

## Original Article

# Prediction of the neurological outcome using regional cerebral oxygen saturation in patients with extracorporeal cardiopulmonary resuscitation after out-of-hospital cardiac arrest: a multicenter retrospective cohort study

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**Aim:** To investigate the association between regional cerebral oxygen saturation (rSO<sub>2</sub>) and neurological outcomes in extracorporeal cardiopulmonary resuscitation (ECPR) patients after out-of-hospital cardiac arrest (OHCA).

**Methods:** We used data from the Japan-Prediction of Neurological Outcomes in Patients Post-Cardiac Arrest Registry. This registry included consecutive comatose patients after OHCA who were transferred to 15 hospitals in Japan from 2011 to 2013. Our primary end-point was a good neurological outcome (cerebral performance categories 1 or 2) at 90 days after OHCA.

**Results:** Among the enrolled patients, 121 (6.3%) received ECPR. Eleven (9.1%) had a good neurological outcome. Receiver operating characteristic curve analysis revealed the optimal cut-off value as >16%. Good neurological outcomes were observed in 19.6% (9/46) and 2.7% (2/74) of patients with rSO<sub>2</sub> >16% and rSO<sub>2</sub> ≤16%, respectively.

**Conclusion:** The neurological outcome of ECPR patients differed according to their rSO<sub>2</sub> values. When considering ECPR, the rSO<sub>2</sub> value could be important in addition to other criteria. Further studies that focus on ECPR patients and serial rSO<sub>2</sub> values are needed.

**Key words:** Cardiac arrest, cardiopulmonary resuscitation, extracorporeal cardiopulmonary resuscitation, neurological outcome, regional cerebral oxygen saturation

## INTRODUCTION

DESPITE RECENT IMPROVEMENTS in advanced resuscitation therapy and post-cardiac arrest care, out-of-hospital cardiac arrest (OHCA) remains a major public health problem.<sup>1</sup> The survival rate after OHCA is low, and

neurological deficits are common among survivors due to ischemic brain injury.<sup>2</sup>

Extracorporeal cardiopulmonary resuscitation (ECPR) is an effective technique to maintain organ perfusion while treating reversible causes of cardiac arrest and recovering spontaneous circulation. The 2015 American Heart Association guidelines recommended considering ECPR in select cardiac arrest patients if rapid induction is available.<sup>3</sup> However, the indication criteria for ECPR vary, and there is no global consensus. Although the indication for ECPR should be carefully considered because of the invasiveness of ECPR and the high costs associated, quick judgment is needed to maximize ECPR efficacy. A previous systematic review showed that shockable rhythm and shorter CPR duration might be good neurological predictors in ECPR patients;<sup>4</sup> however, the quality of evidence was low.

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Recent studies reported that the value of regional cerebral oxygen saturation (rSO<sub>2</sub>) could be useful to assess cerebral oxygen perfusion during CPR<sup>5,6</sup> and predict neurological outcomes in cardiac arrest patients.<sup>7–9</sup> These studies focused on whole cardiac arrest populations; however, the characteristics of patients with ECPR appear to be different from those without ECPR. Although it could be a prognostic factor for ECPR patients, few reports have assessed the rSO<sub>2</sub> value of ECPR patients.<sup>10</sup> Therefore, this study investigated the association between the rSO<sub>2</sub> value and neurological outcome in patients treated with ECPR after OHCA.

## METHODS

### Study design and data source

**T**HIS WAS A secondary analysis of prospectively collected registry data of consecutive OHCA patients who were transferred to 15 tertiary emergency care hospitals in Japan between May 2011 and August 2013, based on the Japan-Prediction of Neurological Outcomes in Patients Post-Cardiac Arrest (J-POP) Registry.<sup>7,11</sup> The database includes pre- and in-hospital data collected from the emergency medical service (EMS) system and the medical records according to the Utstein style. The inclusion criteria of the J-POP registry were unresponsive OHCA patients during and after resuscitation on hospital arrival. Exclusion criteria were trauma, accidental hypothermia, age <18 years, previous completion of the “Do Not Attempt Resuscitation” form, and a Glasgow Coma Scale (GCS) score of >8 on arrival at the hospital. The details of the protocol and main results of the J-POP Registry have been published previously.<sup>7,11,12</sup>

According to the Emergency Life Guards Act, all EMS providers in Japan are obligated to perform CPR, and qualified EMS providers are authorized to intubate OHCA patients and administer i.v. adrenaline before hospital arrival.

Immediately after hospital arrival, two disposal probes for a near-infrared spectrometer (INVOS 5100C; Covidien, Boulder, CO, USA) were bilaterally positioned at the patient’s forehead. After several seconds of stable recordings, rSO<sub>2</sub> was monitored for at least 1 min, and the lowest rSO<sub>2</sub> value was used for the study. The lower limit of measurable rSO<sub>2</sub> was 15%, and rSO<sub>2</sub> values below this threshold were regarded as 15%. To evaluate the usefulness of rSO<sub>2</sub> values in the decision to undertake ECPR, we analyzed patients who received ECPR after OHCA.

### Treatment and outcomes

Advanced life support was provided according to the national guidelines for resuscitation. The study protocol

basically predefined that ECPR would be induced in patients with initially documented ventricular fibrillation or pulseless ventricular tachycardia, if sustained return of spontaneous circulation (ROSC) for at least 20 min was not achieved. If sustained ROSC was achieved, targeted temperature management was induced with blood pressure over 90 mmHg and a GCS score of 3–8. The final decision to undertake all procedures was made by the attending physician.

The primary end-point was a good neurological outcome at 90 days after cardiac arrest. Neurological outcomes were evaluated using cerebral performance categories (CPC);<sup>13</sup> CPC 1 (good performance) and CPC 2 (moderate disability) were defined as “good neurological outcomes”, and CPC 3 (severe disability), CPC 4 (vegetative state), and CPC 5 (brain death or death) as “poor neurological outcomes” according to the Utstein-style guidelines.<sup>14,15</sup> The CPC of an individual patient was determined by at least two physicians who were blinded to the patient’s rSO<sub>2</sub> readings at hospital arrival. A detailed definition of the parameters has been previously published.<sup>7,11,12</sup>

### Statistical analysis

Age and rSO<sub>2</sub> values are expressed as median (interquartile range), and other continuous variables are presented as means (standard deviation). Categorical variables are described as numbers (percentages). Receiver operating characteristic (ROC) curve analysis was carried out, and the optimal rSO<sub>2</sub> cut-off value for good neurological outcomes in patients with ECPR was determined by the Youden index.<sup>16</sup> We divided the patients with ECPR into two groups according to this cut-off point and compared the neurological outcomes and patient backgrounds.

All analyses were undertaken with SAS version 9.4 for Windows (SAS Institute, Cary, NC, USA). The two-sided significance level was set at  $P < 0.05$  for each analysis.

### Sensitivity analysis

We carried out a sensitivity analysis that was restricted to ECPR patients with initially detected shockable rhythm and time to hospital arrival within 45 min, considering the previously reported prognostic factors for neurological outcomes.<sup>4</sup> We also compared the neurological outcomes at cut-off values that we had previously used.<sup>17</sup>

## RESULTS

**O**F 3,086 CONSECUTIVE OHCA patients, 1,921 adult patients whose rSO<sub>2</sub> values had been recorded using near-infrared spectroscopy were enrolled according to the

protocol of the J-POP Registry. Among those, 121 patients (6.3%) received ECPR (Fig. 1). Patient demographics are summarized in Table 1. A total of 11 patients (9.1%) had a good neurological outcome at 90 days after OHCA. As a result, 43% of patients with ECPR initially had detected non-shockable rhythm such as pulseless electrical activity and asystole.

The ROC analysis indicated an optimal rSO<sub>2</sub> cut-off value of >16% for predicting a good neurological outcome (area under the ROC curve 0.76, 95% confidence interval [CI], 0.61–0.91; sensitivity 0.82, 95% CI, 0.52–0.95; specificity 0.66, 95% CI, 0.57–0.75; Fig. 2). We stratified patients into two groups with rSO<sub>2</sub> >16% and rSO<sub>2</sub> ≤16%. The patient characteristics and neurological outcomes of these two groups are shown in Table 1. A good neurological outcome was observed in 19.6% (9/46) and 2.7% (2/75) of patients with rSO<sub>2</sub> >16% and rSO<sub>2</sub> ≤16%, respectively ( $P = 0.003$ ).

In the sensitivity analysis restricted to ECPR patients with initial shockable rhythm and time to hospital arrival within 45 min, patients with rSO<sub>2</sub> values >16% showed significantly better neurological outcomes than those with rSO<sub>2</sub> ≤16% (26.9% versus 3.5%, respectively;  $P = 0.021$ ). Using additional cut-off values, we categorized ECPR patients into four groups: rSO<sub>2</sub> ≤16%, rSO<sub>2</sub> 17–40%, rSO<sub>2</sub> 41–60%, and rSO<sub>2</sub> >60%. The proportion of good neurological outcome was 2.7%, 12.5%, 33.3%, and 40.0%, respectively (Fig. 3).

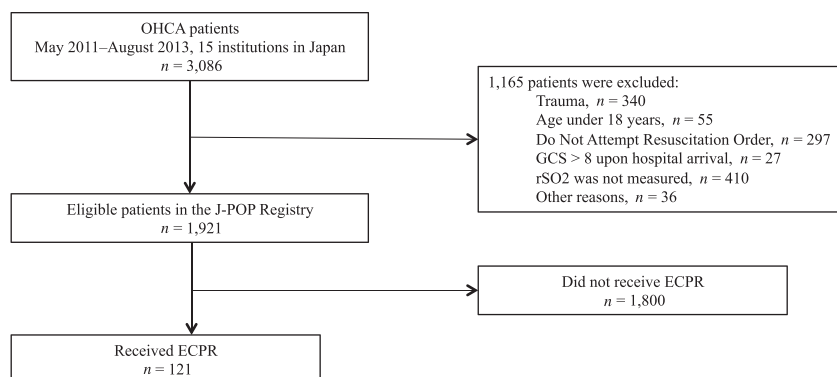
## DISCUSSION

**O**UR RESULTS SHOWED that neurological outcomes of ECPR patients differ according to their rSO<sub>2</sub> values on hospital arrival. This result was maintained when limited

to patients with initial shockable rhythm and time to hospital arrival within 45 min. However, the results of this study should be carefully interpreted because our data only included the initial rSO<sub>2</sub> values, and serial change from the baseline might also provide important information to predict patient outcomes.<sup>6</sup>

A prior systematic review on predictors of neurological outcome for adult patients with ECPR showed that initial shockable rhythm and CPR duration were independent predictors;<sup>4</sup> however, the rSO<sub>2</sub> value was not analyzed. Recent reviews concluded that rSO<sub>2</sub> values during CPR could predict neurological outcome,<sup>18</sup> and potentially facilitate clinical decision-making.<sup>19</sup> Our study also indicated that there was a significant difference in neurological outcomes between patients with rSO<sub>2</sub> >16% and rSO<sub>2</sub> ≤16%. The difference was maintained among patients with initial shockable rhythm and time to hospital arrival within 45 min. This suggests that the rSO<sub>2</sub> value could be important in predicting the neurological outcome in ECPR patients in addition to previously reported parameters.

Because predicting the neurological outcome in ECPR patients is difficult, it is challenging for emergency physicians to establish the indication for ECPR. Although patient characteristics, such as type of bystander-witness status, origin of cardiac arrest, and time to hospital arrival, did not differ between the groups in our study, the neurological outcome was significantly different depending on the rSO<sub>2</sub> value. Those parameters are usually included in ECPR indication criteria;<sup>20–22</sup> however, they may be insufficient to decide for or against ECPR use. The rSO<sub>2</sub> value on hospital arrival could comprehensively reflect the reversibility of brain function impairments at the time, which might be influenced by the quality of prehospital CPR in addition to



**Fig. 1.** Study flow diagram. ECPR, extracorporeal cardiopulmonary resuscitation; GCS, Glasgow Coma Scale; J-POP, Japan-Prediction of Neurological Outcomes in Patients Post-Cardiac Arrest; OHCA, out-of-hospital cardiac arrest; rSO<sub>2</sub>, regional cerebral oxygen saturation.

**Table 1.** Characteristics and neurological outcomes of patients who received extracorporeal cardiopulmonary resuscitation

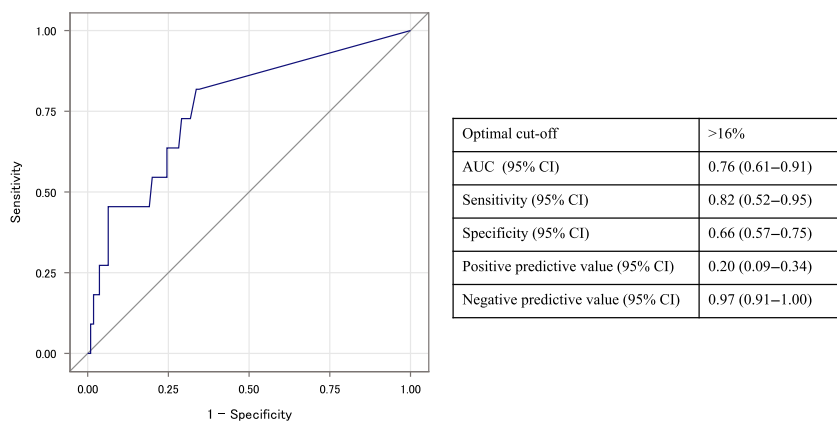
Characteristic	Total (n = 121)	Patients with rSO <sub>2</sub> ≤16% (n = 75)	Patients with rSO <sub>2</sub> >16% (n = 46)
Age, years; median (IQR)	60 (47, 70)	59 (44, 67)	64 (48, 72)
Male sex, n (%)	93 (76.9)	55 (73.3)	38 (82.6)
rSO <sub>2</sub> on arrival at the hospital, median (IQR)	15 (15, 24)	15 (15, 15)	35 (21, 42)
Locations of cardiac arrest, n (%)			
Home	53 (43.8)	32 (42.7)	21 (45.7)
Nursing home/assisted living	2 (1.7)	1 (1.3)	1 (2.2)
Public building	17 (14.1)	10 (13.3)	7 (15.2)
Street	16 (13.2)	8 (10.7)	8 (17.4)
Others	33 (27.3)	24 (32.0)	9 (19.6)
Type of bystander-witness status, n (%)			
No witness	32 (26.5)	21 (28.0)	11 (23.9)
Family member	42 (34.7)	27 (36.0)	15 (32.6)
EMS	12 (9.9)	8 (10.7)	4 (8.7)
Other	35 (28.9)	19 (25.3)	16 (34.8)
Bystander-initiated CPR, n (%)	56 (46.3)	36 (48.0)	20 (43.5)
Presumed cardiac origin, n (%)	95 (78.5)	58 (77.3)	37 (80.4)
Initially documented rhythms at the scene of cardiac arrest, n (%)			
VF/pulseless VT	66 (54.6)	36 (48.0)	30 (65.2)
PEA	32 (26.5)	22 (29.3)	10 (21.7)
Asystole	20 (16.5)	17 (22.7)	3 (6.5)
Prehospital procedures, n (%)			
Advanced airway devices	59 (48.8)	43 (57.3)	16 (34.8)
Intravenous adrenaline administration	34 (28.1)	23 (30.7)	11 (23.9)
Defibrillation	71 (58.7)	39 (52.0)	32 (69.6)
Emergency call to hospital arrival, min; mean (SD)	33 (12.3)	33 (9.8)	34 (15.7)
Rhythms at rSO <sub>2</sub> measurement, n (%)			
VF/pulseless VT	39 (32.2)	21 (28.0)	18 (39.1)
PEA	30 (24.8)	18 (24.0)	12 (26.1)
Asystole	43 (35.5)	35 (46.7)	8 (17.4)
Others (pulses detectable at hospital arrival)	9 (7.4)	1 (1.3)	8 (17.4)
Procedures after hospital arrival, n (%)			
Therapeutic hypothermia	78 (64.5)	46 (61.3)	32 (69.6)
Coronary angiography	68 (56.2)	38 (50.6)	30 (65.2)
Primary percutaneous coronary intervention	32 (26.4)	16 (21.3)	16 (34.8)
Neurological outcomes at 90 days after OHCA			
CPC 1, good performance	10 (8.3)	2 (2.7)	8 (17.4)
CPC 2, moderate disability	1 (0.8)	0 (0.0)	1 (2.2)
CPC 3, severe disability	2 (1.7)	1 (1.3)	1 (2.2)
CPC 4, vegetative state	6 (5.0)	3 (4.0)	3 (6.5)
CPC 5, death	102 (84.3)	68 (91.9)	33 (71.7)

Lower limit of measurable regional cerebral oxygen saturation (rSO<sub>2</sub>) was 15%.

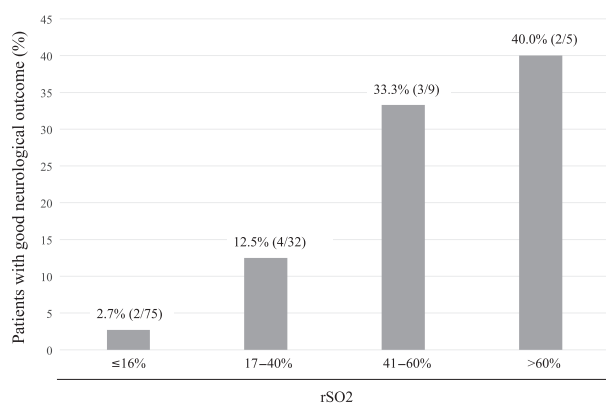
CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; EMS, emergency medical service; IQR, interquartile range; OHCA, out-of-hospital cardiac arrest; PEA, pulseless electrical activity; SD, standard deviation; VF, ventricular fibrillation; VT, ventricular tachycardia.

previously established parameters. To define an indication for ECPR in OHCA patients, we should consider not only these parameters but also the rSO<sub>2</sub> value.

Our determined cut-off for the rSO<sub>2</sub> value was much lower than previously described in OHCA patients. Most studies reported that rSO<sub>2</sub> values in patients with a good



**Fig. 2.** Receiver operating characteristic analysis of the regional cerebral oxygen saturation values in patients with extracorporeal cardiopulmonary resuscitation. AUC, area under the curve; CI, confidence interval.



**Fig. 3.** Proportion of patients with good neurological outcome following extracorporeal cardiopulmonary resuscitation, according to each regional cerebral oxygen saturation (rSO<sub>2</sub>) value.

neurological outcome were above 30%,<sup>19,23–25</sup> which might suggest terminating resuscitation could be considered for patients whose rSO<sub>2</sub> values were constantly below 30% during resuscitation.<sup>26</sup> However, most patients included in those studies did not receive ECPR. After ECPR induction, vital organs can receive almost as much perfusion as in ROSC, and ECPR can recover more severe patients with much lower rSO<sub>2</sub> values.

Our study has several limitations. First, because of the small number of patients, we could not undertake a multivariate analysis. We carried out a sensitivity analysis restricted to patients with initial shockable rhythm and time to hospital arrival within 45 min; the rSO<sub>2</sub> value was still associated with neurological outcome. Second, our registry data included only the initial rSO<sub>2</sub> value. Recently, Takegawa *et al.* reported that the trend pattern of the rSO<sub>2</sub> value

during CPR was important for patient outcome prediction.<sup>6</sup> We agree that only the initial rSO<sub>2</sub> value might be insufficient to assess the prognosis of ECPR patients. However, few studies have assessed the rSO<sub>2</sub> value among ECPR patients, and it is uncertain which rSO<sub>2</sub> value (mean, initial, highest, and serial change from the baseline) should be used for ECPR indication. Further studies focused on ECPR patients and assessing several types of rSO<sub>2</sub> values are needed. Third, the time from OHCA to ECPR initiation was not available. Because all included hospitals were tertiary emergency care hospitals in Japan, we assumed that ECPR could be rapidly implemented. We assessed the time from emergency call to hospital arrival instead; however, this might be insufficient. Fourth, the lower limit of measurable rSO<sub>2</sub> was 15% in the device used in this study, and there were no *in vivo* data to confirm the accuracy of lower rSO<sub>2</sub> values. Several previous studies have used this device for cardiac arrest patients whose rSO<sub>2</sub> values were very low;<sup>27,28</sup> however, lower values could provide more information, especially for ECPR patients. Further studies using devices that can accurately measure lower values are required. Finally, in other countries, where the EMS system and the severity of OHCA patients could differ from those in Japan, the results of this study might not be applicable.

## CONCLUSION

**I**N PATIENTS RECEIVING ECPR, the neurological outcome differed according to their rSO<sub>2</sub> values. It could be important to consider the rSO<sub>2</sub> value in addition to other criteria when deciding the indication for ECPR. Further studies focusing on ECPR patients and serial rSO<sub>2</sub> values are needed to identify the significance of rSO<sub>2</sub> monitoring as an indication criterion for ECPR.



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## DISCLOSURE

Approval of the research protocol: The study protocol was approved by the Ethics Committee of the Kyoto University Graduate School and Faculty of Medicine (No. R1666; 6 September 2018), which also waived the requirement for informed consent.

Informed consent: N/A.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

Conflict of interest: T. Seki received personal fees from Pfizer outside the submitted work. K. Nishiyama has conducted an investigator-sponsored study (Covidien, Japan) entitled “Pre-hospital rSO<sub>2</sub> Study” (“Pre-hospital Resuscitation for Sustaining Cerebral Oxidation: Observational Cohort Study”). K. Kawakami received honoraria from Shin Nippon Biomedical Laboratories, research funds from Olympus, Sumitomo Dainippon Pharma, Bayer Yakuhin, Stella Pharma, Novartis Pharma, CMIC, Amgen Astellas BioPharma, Suntory Beverage & Food, and Medical Platform, advisor fees from JMDC, and holds stocks in Real World Data. There are no patent products under development or marketed products relevant to those companies to declare.

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