Patients With Refractory Out-of-Cardiac Arrest and Sustained Ventricular Fibrillation as Candidates for Extracorporeal Cardiopulmonary Resuscitation

— Prospective Multi-Center Observational Study —

Takahiro Nakashima, MD, PhD; Teruo Noguchi, MD, PhD; Yoshio Tahara, MD, PhD;
Kunihiro Nishimura, MD; Soshiro Ogata, PhD; Satoshi Yasuda, MD, PhD;
Daisuke Onozuka, PhD; Naoto Morimura, MD, PhD; Ken Nagao, MD, PhD;
David F Gaieski, MD; Yasufumi Asai, MD, PhD; Hiroyuki Yokota, MD, PhD;
Satoshi Nara, MD, PhD; Mamoru Hase, MD, PhD; Takahiro Atsumi, MD, PhD;
Tetsuya Sakamoto, MD, PhD for the SAVE-J Group

Background: We investigated whether patients with out-of-hospital cardiac arrest (OHCA) and sustained ventricular fibrillation/pulseless ventricular tachycardia (VF/pVT) or conversion to pulseless electrical activity/asystole (PEA/asystole) benefit more from extracorporeal cardiopulmonary resuscitation (ECPR).

Methods and Results: We analyzed data from the Study of Advanced Life Support for Ventricular Fibrillation with Extracorporeal Circulation in Japan, which was a prospective, multicenter, observational study with 22 institutions in the ECPR group and 17 institutions in the conventional CPR (CCPR) group. Patients were divided into 4 groups by cardiac rhythm and CPR group. The primary endpoint was favorable neurological outcome, defined as Cerebral Performance Category 1 or 2 at 6 months. A total of 407 patients had refractory OHCA with VF/pVT on initial electrocardiogram. The proportion of ECPR patients with favorable neurological outcome was significantly higher in the sustained VF/pVT group than in the conversion to PEA/asystole group (20%, 25/126 vs. 3%, 4/122, $P<0.001$). Stratifying by cardiac rhythm, on multivariable mixed logistic regression analysis an ECPR strategy significantly increased the proportion of patients with favorable neurological outcome at 6 months in the patients with sustained VF/pVT (OR, 7.35; 95% CI: 1.58–34.09), but these associations were not observed in patients with conversion to PEA/asystole.

Conclusions: OHCA patients with sustained VF/pVT may be the most promising ECPR candidates (UMIN000001403).

Key Words: Extracorporeal life support; Extracorporeal membrane oxygenation; Favorable neurological outcome

Extracorporeal life support (ECLS) has been proposed as a type of cardiac resuscitation for patients in cardiac arrest without return of spontaneous circulation (ROSC) during ongoing cardiopulmonary resuscitation (CPR).[1] Based on a previous review of extracorporeal cardiopulmonary resuscitation (ECPR) after 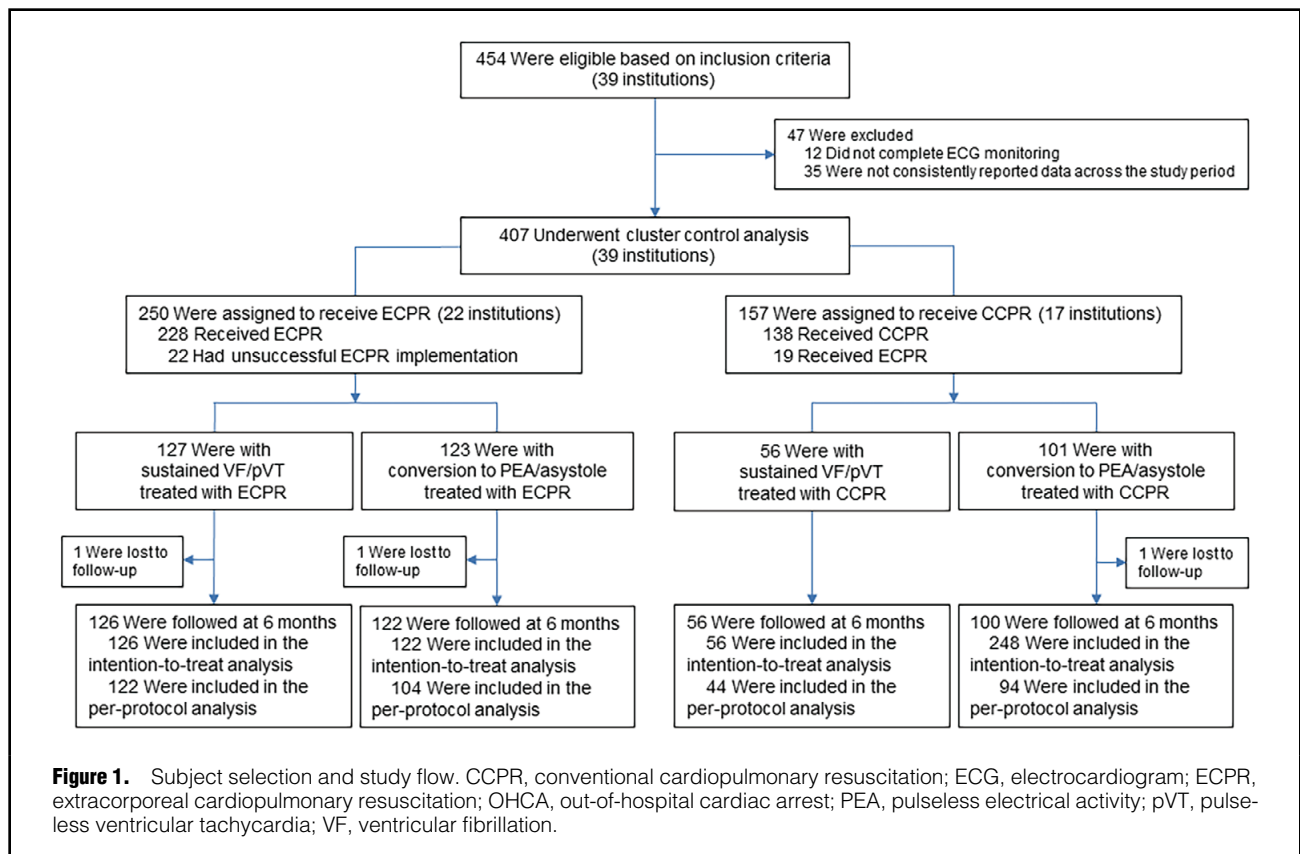out-of-hospital cardiac arrest (OHCA) in Japan that reported that an initial cardiac rhythm of ventricular fibrillation/pulseless ventricular tachycardia (VF/pVT) is a significant predictor of survival,[2] we conducted the Study of Advanced Life Support for Ventricular Fibrillation with Extracorporeal Circulation in Japan (SAVE-J) trial, and showed that patients with refractory OHCA and VF/pVT on initial electrocardiogram (ECG) who received ECPR

Figure 1. Subject selection and study flow. CCPR, conventional cardiopulmonary resuscitation; ECG, electrocardiogram; ECPR, extracorporeal cardiopulmonary resuscitation; OHCA, out-of-hospital cardiac arrest; PEA, pulseless electrical activity; pVT, pulseless ventricular tachycardia; VF, ventricular fibrillation.

have more favorable neurological outcomes at 6 months compared with patients who received conventional CPR (CCPR).[3] There remains, however, a critical knowledge gap regarding the implementation of this advanced resuscitation strategy: are there subgroups of OHCA patients who benefit more from ECPR?

To address this knowledge gap, we focused on 2 subgroups of patients with OCHA: patients with sustained VF/pVT and patients with conversion from VF/pVT on initial ECG to pulseless electrical activity or asystole (PEA/asystole) prior to initiation of ECPR, because cardiac rhythm conversion is an easily understood parameter during an emergency and a considerable percentage of OHCA patients with VT/pVT on initial ECG often convert to PEA/asystole at some point prior to initiation of ECPR in the real world. Therefore, we performed an analysis of the SAVE-J data to test the hypothesis that a higher percentage of patients with sustained VF/pVT prior to initiation of ECPR has favorable neurological outcomes at 6 months compared with patients with conversion from initial VF/pVT to PEA/asystole prior to initiation of ECPR.

Methods

Study Design
We analyzed the data from the SAVE-J trial examining the effect of ECPR on survival and neurological outcomes in patients who had refractory OHCA with VF/pVT on initial ECG between October 2008 and October 2011.[3] Although the SAVE-J trial had been originally designed as a non-randomized cluster controlled study, some institutions familiar with the ECPR strategy for OHCA objected to

cluster assignment because it was against their principles for OHCA therapy. Thus, the SAVE-J trial was conducted as a prospective, multicenter, observational study according to the treatment protocol of each institution. All participating institutions in the original SAVE-J trial were high-quality Japanese resuscitation centers, including national institutes, emergency medical centers designated by local government, and university hospital emergency departments. We addressed the likelihood of favorable neurological outcomes at 6 months in 2 subgroups of OHCA patients: those with sustained VF/pVT and those with rhythm conversion from initial VF/pVT to PEA/asystole before initiation of ECPR.

Participant and Patient Recruitment
Forty-six institutions were divided into either the ECPR group or CCPR group at the request of each institution. **Supplementary Table 1** lists hospital performance for the ECPR group and CCPR group based on 2007 annual ECPR reports from the Japanese Circulation Society. All study institutions perform ECPR for patients with in-hospital cardiac arrest (IHCA). Institutions in both groups provide intensive care and advanced cardiovascular care of similar quality.[4] In the present re-analysis, we excluded 7 participating institutions because 5 registered no patients and 2 did not adhere to the study protocol. Thus, patients from a total of 39 participating institutions, consisting of 22 institutions in the ECPR group and 17 institutions in the CCPR group, were included in this final analysis (**Supplementary Figure**).

Eligibility for and recruitment of patients in the SAVE-J trial have been reported elsewhere.[3] To summarize: patients

Table 1. Baseline Subject Characteristics vs. CPR Status (Intention-to-Treat Analysis)

	ECPR group (n=250)	CCPR group (n=157)	P-value	ECPR group		CCPR group		P-value
				Sustained VF/pVT (n=127)	Converted to PEA/asystole (n=123)	Sustained VF/pVT (n=56)	Converted to PEA/asystole (n=101)	
Age (years)	59 (48~64)	60 (51~68)	0.056	59 (48~64)	59 (49~66)	60 (52~66)	60 (51~69)	0.239
Male sex	227 (91)	139 (89)	0.503	112 (88)	115 (94)	48 (86)	91 (90)	0.354
Witness status	182 (73)	121 (78)	0.348	98 (77)	84 (69)	45 (82)	76 (75)	0.249
Bystander CPR	112 (46)	64 (43)	0.601	67 (53)	45 (37)	26 (48)	38 (40)	0.052
Time from collapse to ECPR implementation (min)	54 (46~65)			54 (45~65)	54 (47~67)			0.407
From collapse to hospital arrival (min)	32 (24~39)	32 (25~39)	0.857	32 (23~40)	32 (26~38)	32 (23~39)	32 (26~40)	0.930
From hospital arrival to ECPR implementation (min)	22 (16~30)			22 (16~29)	22 (17~33)			0.254
Cause of cardiac arrest			0.013					0.066
Acute coronary syndrome	163 (65)	82 (52)		77 (61)	86 (70)	31 (55)	51 (51)	
Valvular disease	2 (1)	2 (1)		1 (1)	1 (1)	1 (2)	1 (1)	
Myocarditis	2 (1)	0 (0)		0 (0)	2 (2)	0 (0)	0 (0)	
Myopathy	16 (7)	5 (4)		8 (6)	8 (7)	2 (4)	4 (4)	
Unknown	67 (26)	67 (43)		41 (32)	26 (21)	22 (39)	45 (44)	

Data given as n (%) or median (IQR). CCPR, conventional cardiopulmonary resuscitation; CPR, cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation; PEA, pulseless electrical activity; VF/pVT, ventricular fibrillation/pulseless ventricular tachycardia.

aged 20–75 years with OHCA of cardiac origin with VF/pVT on the initial ECG who received chest compressions performed by emergency medical service (EMS) personnel with a time from collapse to hospital arrival <45 min and who did not achieve ROSC before hospital arrival were eligible.

This analysis of the SAVE-J trial was approved by the institutional review board. It was registered on the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN000001403).

EMS System in Japan

All EMS personnel are employed by municipal governments.[5] They have been trained to perform CPR based on the 2005 Japan Resuscitation Council guidelines, which are based on the 2005 American Heart Association (AHA) guidelines.[6] EMS personnel are instructed to transport patients with OHCA to the nearest regional high-quality emergency center.[5,7] All patients with OHCA who receive prehospital resuscitation by EMS personnel are transported to a hospital because EMS personnel in Japan are not permitted to terminate resuscitation in the field.

Procedures

All patients who had refractory OHCA with VF/pVT on initial ECG were transported to the nearest regional high-quality resuscitation center, as aforementioned, <45 min after receiving the emergency call, and treated according to the study protocol. After standard advanced life support (ALS) for 15 min in the emergency department, patients underwent ECPR or CCPR based on group assignment. All patients underwent ECG at 3 points: EMS contact; hospital arrival; and ECPR initiation. Targeted temperature management (TTM) was considered completed when target core body temperature had been maintained at 32–34°C for >24 h. In the CCPR group, TTM was introduced when patients had ROSC with stable hemodynamic status and had received ALS for ≥15 min.

Data Collection and Quality Control

Data elements were collected prospectively from prehospital and subsequent hospital medical records by individual sites and provided to the Center for Health Service, Outcomes Research and Development – Japan (CHORD-J), which serves as the data center, in the manner described here. CHORD-J provides the registry system on Web-based forms in order to collect necessary information from the participating sites (URL: http://www.chord-j.info), and the study data form was filled out by physicians. Data encryption and authentication methods were used. The data were checked for consistency using the computer system and were confirmed by CHORD-J. Diagnosis of cause of cardiac arrest was made by the physician in charge. All event times in the prehospital setting were synchronized by the dispatch center clock. The time of collapse was obtained by EMS interview with the bystander. The time of ECLS implementation was defined as when blood flow was established with ECLS. ROSC was defined as ≥1 min of confirmed continuous pulse in both the ECPR and CCPR groups. All survivors were followed for up to 6 months after the OHCA by physicians who had provided the emergency or post-cardiac arrest care, with the use of the Cerebral Performance Category (CPC) scale based on a telephone or in-person interview.[8,9]

Outcomes

The primary endpoint was favorable neurological outcome, based on the CPC scale,[8,9] at 6 months of follow-up. A favorable outcome was defined as CPC 1 (good cerebral performance) or 2 (moderate cerebral disability) after cardiac arrest.

Statistical Analysis

The sample size justification for the SAVE-J trial is described in the **Supplementary Material**. We categorized study patients into 4 subgroups by cardiac rhythm and cluster: sustained VF/pVT treated with ECPR; conversion

Table 2. Effect of ECPR on Outcome According to Cardiac Rhythm

Cardiac rhythm / Outcome	No. patients with outcome/total patients (%)		Univariable mixed logistic regression models			Multivariable mixed logistic regression models[†]			IPTW-PS models[‡]		
	ECPR	CCPR	OR	P-value	95% CI	OR	P-value	95% CI	ATE (%)	P-value	95% CI
Sustained VF/pVT											
Favorable neurological outcome at 6 months	25/126 (20)	2/56 (4)	6.97	0.014	1.48~32.70	7.35	0.011	1.58~34.09	18.4	0.039	0.9~35.9
Survival at 6 months	41/126 (33)	4/56 (7)	7.73	0.003	2.02~29.45	8.21	0.004	1.99~33.82	14.4	0.004	4.6~24.0
Conversion to PEA/asystole											
Favorable neurological outcome at 6 months	4/122 (3)	2/100 (1)	3.21	0.411	0.19~52.14	1.15	0.964	0.01~595.50	0.9	0.701	−4.0~6.0
Survival at 6 months	14/122 (11)	2/100 (2)	6.72	0.019	1.36~33.19	5.58	0.030	1.17~26.43	10.8	0.022	1.5~20.1

[†]Adjusted for age, gender, witness status, bystander CPR, and time from collapse to hospital arrival. [‡]Patients who received ECPR at any given minute of treatment were matched with patients eligible to receive ECPR in the same minute of treatment (i.e., patients in the CCPR group still receiving resuscitation) based on time-dependent IPTW-PS-adjusted models that included age, gender, witness status, bystander CPR, cause of cardiac arrest and time from collapse to hospital arrival. ATE, absolute treatment effect; IPTW-PS, inverse probability of treatment weighting propensity score. Other abbreviations as in Table 1.
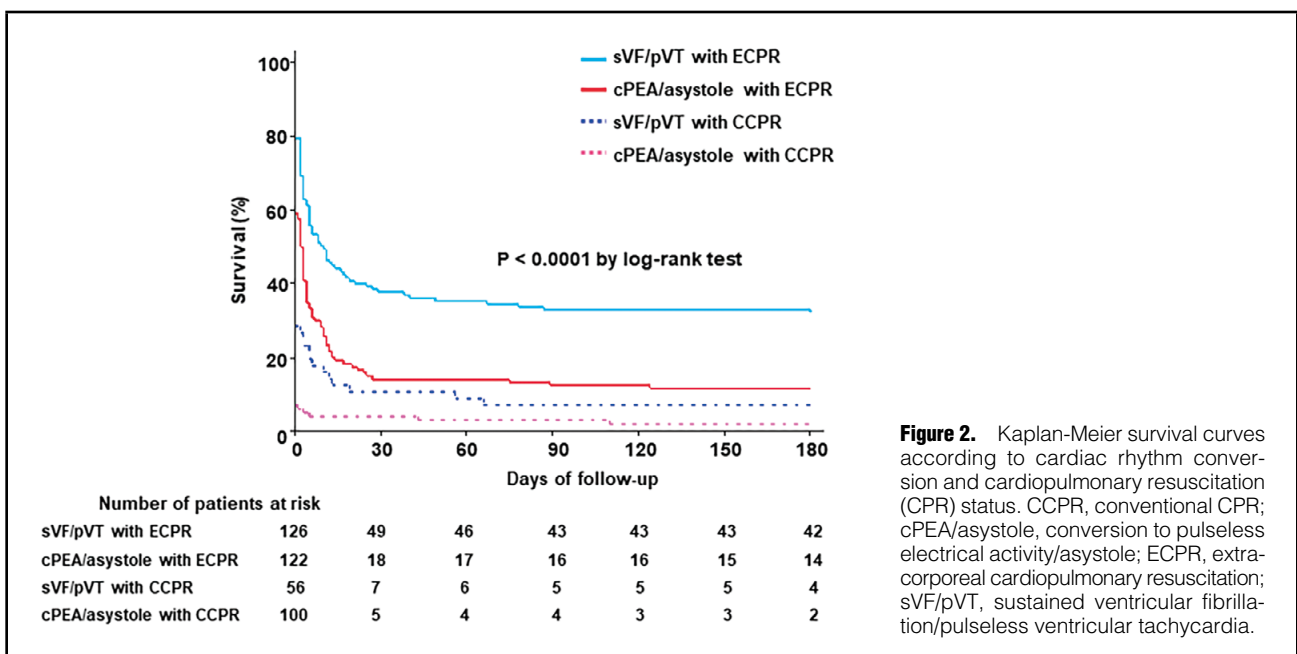

Figure 2. Kaplan-Meier survival curves according to cardiac rhythm conversion and cardiopulmonary resuscitation (CPR) status. CCPR, conventional CPR; cPEA/asystole, conversion to pulseless electrical activity/asystole; ECPR, extracorporeal cardiopulmonary resuscitation; sVF/pVT, sustained ventricular fibrillation/pulseless ventricular tachycardia.

from initial VF/pVT to PEA/asystole treated with ECPR; sustained VF/pVT treated with CCPR; and conversion from initial VF/pVT to PEA/asystole treated with CCPR. We conducted multivariable mixed logistic regression with adjustment for age, gender, witness status, bystander CPR, and time from collapse to hospital arrival to account for group differences between institutions. Then, to control for the time from collapse to ECPR implementation, we also conducted time-dependent inverse probability of treatment weighting (IPTW) propensity score analysis. Patients who received ECPR at any given minute of treatment were matched with patients eligible to receive ECPR in the same minute of treatment based on time-dependent IPTW propensity score adjusted models that included age, gender, witness status, bystander CPR, cause of cardiac arrest, and time from collapse to hospital arrival. This approach has previously been used in studies analyzing time-dependent cardiac arrest interventions.[10–12] Moreover, to investigate the temporal association between ECPR and subsequent events and treatments, we conducted structural equation modeling (SEM) analysis. The path models and estimates (95% Bayesian credible intervals) were evaluated using a Markov chain Monte Carlo method.[13,14] Details about statistical analyses are described in **Supplementary Material**.

All statistical analysis was performed using JMP version 11 (SAS Institute, Cary, NC, USA), Stata version 14 (StataCorp, College Station, TX, USA), or Mplus version 8 (Muthén & Muthén, Los Angeles, CA, USA).

Results

Enrollment and Patient Characteristics

A total of 454 consecutive patients with OHCA of cardiac origin were initially screened and 407 patients were ultimately enrolled (**Figure 1**). After ≥15 min of ALS, 250 patients underwent ECPR. ECLS implementation was suc-

Table 3. Patients With ROSC: Comparison of ECPR and Subsequent Treatment (Intention-to-Treat Analysis)

	ECPR group (n=189)	CCPR group (n=48)	P-value	ECPR group Sustained VF/pVT (n=107)	ECPR group Converted to PEA/asystole (n=82)	P-value
ECPR						
Initial ECPR maximum flow (L/min)	3.0 (2.5~3.5)			3.0 (2.5~3.5)	3.0 (2.5~3.5)	0.225
Duration of ECPR (h)	49 (19~93)			54 (24~101)	46 (11~81)	0.045
Complication	89 (36)			48 (39)	41 (33)	1.000
Transfusion	82 (35)			46 (37)	41 (33)	
Bleeding at puncture site	60 (24)			30 (24)	30 (24)	
Hemolysis related to ECPR	27 (11)			16 (13)	11 (9)	
Peripheral ischemia	2 (1)			2 (2)	0 (0)	
Infection	0 (0)			0 (0)	0 (0)	
TTM						
Completed†	168 (89)	22 (46)	<0.001	96 (91)	72 (88)	0.635
Target temperature (°C)	34 (34~34)	34 (34~34)	0.279	34 (34~34)	34 (34~34)	0.913
Time to achieve TT (h)	1.9 (1.0~3.5)	4.8 (3.4~6.0)	<0.001	2.0 (1.0~3.6)	1.4 (1.0~3.0)	0.700
TT maintenance (h)	24 (24~48)	24 (20~31)	0.123	24 (24~48)	24 (24~48)	0.605
Not indicated due to GCS >8	2 (1)	3 (6)	0.105	2 (2)	0 (0)	0.509
Discontinuation in ≤24 h	18 (10)	23 (48)	<0.001	9 (9)	10 (12)	0.726
Unstable hemodynamic status	14 (8)	18 (38)		6 (6)	8 (10)	
Irreversible brain damage	2 (1)	1 (2)		1 (1)	1 (1)	
Unknown	2 (1)	4 (8)		2 (2)	1 (1)	
IABP	173 (94)	17 (41)	<0.001	101 (96)	72 (90)	0.131
CAG	170 (90)	27 (56)	0.002	96 (91)	74 (90)	0.802
PCI	106 (57)	16 (37)	0.149	58 (55)	48 (59)	0.655

Data given as n (%) or median (IQR). †TTM was considered completed when target core body temperature could be maintained at 32~34°C for >24 h. CAG, coronary angiography; ECPR, extracorporeal cardiopulmonary resuscitation; GCS, Glasgow coma scale; IABP, intra-aortic balloon pump; PCI, percutaneous coronary intervention; ROSC, return of spontaneous circulation; TT, target temperature; TTM, targeted temperature management. Other abbreviations as in Table 1.

cessful in 228 patients (91%). Of the 157 patients assigned to receive CCPR, 19 patients (12%) received ECPR, which was non-compliant with group assignment. Except for the cause of cardiac arrest, there were no significant differences in prehospital parameters between the ECPR and CCPR groups (**Table 1**). The median time from cardiac arrest to hospital arrival was 32 min (IQR, 25–39 min). The most common cause of cardiac arrest was acute coronary syndrome (ACS; 60%, n=245). Of the 245 ACS patients, 171 (70%) underwent coronary angiography (CAG) and 132 (54%) underwent percutaneous coronary intervention (PCI). Of the patients with sustained VF/pVT treated with ECPR (n=127); patients with conversion from initial VF/pVT to PEA/asystole treated with ECPR (n=123); patients with sustained VF/pVT treated with CCPR (n=56); and patients with conversion from VF/pVT to PEA/asystole treated with CCPR (n=101), there were no significant differences in baseline clinical characteristics except for the rate of patients who received shock and the number of delivered shocks in the prehospital setting (**Table 1**).

Neurological Outcome and Survival
With a 99% follow-up rate (n=404), the proportion of patients with favorable neurological outcome at 6 months was significantly higher in the subgroup with sustained VF/pVT treated with ECPR (20%, 25/126) vs. conversion from initial VF/pVT to PEA/asystole treated with ECPR (3%, 4/122) vs. sustained VF/VT treated with CCPR (4%, 2/56), vs. conversion from initial VF/pVT to PEA/asystole treated

with CCPR (1%, 2/100; P<0.001; **Table 2**).

On Kaplan-Meier analysis, there was a significantly higher 6-month survival rate in the subgroup with sustained VF/pVT treated with ECPR (32%, 42/126) vs. conversion from initial VF/pVT to PEA/asystole treated with ECPR (12%, 14/122), vs. sustained VF/pVT treated with CCPR (7%, 4/56), vs. conversion from initial VF/pVT to PEA/asystole treated with CCPR (2%, 2/100; P<0.001; **Figure 2**).

Stratifying by cardiac rhythm, on multivariable mixed logistic regression analysis with each institution modeled as a random intercept, an ECPR strategy significantly increased the proportion of patients with favorable neurological outcome at 6 months in the patients with sustained VF/pVT (OR, 7.35; 95% CI: 1.58–34.09; **Table 3**). Moreover, time-dependent IPTW propensity score analysis based on time to ECPR implementation also identified a similar association (absolute treatment effect 18.4%; 95% CI: 0.9–35.9). These associations, however, were not observed in patients with conversion from initial VF/pVT to PEA/asystole (**Table 2**).

Subsequent Treatment
Treatment subsequent to ROSC was performed for 237 patients. Of these, a higher proportion in the ECPR group had ROSC after cardiac arrest compared with the CCPR group (76%, 189/250 vs. 30%, 48/157, P<0.001). **Table 3** lists the subsequent treatments that patients with ROSC received. The ECPR group had a significantly higher pro-
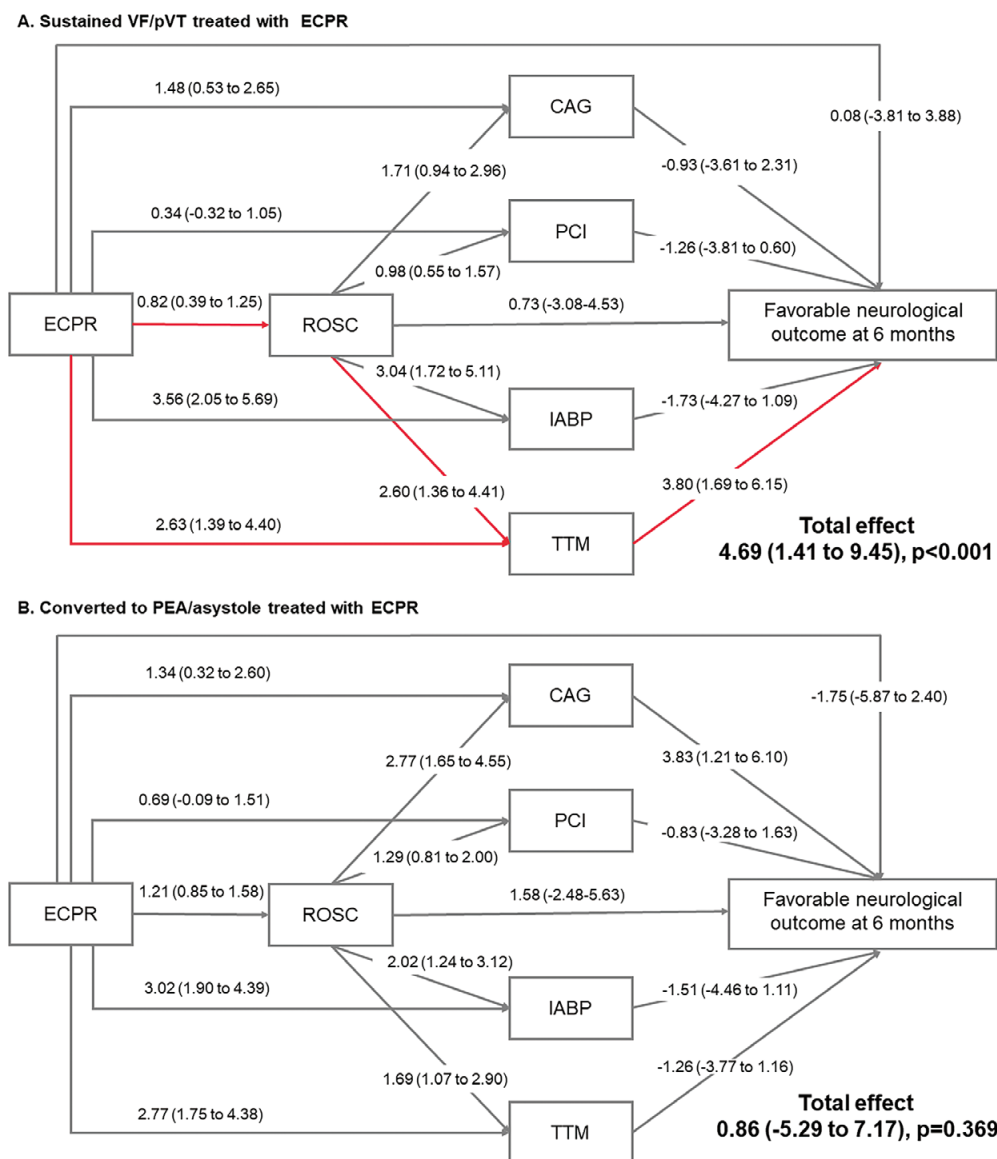
Figure 3. Paths from extracorporeal cardiopulmonary resuscitation (ECPR) to favorable neurological outcome based on structural equation modeling with probit models, in patients with (**A**) sustained ventricular fibrillation/pulseless ventricular tachycardia (VF/pVT) and (**B**) pulseless electrical activity (PEA)/asystole. Data given as probit coefficients (95% Bayesian credible interval). Red lines, statistically significant paths from ECPR to favorable neurological outcome at 6 months. CAG, coronary angiography; IABP, intra-aortic balloon pump; PCI, percutaneous coronary intervention; ROSC, return of spontaneous circulation; TTM, targeted temperature management.

portion of patients who completed TTM than the CCPR group (89%, 168/189 vs. 46%, 22/48, P<0.001). In the CCPR group, TTM was discontinued in 38% of patients with ROSC (18/48) due to unstable hemodynamic status. In the ECPR group, subgroups stratified by cardiac rhythm did not differ significantly in initial ECPR maximum flow, complications related to ECPR, or prevalence of completed TTM, intra-aortic balloon pump (IABP), CAG, or PCI (**Table 3**).

Stratifying by cardiac rhythm, on mixed logistic regression model analysis ECPR increased the rate of IABP implementation and completed TTM in both the sustained VF/pVT

and conversion from initial VF/pVT to PEA/asystole subgroups (**Supplementary Table 2**). Moreover, in patients with sustained VF/pVT, on SEM analysis a significant total effect of ECPR on the primary outcome was seen (probit coefficient, 4.69; 95% Bayesian credible interval 1.14–9.45). Regarding the role of subsequent treatment in ECPR, the causal pathway from ECPR to the primary outcome was significant only through TTM and through ROSC via TTM (**Figure 3A**). In contrast, these associations were not observed in patients with conversion from initial VF/pVT to PEA/asystole (**Figure 3B**).

Discussion

This secondary analysis of data from SAVE-J, the largest prospective, multicenter, observational study of ECPR, showed that sustained VF/pVT before initiation of ECPR is a significant predictor of favorable neurological outcome when an ECPR strategy is used in patients with OHCA unresponsive to CCPR. If the rhythm converts from initial VF/pVT to PEA/asystole before initiation of ECPR, no neurological benefit was observed with ECPR.

In 2008, an observational study by Chen et al reported that ECPR is associated with long-term survival benefit compared with CCPR in patients with IHCA.[1] In 2014, the original unadjusted primary intention-to-treat analysis of SAVE-J data showed that ECPR is more strongly associated with favorable neurological outcome at 6 months than CCPR in patients with OHCA (11.2% vs. 2.6%, P<0.001).[3] It remains unclear, however, whether some subgroups of OHCA patients benefit more from ECPR. A recent meta-analysis by Debaty et al reported that shockable cardiac rhythm on initial ECG was associated with better outcomes for ECPR recipients after OHCA.[15] The cardiac rhythm inclusion criterion of the SAVE-J trial was based only on VF/pVT on initial ECG. In contrast, a considerable percentage of OHCA patients with VT/pVT on initial ECG often convert to PEA/asystole at some point during EMS treatment or after admission to the resuscitation center. No studies on the association between cardiac rhythm conversion during CPR and ECPR have been reported to date.

We have demonstrated that sustained VF/pVT before initiation of ECPR is a significant predictor of favorable neurological outcome after adjusting for confounding factors and selection bias (Table 2). In contrast, in this analysis, patients with rhythm conversion from initial VF/pVT to PEA/asystole prior to initiation of ECPR did not benefit from this advanced resuscitation strategy. Given that oxygen delivery and myocardial energy substrates might persist in patients with sustained VF/pVT,[16] establishment of sufficient perfusion of the injured myocardium with ECPR may lead to a higher chance of ROSC and organ recovery. In 2002 Weisfeldt and Becker proposed the 3-phase model of CPR (electrical phase, circulatory phase, and metabolic phase) to reflect the time-sensitive progression of resuscitation physiology in patients with an initial rhythm of VF/pVT.[17] Especially during the metabolic phase, depletion of oxygen and energy substrates in the myocardium may cause rhythm conversion from initial VF/pVT to PEA/asystole. If the time from collapse to ECPR implementation is prolonged, rhythm conversion from initial VF/pVT to PEA/asystole would occur more frequently with CCPR.[16,17] In this study, the median time from collapse to hospital arrival was similar between the patients with sustained VF/pVT and the patients with rhythm conversion from initial VF/pVT to PEA/asystole in the ECPR group (32 min, IQR, 23–40 min vs. 32 min, IQR, 26–38 min; P=0.625). The rate of bystander CPR for patients with sustained VF/pVT was higher than the rate for patients with rhythm conversion from initial VF/pVT to PEA/asystole, but the difference was not statistically significant (53%, 67/127 vs. 37%, 45/123, P=0.052). Based on these results, we speculate that in OHCA patients with VF/pVT on initial ECG, favorable neurological outcomes may depend on duration of sustained VF/pVT, during which oxygen and energy substrates of the myocardium

persist, rather than absolute time from collapse to implementation of ECPR. In most cases of OHCA, the comorbidities, the causes and the exact timing of cardiac arrest are not known at hospital arrival. In contrast, cardiac rhythm conversion can be an easily understood parameter for predicting outcome during an emergency, even if these types of information are not known. Moreover, a higher rate of bystander CPR might sustain VF/pVT in these patients. Therefore, in OHCA patients with initial VF/pVT, an advanced resuscitation strategy may include high-quality CPR to sustain VF/pVT in the prehospital setting, rapid transport to a facility capable of providing ECLS and prehospital ECLS on the field before conversion to PEA/asystole. This novel finding provides further insights into the primary results from SAVE-J and may be generalized to an advanced resuscitation strategy incorporating ECPR for OHCA patients refractory to CCPR at high-quality resuscitation centers around the world.

In 2015, the International Liaison Committee on Resuscitation and AHA guidelines gave TTM at 32–36°C for 24 or 48 h a class I recommendation for OHCA.[18,19] In the present study, 89% of patients in the ECPR group completed TTM, compared with only 46% in the CCPR group (Table 3). In the CCPR group, TTM was discontinued in 38% of patients with ROSC due to unstable hemodynamic status. After adjusting for prehospital parameters, the ECPR group had a significantly higher rate of completed TTM than the CCPR group (Supplementary Table 2). Regarding subsequent treatment, on SEM analysis ECPR was shown to affect neurological outcome at 6 months only through TTM in patients with sustained VF/pVT, but not through IABP, CAG, or PCI (Figure 3A). Based on these results, we speculate that the advantages of ECPR over CCPR with respect to favorable neurological outcome are due to maintaining stable hemodynamic status in patients with OHCA during CPR or after ROSC, as a bridge to TTM, which leads to a synergistic effect on favorable neurological outcome. Recently, Yannopoulos et al described a cohort of 72 cardiac arrest patients with refractory VF/pVT transported to the University of Minnesota cardiac catheterization laboratory.[20] They found that a comprehensive treatment strategy incorporating ECPR, TTM, CAG, and PCI might improve survival and neurological outcomes (42%). This is consistent with the present results. In addition, we found that this synergic effect between ECPR and TTM was not observed in patients with conversion from initial VF/pVT to PEA/asystole (Figure 3B).

Study Limitations

One limitation of this study is that it was not a randomized controlled trial. Thus, there is the possibility of selection bias related to the quality of treatment between the participating institutions. To address this possibility, we adjusted for clustering difference and the potential selection bias by using a mixed logistic regression model and time-dependent IPTW propensity score analysis. Second, we were not able to evaluate the quality of CPR in the prehospital setting. According to the All-Japan Utstein Registry of the Fire and Disaster Management Agency, however, there were no significant differences in the rate of favorable neurological outcome after OHCA of cardiac origin observed between the ECPR and CCPR groups in their domestic regions (Japanese prefectures) during the study period (Supplementary Table 3).[5,7] Third, in this

study, only 454 patients from 36 centers were included and the overall survival rate was low. This low survival might be explained by the highly selective inclusion criteria for the SAVE-J trial and the presence of refractory OHCA. According to the All-Japan Utstein Registry of the Fire and Disaster Management Agency, they comprised only 2.8% of all OHCA patients in Japan during the study period, that is, a median of 3.9 OHCA patients met the SAVE-J trial inclusion criteria at each institution per year. Thus, the number of patients enrolled in SAVE-J is consistent with data from across Japan during the enrollment period. Moreover, the rate of overall survival (33%) in patients with VF/pVT on initial ECG at 1 month was similar to that in European cities during the study period (**Supplementary Table 3**).[21] Finally, >90% of patients with ECPR underwent IABP in the SAVE-J trial. When the SAVE-J trial began in 2008, IABP was still being recommended by the AHA guidelines for cardiogenic shock, but it has since been downgraded to a class III recommendation.

Conclusions

The most promising candidates for ECPR among patients with refractory OHCA might be those with sustained VF/pVT before initiation of ECPR. In contrast, patients with conversion from VF/pVT to PEA/asystole before initiation of ECPR might be unlikely to experience favorable neurological outcomes with this advanced resuscitation strategy as currently implemented.

References

1. Chen YS, Lin JW, Yu HY, Ko WJ, Jerng JS, Chang WT, et al. Cardiopulmonary resuscitation with assisted extracorporeal life-support versus conventional cardiopulmonary resuscitation in adults with in-hospital cardiac arrest: An observational study and propensity analysis. *Lancet* 2008; **372:** 554–561.
2. Morimura N, Sakamoto T, Nagao K, Asai Y, Yokota H, Tahara Y, et al. Extracorporeal cardiopulmonary resuscitation for out-of-hospital cardiac arrest: A review of the Japanese literature. *Resuscitation* 2011; **82:** 10–14.
3. Sakamoto T, Morimura N, Nagao K, Asai Y, Yokota H, Nara S, et al. Extracorporeal cardiopulmonary resuscitation versus conventional cardiopulmonary resuscitation in adults with out-of-hospital cardiac arrest: A prospective observational study. *Resuscitation* 2014; **85:** 762–768.
4. King JC Jr, Stoddard JJ, Gaglani MJ, Moore KA, Magder L, McClure E, et al. Effectiveness of school-based influenza vaccination. *N Engl J Med* 2006; **355:** 2523–2532.
5. Kitamura T, Iwami T, Kawamura T, Nagao K, Tanaka H, Hiraide A, et al. Nationwide public-access defibrillation in Japan. *N Engl J Med* 2010; **362:** 994–1004.
6. ECC Committee, Subcommitees and Task Forces of the American Heart Association. 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2005; **112**(24 Suppl): IV1–IV203.
7. Nagao K, Nonogi H, Yonemoto N, Gaieski DF, Ito N, Takayama M, et al. Duration of Prehospital resuscitation efforts after out-of-hospital cardiac arrest. *Circulation* 2016; **133:** 1386–1396.
8. Cummins RO, Chamberlain DA, Abramson NS, Allen M, Baskett PJ, Becker L, et al. A statement for health professionals from a task force of the American Heart Association, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, and the Australian Resuscitation Council. *Circulation* 1991; **84:** 960–975.
9. Jennett B, Bond M. Assessment of outcome after severe brain damage. *Lancet* 1975; **1:** 480–484.
10. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med* 2015; **34:** 3661–3679.
11. Dondo TB, Hall M, West RM, Jernberg T, Lindahl B, Bueno H, et al. Beta-blockers and mortality after acute myocardial infarction in patients without heart failure or ventricular dysfunction. *J Am Coll Cardiol* 2017; **69:** 2710–2720.
12. Andersen LW, Granfeldt A, Callaway CW, Bradley SM, Soar J, Nolan JP, et al. Association between tracheal intubation during adult in-hospital cardiac arrest and survival. *JAMA* 2017; **317:** 494–506.
13. Nguyen TQ, Webb-Vargas Y, Koning IM, Stuart EA. Causal mediation analysis with a binary outcome and multiple continuous or ordinal mediators: Simulations and application to an alcohol intervention. *Struct Equ Modeling* 2016; **23:** 368–383.
14. Laptook AR, Shankaran S, Tyson JE, Munoz B, Bell EF, Goldberg RN, et al. Effect of therapeutic hypothermia initiated after 6 hours of age on death or disability among newborns with hypoxic-ischemic encephalopathy: A randomized clinical trial. *JAMA* 2017; **318:** 1550–1560.
15. Debaty G, Babaz V, Durand M, Gaide-Chevronnay L, Fournel E, Blancher M, et al. Prognostic factors for extracorporeal cardiopulmonary resuscitation recipients following out-of-hospital refractory cardiac arrest: A systematic review and meta-analysis. *Resuscitation* 2017; **112:** 1–10.
16. Kern KB, Garewal HS, Sanders AB, Janas W, Nelson J, Sloan D, et al. Depletion of myocardial adenosine triphosphate during prolonged untreated ventricular fibrillation: Effect on defibrillation success. *Resuscitation* 1990; **20:** 221–229.
17. Weisfeldt ML, Becker LB. Resuscitation after cardiac arrest: A 3-phase time-sensitive model. *JAMA* 2002; **288:** 3035–3038.
18. Callaway CW, Soar J, Aibiki M, Bottiger BW, Brooks SC, Deakin CD, et al. Part 4: Advanced life support: 2015 International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Circulation* 2015; **132:** S84–S145.
19. Callaway CW, Donnino MW, Fink EL, Geocadin RG, Golan E, Kern KB, et al. Part 8: Post-cardiac arrest care: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2015; **132:** S465–S482.
20. Yannopoulos D, Bartos JA, Raveendran G, Conterato M, Frascone RJ, Trembley A, et al. Coronary artery disease in patients with out-of-hospital refractory ventricular fibrillation cardiac arrest. *J Am Coll Cardiol* 2017; **70:** 1109–1117.
21. Grasner JT, Lefering R, Koster RW, Masterson S, Bottiger BW, Herlitz J, et al. EuReCa ONE-27 Nations, ONE Europe, ONE Registry: A prospective 1 month analysis of out-of-hospital cardiac arrest outcomes in 27 countries in Europe. *Resuscitation* 2016; **105:** 188–195.

Supplementary Files

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-18-1257