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Clinical Paper

Noninvasive regional cerebral oxygen saturation for neurological prognostication of patients with out-of-hospital cardiac arrest: A prospective multicenter observational study[☆,☆☆]

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ABSTRACT

Aim: To investigate the association between regional brain oxygen saturation (rSO_2) at hospital arrival and neurological outcomes at 90 days in patients with out-of-hospital cardiac arrest (OHCA).
Methods: The Japan-Prediction of neurological Outcomes in patients post cardiac arrest (J-POP) registry is a prospective, multicenter, cohort study to test whether rSO_2 predicts neurological outcomes after OHCA. We measured rSO_2 in OHCA patients immediately after hospital arrival using a near-infrared spectrometer placed on the forehead with non-blinded fashion. The primary endpoint was "neurological outcomes" at 90 days after OHCA.
Results: EMS providers are not permitted to terminate CPR in the field in Japan, and so most patients with OHCA who are treated by EMS personnel are transported to emergency hospitals. Among 1017 OHCA patients, 672 patients including 52 comatose patients with pulses detectable (8%) and 620 cardiac arrest patients (92%) at hospital arrival were enrolled prospectively and consecutively. Twenty-nine

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patients with good neurological outcome had a significantly higher value of rSO_2 at hospital arrival than 643 patients with poor neurological outcome (mean [±SD] 55.6 ± 20.8% vs. 19.7 ± 11.0%, $p < 0.001$). Receiver operating curve analysis indicated an optimal rSO_2 cutoff point of >42% for predicting good neurological outcome, with sensitivity 0.79 (95% confidence interval [CI], 0.60–0.92), specificity 0.95 (95% CI, 0.93–0.96), positive predictive value, 0.41 (95% CI, 0.28–0.55), negative predictive value, 0.99 (95% CI, 0.98–1.00), and area under the curve 0.90 (95% CI, 0.88–0.92).

Conclusion: The rSO_2 at hospital arrival can predict good neurological outcome at 90 days after OHCA.

1. Introduction

Sudden death from cardiac arrest is a major public health problem in industrialized countries.[1–4] The brain is the organ most vulnerable to ischemia, and global cerebral ischemia often results in poor neurological outcome for patients with out-of-hospital cardiac arrest (OHCA).[5] The 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care have emphasized that cardiocerebral resuscitation (CCR) is critically important to promote the survival of patients with OHCA.[1–4] A real-time indicator of cerebral perfusion or function during CCR efforts would be useful for estimating the chance of favorable rehabilitation after hospital discharge.[6,7]

Regional cerebral oxygen saturation (rSO_2) is a noninvasive indicator of cerebral perfusion. Even during cardiac arrest, rSO_2 is measurable because near-infrared spectroscopy (NIRS) does not require vascular pulsation.[8,9] Therefore, we conducted this prospective, multicenter, observational study to validate the ability of rSO_2 at hospital arrival to predict neurological outcomes at 90 days[10] after OHCA.

2. Methods

2.1. Study design

The Japan-Prediction of neurological Outcomes in patients Post-cardiac arrest (J-POP) Registry is a prospective, multicenter, cohort study. From May 15, 2011, through January 31, 2012, 13 tertiary emergency hospitals in Japan participated in this study. Of 1017 OHCA patients who were transported to the hospital, 672 were enrolled prospectively and consecutively. The inclusion criteria were unresponsive patients during and after resuscitation at hospital arrival after OHCA. The exclusion criteria were as follows: (1) trauma, (2) accidental hypothermia, (3) age under 18, (4) previous completion of the “Do Not Attempt Resuscitation” form, and (5) a Glasgow Coma Scale (GCS) score of >8 at hospital arrival. The study protocol was approved by the institutional review board or ethics committee at each participating medical institution. The requirement of written informed consent was waived according to the guidelines.[11]

2.2. Emergency medical care system in Japan

All emergency medical service (EMS) providers perform cardiopulmonary resuscitation (CPR) according to the current CPR guidelines.[12,13] Emergency lifesaving technicians are permitted to insert tracheal tubes and to administer intravenous epinephrine.[1] However, EMS providers are not permitted to terminate CPR in the field.

2.3. Data collection

Using the Utstein style,[14] data were collected prospectively. Baseline patient characteristics and in-hospital information were collected from medical records and databases. Data management and statistical analyses were performed by an independent data coordinating center (Kyoto University Graduate School of Medicine, Kyoto, Japan).

Cardiac arrest was defined as the absence of spontaneous respiration, palpable pulse, and responsiveness to stimuli.[14,15] The arrest was presumed to be of cardiac origin unless it was caused by cerebrovascular disease, respiratory disease, external factors (e.g., drug overdose and asphyxia), or any other noncardiac factors. The cardiac or noncardiac origin was determined clinically by the physician in charge.

2.4. Procedures after hospital arrival

The CPR protocol is as described below. After arrival at the emergency department, all patients receive advanced life support (ALS) in accordance with the national guidelines for resuscitation. Patients, whose initially documented ECG rhythm was ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT), receive extracorporeal CPR using extracorporeal circulatory support or cardiopulmonary bypass if sustained return of spontaneous circulation (ROSC)—restoration of palpable pulse that is sustained for at least 20 min—was not obtained by standard ALS. For patients with sustained ROSC, therapeutic hypothermia is conducted if systolic blood pressure increases above 90 mmHg and the GCS score remains ≤8.[16]

2.5. Near-infrared spectroscopy procedures

Immediately after hospital arrival aiming within 3 min, two disposable probes of a near-infrared spectrometer (INVOS^{TM} 5100C, Covidien, Boulder, CO, USA) were applied carefully and bilaterally onto the patient’s forehead. rSO_2, once stabilized in several seconds, was monitored at least for 1 min with the probes, and the lowest rSO_2 reading was used.[8,9] The cerebral oximeter emits 2 wavelengths of near-infrared rays (730 and 805 nm) into the patient’s forehead, calculates spatial depth resolution by subtracting the shallow measurement from the deep, minimizes superficial signal contamination from the scalp and skull, and detects changes in oxygen saturation in the brain.[8,9] We could not blind investigators because the rSO_2 monitoring requires real-time visual confirmation during CCR efforts. Regardless of the rSO_2 readings, however, all patients received the best available therapy including post cardiac arrest interventions.[17]

2.6. Study endpoints

The primary endpoint was “neurological outcomes” at 90 days after OHCA according to the American Heart Association consensus statement,[10] which were categorized in accordance with Glasgow-Pittsburgh Cerebral Performance Categories described in the “Utstein style” guidelines[14]; the guidelines defined cerebral performance category (CPC) levels as follows: CPC 1 (good performance) and CPC 2 (moderate disability) as “good neurological

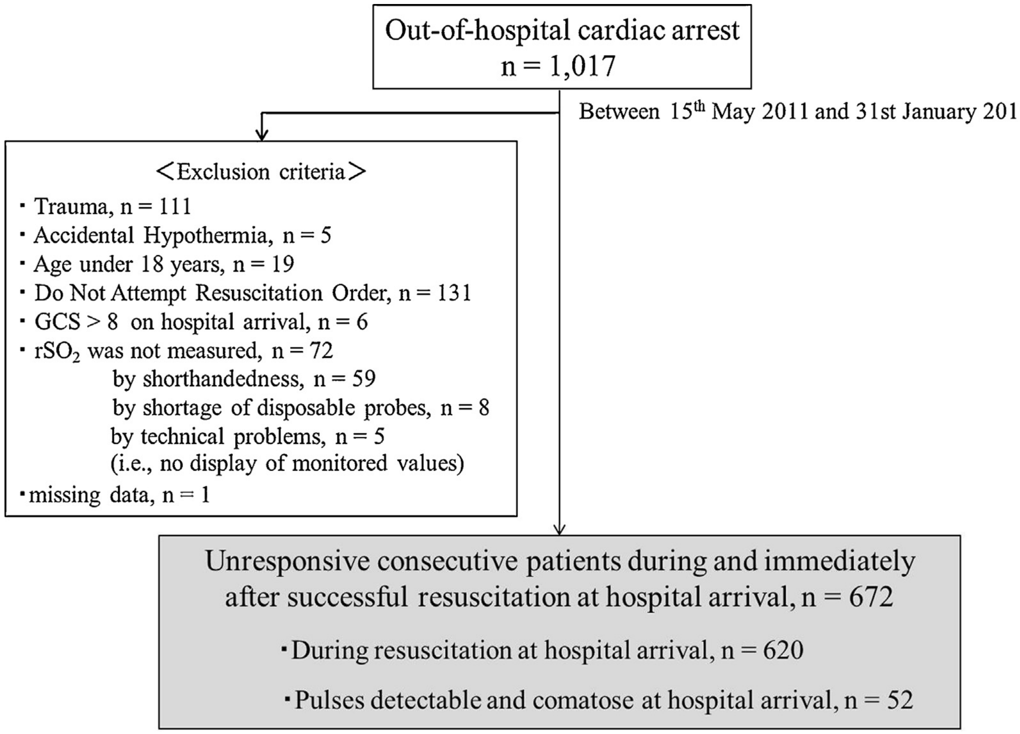

Fig. 1. Enrollment of study patients.

outcome"; and CPC 3 (severe disability), CPC 4 (vegetative state), and CPC 5 (brain death or death) as "poor neurological outcome". CPC was evaluated by more than two physicians in charge who were not aware of the rSO_2 readings at hospital arrival.

2.7. Statistical analyses

The unpaired *t*-test or the Mann–Whitney test was conducted for unpaired comparisons. The chi-square test and Fisher's exact test were made to examine differences between categorical variables. The ROC analysis was performed to evaluate the prognostic accuracy of good neurological outcome, and the optimal cutoff point was determined by estimating the Zero-One index. In patients to whom lactate and base excess (BE) were measured concurrently with rSO_2 at hospital arrival, we compared the AUC of rSO_2, lactate, and BE, and the method of DeLong et al.[18] was used to for the calculation of the standard error of the AUC and the difference between two AUCs. All statistical tests were two-tailed; a p value less than 0.05 was considered statistically significant.

The JMP software version 10.0.0 (SAS Institute, Cary, NC, USA), the MedCalc software version 12.3.0 (MedCalc Software, Gent, Belgium), and the STATA software version 11.1 (Stata Corp., College Station, TX, USA) were used by two authors (N.I. and K.N.) to make all statistical analyses. The primary authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

2.8. Roles of the funding source

The funding organizations had no role in study design, data analysis, data interpretation, writing of the article, or the decision to submit it for publication. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

3. Results

3.1. General characteristics

During the study period, we collected data on 1017 consecutive patients with OHCA who were referred to 13 tertiary emergency hospitals. Patients were excluded because of the following causes: 111 patients, cardiac arrest caused by trauma; 19 patients, age under 18; 131 patients, the completion of the "Do Not Attempt Resuscitation Order" form; six patients, a GCS score of >8 at hospital arrival; five patients, accidental hypothermia; one patient, missing data; and 72 patients, no monitoring of rSO_2 due to insufficient personnel (59), shortage of disposable probes (8), or technical problems (5, i.e., no display of monitored values). Consequently, we consecutively enrolled a total of 672 unresponsive patients during and after resuscitation at hospital arrival (Fig. 1). Table 1 shows the characteristics and neurological outcomes of patients; among them, 482 (71.7%) were pronounced dead in the emergency department. Of remaining 190 patients, 152 (22.6%) died after admission to the hospital, whereas 38 (5.7%) survived at 90 days after OHCA, with CPCs 1, 2, 3, and 4 in 23 (3.4%), 6 (0.9%), 1 (0.2%), and 8 patients (1.2%), respectively.

3.2. Regional cerebral oxygen saturation at hospital arrival

For the enrolled 672 patients, the mean (±SD) rSO_2 at hospital arrival was 21 ± 14%. Twenty-nine patients with good neurological outcome (CPC1, 2 at 90 days after OHCA) had a significantly higher value of rSO_2 at hospital arrival than 643 patients with poor neurological outcome (55.6 ± 20.8% vs. 19.7 ± 11.0%, $p < 0.001$) (Fig. 2). Fifty-two comatose patients with pulses detectable at hospital arrival had a significantly higher value of rSO_2 at hospital arrival than 620 patients with cardiac arrest at hospital arrival (51.0 ± 20.2% vs. 18.8 ± 9.5%, $p < 0.001$). One hundred eighty patients with transient or sustained ROSC after hospital arrival had a significantly higher value of rSO_2 at hospital arrival than 492

Table 1
Characteristics and neurological outcomes of 672 consecutive unresponsive patients during and after resuscitation at hospital arrival.

Characteristics	Total ($n = 672$)
Age—year, mean (SD)	71 (16)
Male gender—no. (%)	406 (60)
Locations of cardiac arrest—no. (%)	
Home	463 (69)
Nursing home/assisted living	61 (9)
Public building	33 (5)
Street	29 (4)
Others	86 (13)
Type of bystander-witness status—no. (%)	
No witness	361 (47)
Family members	227 (30)
EMS	48 (6)
Others	128 (17)
Bystander-initiated CPR—no. (%)	263 (39)
Types of origin—no. (%)	
Cardiac	351 (52)
Non-cardiac	321 (48)
Initially documented rhythms on the scene of cardiac arrest—no. (%)	
VF/pulseless VT	82 (12)
PEA	167 (25)
Asystole	423 (63)
Prehospital procedures—no. (%)	
Advanced airway devices	352 (52)
Intravenous epinephrine administration	126 (19)
Defibrillation	98 (15)
Emergency call to hospital arrival—min, mean (SD)	33 (12)
Rhythms at rSO_2 measurement—no. (%)	
VF/pulseless VT	25 (3.7)
PEA	114 (17)
Asystole	481 (71.6)
Others (pulses detectable at hospital arrival)	52 (7.7)
Procedures after hospital arrival—no. (%)	
Standard ALS	654 (97)
Extracorporeal CPR	40 (6)
Therapeutic hypothermia	81 (12)
Coronary angiography	63 (9)
Primary percutaneous coronary intervention	29 (4)
Neurological outcomes at 90 days after OHCA	
Survival (CPCs 1–4)	38 (5.6)
CPC 1, good performance	23 (3.4)
CPC 2, moderate disability	6 (0.9)
CPC 3, severe disability	1 (0.2)
CPC 4, vegetative state	8 (1.2)
Deaths (CPC 5)	634 (94.3)
Deaths pronounced in the emergency department	482 (71.7)
Deaths after hospital admission	152 (22.6)

ALS, advanced cardiac life-support; CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; EMS, emergency medical service; PEA, pulseless electrical activity; rSO_2, regional cerebral oxygen saturation; SD, standard deviation; VF, ventricular fibrillation; VT, ventricular tachycardia; OHCA, out-of-hospital cardiac arrest.

patients without ROSC ($28.7 \pm 19.1\%$ vs. $18.5 \pm 9.8\%$, $p < 0.001$). One hundred ninety patients who survived to hospital admission had a significantly higher value of rSO_2 at hospital arrival than 482 patients who were pronounced dead in the emergency department ($31.6 \pm 21.1\%$ vs. $17.2 \pm 5.3\%$, $p < 0.001$).

3.3. Relationship of regional cerebral oxygen saturation to neurological outcomes

The optimal cutoff point in the ROC analysis for predicting good neurological outcome in all 672 patients was rSO_2 >42%; sensitivity, 0.79 (95% CI, 0.60–0.92); specificity, 0.95 (95% CI, 0.93–0.96); positive predictive value, 0.41 (95% CI, 0.28–0.55); negative predictive value, 0.99 (95% CI, 0.98–1.00); AUC, 0.90 (95% CI, 0.88–0.92); and $p < 0.001$ (Fig. 3A).

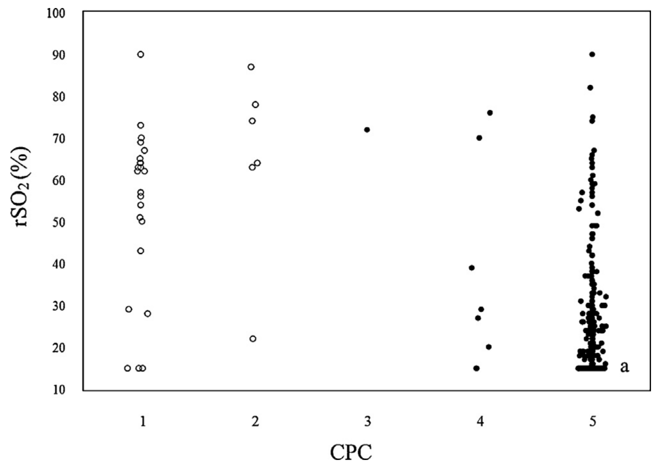

Fig. 2. Relationships between cerebral performance category and regional cerebral oxygen saturation. [a] Of 446 (66%) patients with an rSO_2 value of ≤15%, 441 were categorized to CPC 5. CPC, cerebral performance category; rSO_2, regional cerebral oxygen saturation.

ROC analysis of subsets of patients demonstrated that the optimal cutoff point for predicting good neurological outcome was rSO_2 >62% in comatose patients with pulses detectable at hospital arrival ($n = 52$) (AUC: 0.75 [95% CI, 0.61–0.86], $p < 0.001$ Fig. 3B). In patients with persistent cardiac arrest at hospital arrival, on the other hand, the optimal cutoff point for predicting good neurological outcome was rSO_2 >21% (AUC, 0.73 [95% CI, 0.69–0.76], $p = 0.04$, Fig. 3C).

In a post hoc analysis, we categorized all 672 subjects into three groups based on cutoff values of rSO_2 ≤15% ("15%" reading of this device is interpreted as equivalent to no detectable cortical oxygen[8,9]) and rSO_2 of >42% (optimal cutoff in ROC analysis above): patients with an rSO_2 ≤15% ($n = 449$); patients with an rSO_2 = 16–42% ($n = 167$); and patients with an rSO_2 >42% ($n = 56$). Good neurological outcome occurred in 3/449 (0.7%) with an rSO_2 value ≤15%; 3/167 (1.8%) with an rSO_2 value of 16–42%, and 23/56 (41%) with an rSO_2 value >42% (Fig. 4). A significant difference ($p < 0.001$) was found among categorical variables.

Among the 52 comatose patients with pulses detectable at hospital arrival, only 35 (67%) had rSO_2 value >42%, of whom 20 (57%) had good neurological outcome. Only 1 (6%) of 17 patients with rSO_2 value of ≤42%, had good neurological outcome (rSO_2 = 29%).

3.4. Comparisons of regional cerebral oxygen saturation, lactate, and base excess

In 633 patients (94%), lactate and BE were measured concurrently with rSO_2 at hospital arrival. The AUCs for rSO_2, lactate, and BE to predict good neurological outcome were 0.90 (95% CI, 0.88–0.92), 0.84 (95% CI, 0.80–0.86), and 0.79 (95% CI, 0.76–0.82), respectively (Table 2). The AUC was greater with respect to the prognostication of good neurological outcome for rSO_2 than for BE ($p = 0.007$).

4. Discussion

4.1. Regional cerebral oxygen saturation at hospital arrival and neurological outcomes at 90 days after OHCA

This study demonstrated that the rSO_2 at hospital arrival can predict good neurological outcome at 90 days after OHCA, with high specificity and positive predictive value (Figs. 3 and 4; Table 2). We determined that an rSO_2 value of >42% at hospital arrival was an optimal value for predicting good neurological outcome after OHCA. Furthermore, we note that the rSO_2 is a neurological

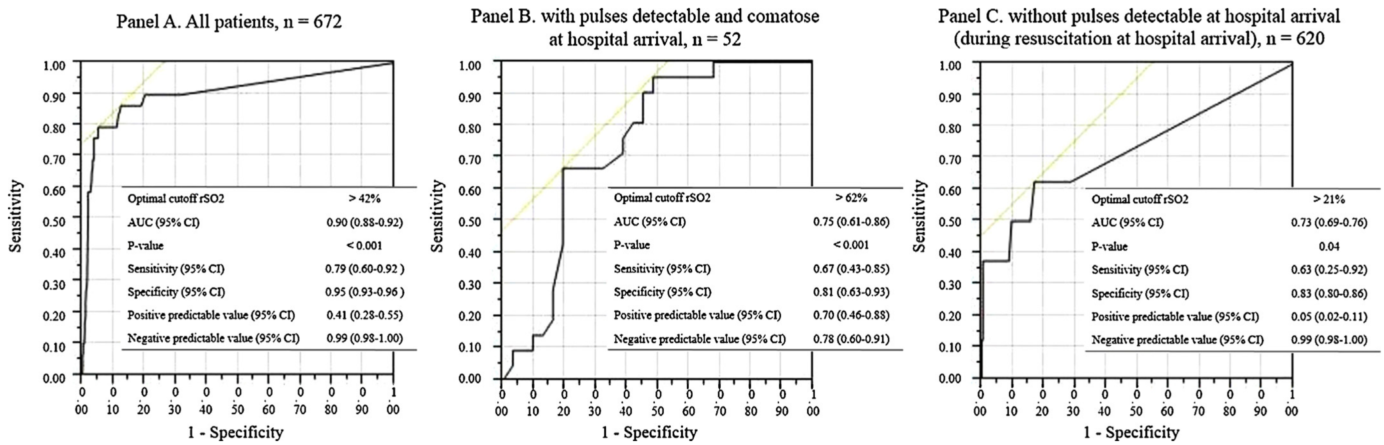

Fig. 3. The area under the receiver operating curve of regional cerebral oxygen saturation to predict good neurological outcome at 90 days after out-of-hospital cardiac arrest. Panel A: all unresponsive patients during and after resuscitation at hospital arrival ($n = 672$). Panel B: Comatose patients with pulses detectable at hospital arrival ($n = 52$). Panel C: Patients with cardiac arrest at hospital arrival ($n = 620$). CI, confidence interval; OHCA, out-of-hospital cardiac arrest; rSO_2, regional cerebral oxygen saturation.

Table 2
Characteristics of prognostic indexes for good neurological outcome at 90 days: regional cerebral oxygen saturation, lactate, and base excess.

	Optimal cutoff	AUC (95% CI)	*p*-Value	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	*p*-Value (versus rSO_2)
rSO_2	>42%	0.90 (0.88–0.92)	<0.001	0.79 (0.60–0.92)	0.95 (0.93–0.96)	0.41 (0.28–0.55)	0.99 (0.98–1.00)	N/A
Lactate	<10.2 mmol/L	0.82 (0.79–0.85)	<0.001	0.76 (0.61–0.88)	0.76 (0.72–0.79)	0.16 (0.11–0.22)	0.98 (0.97–0.99)	0.110
Base excess	>−17.4 mmol/L	0.79 (0.76–0.82)	<0.001	0.95 (0.84–0.99)	0.55 (0.51–0.58)	0.11 (0.08–0.15)	0.99 (0.98–1.00)	0.007

AUC, area under the curve; CI, confidence interval; PPV, positive predictive value; N/A, not applicable; NPV, negative predictive value; rSO_2, regional cerebral oxygen saturation.

prognostic index with advantages over lactate and base excess because of its noninvasiveness and immediate availability, as well as its specificity, positive predictive value, and AUC (Table 2). The AUC was greater for rSO_2 than for BE which had been shown to be associated with poor neurological outcome.[19,20] We could measure rSO_2 non-invasively immediately after hospital arrival, however it took at least 10 min to obtain the BE and lactate values at the hospital,[21,22] because of technical difficulties associated with blood sampling in patients with OHCA.

Even when patients had pulses detectable at hospital arrival, they had a very low chance of obtaining good neurological outcome unless achieving the rSO_2 >42% at hospital arrival. These data suggest that in patients without the rSO_2 value of >42%, regardless of the presence or absence of pulses detectable at hospital arrival,

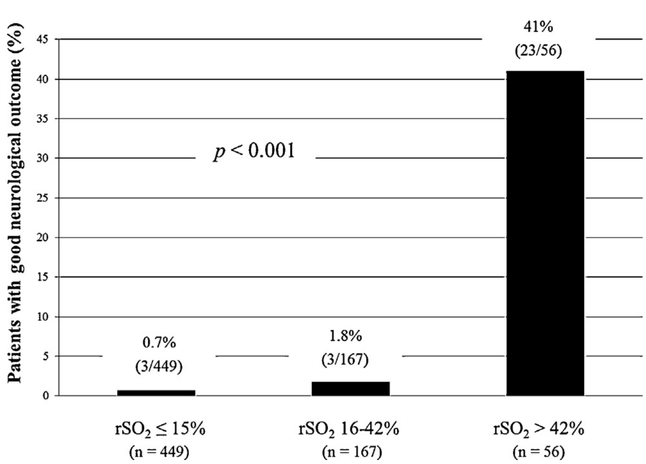

Fig. 4. Three regional cerebral oxygen saturation groups of patients with good neurological outcome at 90 days after out-of-hospital cardiac arrest. The chi-square test was used to examine differences between categorical variables rSO_2, regional cerebral oxygen saturation; OHCA, out-of-hospital cardiac arrest.

poor cerebral perfusion may persist from the onset of cardiac arrest through to the monitoring of rSO_2. Consequently, irreversible cerebral ischemia may preclude good recovery.

There is also increasing awareness that systematic post cardiac arrest intensive care can improve the likelihood of patient survival with good quality of life.[2] American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care emphasized that early prognostication of neurological outcome is an essential component of post-cardiac arrest care.[17,23–25] Our data suggest that rSO_2 may help predict good neurological outcome at 90 days in OHCA patients, which suggest rSO_2 monitoring was promising tool to select good candidates for post cardiac arrest intensive care containing therapeutic mild hypothermia, percutaneous coronary intervention, and extracorporeal cardiopulmonary resuscitation. On the other hands, in our data we found three patients with good neurological outcome at 90 days and low rSO_2 (≤15%). So even though this large cohort showed that low rSO_2 (≤15%) at hospital arrival indicate the high rate of poor neurological outcome at 90 days, we concluded from this study that this index could not be used alone for termination of resuscitative efforts because of the possibility of false prediction.

4.2. Limitations

This study has several limitations. First, although it would be desirable to continuously monitor rSO_2 prior to hospital arrival, the absence of a portable NIRS device made this impossible. Nevertheless, we consider that such monitoring of rSO_2 with a portable device to be available in the future would allow the real-time assessment of the effects of prehospital cardiovascular care on cerebral perfusion. Second, rSO_2 was monitored for a limited time after hospital arrival. We recognized that time-course changes in rSO_2 are an important factor for the prognostication of neurological outcomes. Therefore, we are prospectively collecting the rSO_2 data during postresuscitation care after hospital arrival. Of special note was the fact that good neurological outcome was considerably more likely in patients who had rSO_2 >42% at hospital arrival, although the duration of monitoring at hospital arrival was short ($\geq$1 min). Third, rSO_2 measured by NIRS reflects only cerebral perfusion at the superficial layers in the limited frontal lobe areas[8,9] and rSO_2 is not a reliable marker of brain tissue oxygen partial pressure. However, rSO_2 measured by NIRS is closely related to oxygen saturation in the jugular bulb that represents venous oxygenation of the whole brain.[26] Fourth, compared with previous studies, we found lower rate of patients whose initially documented rhythms on the scene of cardiac arrest were VT/VF and very poor clinical outcomes at 90 days, especially in patients with cardiac arrest at hospital arrival, since EMS providers are not permitted to terminate CPR in the field in Japan, most patients with OHCA who are treated by EMS personnel are transported to emergency hospitals. It is conceivable that the practice of EMS system could be modified using tools such as, rSO_2, in combination with existing termination of resuscitation rules.[27] Therefore, these results may not be generalizable to other countries with different EMS practices. Fifth, the small number of outcome events limits the ability to perform multivariable modeling. Sixth, as with any observational study, residual confounding could still account for at least part of the association. Seventh, we could not blind investigators because the rSO_2 monitoring requires real-time visual confirmation during CCR efforts. In pre-specified protocol all patients received the best available therapy including post cardiac arrest interventions regardless of the rSO_2 readings, however we could not eliminate the possibility that low rSO_2 might have influence the decision of stopping the resuscitation.

5. Conclusions

This prospective multicenter cohort study demonstrated that the rSO_2 at hospital arrival can predict good neurological outcome at 90 days after OHCA. Future studies should corroborate if rSO_2 can serve as a real-time indicator of cerebral perfusion during CCR and postresuscitation care for their improvement and for improvement of neurological outcome.

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Conflict of interest statement

All authors had no conflict of interest.

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Appendix A. Additional members of the J-POP Registry

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