.66–3.81, $p=0.31$). In the non-shockable group, patients with good outcomes had a higher rate of transient ROSC, and pulmonary embolism was the leading etiology. **Conclusions** The outcomes of patients with an initial non-shockable rhythm are comparable with those having an initial shockable rhythm. OHCA patients with an initial non-shockable rhythm could be candidates for ECPR, if they are presumed to have reversible etiology and potential for good neurological recovery.

Background

Recently, extracorporeal cardiopulmonary resuscitation (ECPR) has been reported to be a promising treatment for refractory out-of-hospital cardiac arrest (OHCA) [1, 2, 3]. In OHCA patients with an initial shockable rhythm, several studies have reported better survival and neurological outcome in patients treated with ECPR compared with conventional cardiopulmonary resuscitation (CCPR) [4, 5]. However, there are only few reports evaluating the efficacy of ECPR in OHCA patients with an initial non-shockable rhythm. For in-hospital cardiac arrest patients treated with ECPR, non-shockable rhythm is more frequent as the initial rhythm than shockable rhythm [6, 7]. Even in OHCA patients, some case series have reported successful treatment with ECPR in selected etiologies such as pulmonary embolism and accidental hypothermia. [8, 9]. This study aimed to evaluate the efficacy of ECPR in OHCA patients with an initial non-shockable rhythm, with reference to the outcomes of patients with an initial shockable rhythm at our center.

Methods

Patients

This retrospective study included OHCA patients who were treated with ECPR at the tertiary emergency care center of Tokyo Metropolitan Bokutoh Hospital between January 2011 and December 2018. Patients aged below 18 years were excluded from the study. The patients were classified into two groups according to the initial rhythm: the shockable rhythm group and the non-shockable rhythm group. Data of the baseline demographic and clinical characteristics of the patients were obtained from patients' medical records, and the timing of pre-hospital events was recorded according to the reports of emergency medical service (EMS) personnel. The institutional review board of Tokyo Metropolitan Bokutoh Hospital approved the study (institutional approval reference number 02-003), which complied with the tenets of the Declaration of Helsinki. The requirement for informed consent was waived owing to the retrospective design of the study.

Protocol for ECPR and post-cardiac arrest care

The indications for ECPR at our institution are as follows: (i) OHCA patients aged ≤ 65 years with an initial shockable rhythm and witness and (ii) OHCA patients aged ≤ 70 years with presumed reversible etiology who collapsed after the arrival of EMS personnel. In this case, any initial rhythm was acceptable. Patients with very long transfer times and terminal illnesses were excluded. The implementation of ECPR was decided at the discretion of the individual emergency physician. Therefore, some cases did not meet the rigid indications.

ECPR was implemented immediately after the patient's arrival at the emergency room. In all cases, we selected the ipsilateral or contralateral femoral vein and artery for insertion of venous and arterial cannulas. Further, 16-French (Fr) and 22-Fr cannulas were chosen for femoral artery and vein, respectively. Cannulation was performed percutaneously using the Seldinger technique under ultrasonic guidance. When our emergency room was renovated in August 2014, an interventional radiology-computed tomography (CT) system was installed [10]. Before this (until July 2014), a cannula was placed under ultrasonic guidance only, and after August 2014, cannulas were placed under both ultrasonic and fluoroscopic guidance. The extracorporeal membrane oxygenation (ECMO) circuit, consisting of a centrifugal pump, a hollow fiber oxygenator (MERA CPB circuit; Senko Medical Instrument Mfg. Co. Ltd., Tokyo, Japan, or Capiiox EBS; Terumo Corporation, Tokyo, Japan), and a heparin-coated surface circuit, was primed using normal saline with 3,000 units of heparin. After the successful insertion of the venous and arterial cannulas, the ECMO circuit was connected and the ECMO pump flow was set at 4 L/min initially. After the initiation of ECMO, a 4-Fr sheath was placed in the superficial femoral artery to prevent distal limb ischemia.

All patients were resuscitated according to the recommendations at each period [11,12,13,14]. The patients received appropriate amounts of fluid or vasopressors to maintain the mean blood pressure above 65 mmHg and were placed under ventilation to maintain normocarbida and adequate oxygenation.

Patients in whom cardiac etiology was suspected underwent coronary angiography (CAG) and percutaneous coronary intervention, if indicated. Patients who remained comatose after ECMO initiation were treated with targeted temperature management at 34°C for 24 h and subsequently rewarmed to 36°C for the next 12 h using a heat exchanger in the circuit.

Neurological outcomes were predicted according to the results of clinical examinations performed at least 72 h after the return of spontaneous circulation (ROSC) and of brain CT. Neurological outcomes were predicted as poor when (1) a patient remained unconscious for at least 72 h post-ROSC with a Glasgow Coma Scale motor response score of ≤ 2 ; (2) there was no pupillary reflex; and (3) diffuse anoxic injury was recognized post-ROSC or during follow-up brain CT (on days 4–5) [12,14]. Even in these patients, we did not withdraw treatment, and ongoing life-sustaining measures were retained. However, additional aggressive treatment modalities such as hemodialysis and additional mechanical circulatory support devices were withheld.

Outcomes

The cerebral performance category (CPC) scale was used to assess the outcomes of neurological function at hospital discharge [15], and this was the primary outcome. The CPC scores were determined by reviewing the report from the rehabilitation department. The outcome of neurological function was considered good if the CPC score was 1 or 2, and poor if the CPC score was 3–5.

Statistical analysis

Continuous variables were reported as medians with interquartile ranges (IQRs), and dichotomous variables were reported as numbers with percentages. Univariate analysis was performed using Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables. All reported p-values were two-tailed, and values less than 0.05 were considered to indicate statistical significance.

First, the rate of good neurological outcome was compared between the shockable and non-shockable rhythm groups. A multivariate logistic regression analysis was then performed to evaluate the association between the initial rhythm and good neurological outcomes to control for potential confounders. We selected potential confounders that appeared to be clinically important by referring to those used in previous studies (age, bystander CPR, witness, low flow time, and transient ROSC) [16].

Second, the background characteristics of the patients were compared between those with good and poor neurological outcomes in the non-shockable group.

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [17], which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 5,203 OHCA patients were transferred to our center during the study period. Of them, 187 were treated with ECPR for refractory cardiac arrest. One patient aged below 18 years was excluded, and a total of 186 patients were eligible for the study. Among them, 124 patients had an initial shockable rhythm and 62 patients had an initial non-shockable rhythm (Fig. 1).

The background characteristics of all patients and patients in each group are shown in Table 1. Of the total 186 patients, 158 (85%) were male, with a median age of 59 (IQR, 48–65) years. Collapse was witnessed in 169 (91%) patients, and 119 (64%) patients received bystander CPR. Fifty-five (30%) patients collapsed after the arrival of EMS personnel. Median low flow time was 41 (IQR 33–48) min. Thirty-six patients (19%) achieved ROSC transiently and collapsed again during the period between the collapse and the initiation of ECMO.

The proportion of female patients, presence of bystander CPR, and collapse after the arrival of EMS personnel were significantly higher in the non-shockable rhythm group. Low flow time was not significantly different. In the shockable rhythm group, the most frequent etiology of cardiac arrest was acute coronary syndrome (ACS) (55 patients), followed by idiopathic ventricular fibrillation (41 patients) and cardiomyopathy (12 patients). In the non-shockable rhythm group, the most frequent etiology was also ACS (22 patients), followed by pulmonary embolism (9 patients), and respiratory failure (7 patients). CAG was performed more frequently in the shockable rhythm group than in the non-shockable rhythm group.

Among all patients, 55 (30%) survived to hospital discharge, and 34 (18%) had good neurological outcomes at hospital discharge. The rate of good neurological outcomes at hospital discharge was not significantly different between the shockable and non-shockable rhythm groups (19% vs. 16%, $p = 0.69$). Additionally, the rate of survival at hospital discharge was not different between the two groups (33% vs. 23%, $p = 0.17$) (Table 2).

After controlling for potential confounders, we found that the adjusted odds ratio of the initial shockable rhythm as compared to that of the non-shockable rhythm for good neurological outcomes was 1.58 (95% confidence interval: 0.66–3.81, $p = 0.31$). In this model, the presence of bystander CPR and transient ROSC was significantly associated with good neurological outcomes (Table 3).

In the non-shockable group, patients with good neurological outcomes were predominantly female, with a higher rate of transient ROSC than that in those with poor neurological outcomes. Pulmonary embolism was the most frequent etiology in patients with good neurological outcomes (Table 4).

Discussion

In the present study, the outcomes of patients with an initial non-shockable rhythm were compared with those of patients with an initial shockable rhythm among all patients treated with ECPR at our center. We found that the initial rhythm was not significantly associated with neurological outcome, and the neurological outcome of the non-shockable group was almost comparable with that of the shockable

rhythm group. In the non-shockable rhythm group, pulmonary embolism was the leading etiology in patients with good neurological outcome, and the rate of transient ROSC during resuscitation was higher in patients with good neurological outcomes.

In the last decade, several studies have reported the efficacy of ECPR in patients with refractory OHCA. Most of these studies included patients with an initial rhythm of ventricular fibrillation or ventricular tachycardia [1, 2, 4, 18]. In another study evaluating the factors associated with good outcomes, the initial shockable rhythm has been reported to be a significant predictor of good outcome [19]. In patients with refractory cardiac arrest, the reversibility of both cardiac and brain function is the major determinant of the prognosis. OHCA patients with an initial shockable rhythm are more likely to have reversible etiology such as ACS. The leading cause of refractory ventricular fibrillation is reported to be ACS in most studies [4, 18]. Furthermore, sudden onset of lethal arrhythmia is commonly noted; therefore, normal cerebral perfusion and oxygenation were generally maintained prior to the event. This is considered an important factor contributing to good prognosis in patients with an initial shockable rhythm. Generally, OHCA patients with non-shockable rhythm had poor outcomes compared with those having shockable rhythm [20]. They tend to have various etiologies refractory to treatment, often experiencing the symptomatic period preceding the cardiac arrest, and they might suffer from shock or hypoxia before collapsing. These factors lead to the difficulty in treating the underlying etiology and achieving brain recovery when performing ECPR in patients with an initial non-shockable rhythm. However, several case reports have reported the efficacy of ECPR in OHCA patients with non-shockable rhythm. Patients with accidental hypothermia or pulmonary embolism have been reported to be treated successfully in these case reports [8, 9, 21, 22, 23]. Bunya et al. reported two cases of refractory cardiac arrest with an initial non-shockable rhythm and agonal respiration at the presentation. Both patients were treated with ECPR and had good neurological outcomes [24]. The results of the present study and the case series show that the initial non-shockable rhythm alone might not fully dismiss the possibility of ECPR in OHCA patients. If the patients had a reversible etiology and potential for good brain recovery, then the indication of ECPR even in those with non-shockable rhythm should be considered.

In the non-shockable rhythm group, patients with good neurological outcome had a higher rate of transient ROSC. The transient ROSC between the collapse and the initiation of ECMO might shorten the actual low flow time and lessen anoxic brain injury. Furthermore, pulmonary embolism is the leading etiology among patients with good outcome. Pulmonary embolism causes acute right heart failure, and veno-arterial ECMO could be a highly effective treatment for this condition [25, 26]. The results of our study emphasize the importance of appropriate etiologic diagnosis and the prediction of the potential for good brain recovery during cardiac arrest.

It is very challenging to diagnose the etiology of OHCA during cardiopulmonary resuscitation (CPR). The efficacy of point-of-care ultrasonography has been emphasized in patients during cardiac arrest. Cardiac tamponade, pulmonary embolism, and ACS could be diagnosed with this method [27]. However, the evaluation of potential for brain function recovery during CPR is further challenging. There are some promising physiological parameters such as presence of agonal breathing [28], regional cerebral oxygen

saturation [29], and quantitative pupillometry [30] that have been reported to be associated with the neurological outcome and might indicate the residual function of the brain. These diagnostic methods and neurological physiological parameters during CPR should be investigated in future studies to establish the appropriate indication criteria for ECPR beyond the initial rhythm and to improve the effectiveness of ECPR.

There are several important limitations to this study. First, this was a retrospective single-center study with a small sample size. Second, the indication of ECPR at our center for patients with non-shockable rhythm is relatively limited, which includes only patients who collapse after the arrival of EMS personnel and are speculated to have treatable etiology estimated from the symptom before collapse. This protocol aimed to shorten the low flow time and to obtain a more precise patient history at the scene. However, one-third of patients actually collapsed before the arrival of EMS personnel because the final decision was at the discretion of the attending physician. As a result, there was no significant difference in the low flow time between patients with shockable rhythm and those with non-shockable rhythm. The results of this study emphasize the importance of patient selection but do not demonstrate the efficacy of ECPR in unselected patients with an initial non-shockable rhythm. Third, neurological outcomes were evaluated only at the time of hospital discharge, and long-term outcomes were not evaluated. Fourth, the outcome of ECPR in patients with OHCA is influenced by the system of emergent medical services and pre-hospital treatment. Therefore, the results of this study could not be generally applied to various clinical settings. Finally, the cost-effectiveness of the method was not evaluated in this study. Some studies reported that ECPR could be cost-effective, particularly in patients with an initial shockable rhythm [31, 32, 33]. The cost-effectiveness of ECPR in patients with non-shockable rhythm should be evaluated in future studies.

Conclusions

Among the OHCA patients treated with ECPR at our center, the outcomes of patients with an initial non-shockable rhythm were comparable to those of patients with an initial shockable rhythm. OHCA patients with an initial non-shockable rhythm could be considered as candidates for ECPR, if they are presumed to have reversible etiology and the potential for good neurological recovery. Further studies focusing on the diagnosis and prognostication during cardiac arrest are needed.

List Of Abbreviations

ACS, acute coronary syndrome; CAG, coronary angiography; CCPR, conventional cardiopulmonary resuscitation; CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; CT, computed tomography; ECPR, extracorporeal cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; EMS, emergency medical service; IQRs, interquartile range; OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation

Declarations

Ethics approval and consent to participate

The institutional review board of Tokyo Metropolitan Bokutoh Hospital approved the study (institutional approval reference number 02-003), which complied with the tenets of the Declaration of Helsinki. The requirement for informed consent was waived owing to the retrospective design of the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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No funding was received for this research from any source.

Authors' contributions

AT conceptualized and designed the study and critically revised the article for important intellectual content. KS, MT, KK, and AK collected and assembled the data. YH revised the article. All authors read and approved the final version of the manuscript.

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Tables

Table 1. Characteristics of all patients and each group

	All patients n=186	Non-shockable rhythm n=62	Shockable rhythm n=124	p-value
Age, median (IQR)	59 (48, 65)	60 (49, 66)	58 (46, 65)	0.24
Sex, male, n (%)	158 (85)	46 (74)	112 (90)	<0.01
Witness, n (%)	169 (91)	59 (95)	110 (89)	0.19
Bystander CPR, n (%)	119 (64)	51 (82)	68 (55)	<0.01
Cardiac arrest after EMS personnel arrival, n (%)	55 (30)	41 (66)	14 (11)	<0.01
Low flow time, median (IQR)	41 (33, 48)	40 (31, 51)	41(34, 48)	0.84
Transient ROSC, n (%)	36 (19)	12 (19)	24 (19)	1
Etiology, n (%)				0.06
Acute coronary syndrome	77 (41)	22 (36)	55 (44)	
Vasospastic angina	5 (3)	2 (3)	3 (2)	
Idiopathic ventricular fibrillation	42 (23)	1 (2)	41 (33)	
Cardiomyopathy	16 (9)	4 (6)	12 (10)	
Pulmonary embolism	10 (5)	9 (15)	1 (1)	
Accidental hypothermia	3 (2)	2 (3)	1 (1)	
Aortic dissection	11 (6)	6 (10)	5 (4)	
Respiratory failure	7 (4)	7 (11)	0	
Others	15 (8)	9 (15)	6 (5)	
Coronary angiography	137 (74)	31 (50)	106 (86)	<0.01

CPR, cardiopulmonary resuscitation; EMS, emergency medical service; IQR, interquartile range; ROSC, return of spontaneous circulation

Table 2. Outcomes of all patients and each group

	All patients	Non-shockable rhythm	Shockable rhythm	p-value
	n=186	n=62	n=124	
Survival, n (%)	55 (30)	14 (23)	41 (33)	0.17
Good neurological outcome, n (%)	34 (18)	10 (16)	24 (19)	0.69
Successful weaning from ECMO, n (%)	86 (46)	26 (42)	60 (48)	0.44

ECMO, extracorporeal membrane oxygenation

Table 3. Multivariate logistic regression analysis of the prognostic factors of good neurological outcomes

	Adjusted odds ratio	95% confidence interval	p-value
Initial shockable rhythm	1.58	0.66-3.81	0.31
Age	0.99	0.97-1.03	0.97
Bystander CPR	3.6	1.30-9.95	0.01
Low flow time	0.97	0.94-1.01	0.1
Witness	1.19	0.23-6.23	0.84
Transient ROSC	5.04	2.12-12.00	<0.01

CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous resuscitation

Table 4. Background characteristics of the patients with good and poor neurological outcomes in the non-shockable group

	Good neurological outcome n=10	Poor neurological outcome n=52	p -value
Age, median (IQR)	62 (54, 65)	59 (49, 66)	0.66
Sex, male, n (%)	4 (40)	42 (81)	0.01
Low flow time, median (IQR)	33 (26, 45)	42 (32, 52)	0.24
Transient ROSC, n (%)	5 (50)	7 (14)	0.02
Initial rhythm, n (%)			1
PEA	9 (90)	44 (85)	
Asystole	1 (10)	8 (15)	
Etiology, n (%)			0.06
	2 (20)	20 (39)	
Acute coronary syndrome			
Vasospastic angina	1 (10)	1 (2)	
Idiopathic ventricular fibrillation	0	1 (2)	
Cardiomyopathy	1 (10)	3 (6)	
Pulmonary embolism	4 (40)	5 (10)	
Accidental hypothermia	1 (10)	1 (2)	
Aortic dissection	0	6 (12)	
Respiratory failure	1 (10)	6 (12)	
Others	0	9 (17)	

IQR, interquartile range; ROSC, return of spontaneous resuscitation

Figures

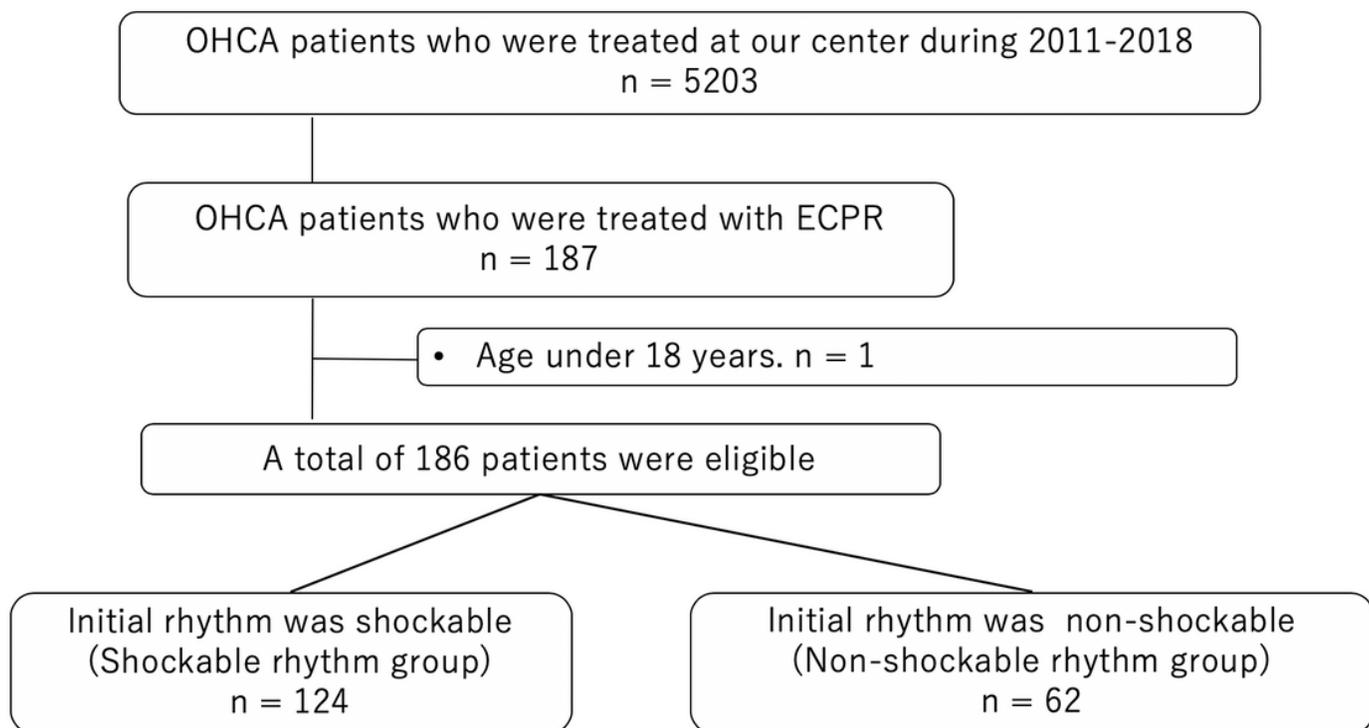


Figure 1

Flow chart of patient selection. OHCA, out-of-hospital cardiac arrest;