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Clinical paper

Regional cerebral oxygen saturation monitoring for predicting interventional outcomes in patients following out-of-hospital cardiac arrest of presumed cardiac cause: A prospective, observational, multicentre study☆

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ABSTRACT

Aim: This study investigated the value of regional cerebral oxygen saturation (rSO_2) monitoring upon arrival at the hospital for predicting post-cardiac arrest intervention outcomes.
Methods: We enrolled 1195 patients with out-of-hospital cardiac arrest of presumed cardiac cause from the Japan-Prediction of Neurological Outcomes in Patients Post-cardiac Arrest Registry. The primary endpoint was a good neurologic outcome (cerebral performance categories 1 or 2 [CPC1/2]) 90 days post-event.
Results: A total of 68 patients (6%) had good neurologic outcomes. We found a mean rSO_2 of 21% ± 13%. A receiver operating characteristic curve analysis indicated an optimal rSO_2 cut-off of ≥40% for good

Abbreviations: AUC, area under the curve; CAG, coronary angiography; CI, confidence interval; CPC, Glasgow–Pittsburgh cerebral performance category; CPR, cardiopulmonary resuscitation; GCS, Glasgow Coma Scale; J-POP, Japan-Prediction of Neurological Outcomes in Patients Post-Cardiac Arrest; OHCA, out-of-hospital cardiac arrest; PCAI, post-cardiac arrest intervention; PCI, percutaneous coronary intervention; ROC, receiver operating characteristic; ROSC, return of spontaneous circulation; rSO_2, regional cerebral oxygen saturation; TH, therapeutic hypothermia.

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neurologic outcomes (area under the curve 0.92, sensitivity 0.81, specificity 0.96). Good neurologic outcomes were observed in 53% (55/103) and 1% (13/1092) of patients with high (≥40%) and low (<40%) rSO_2, respectively. Even without return of spontaneous circulation (ROSC) upon arrival at the hospital, 30% (9/30) of patients with high rSO_2 had good neurologic outcomes. Furthermore, 16 patients demonstrating ROSC upon arrival at the hospital and low rSO_2 had poor neurologic outcomes. Multivariate analyses indicated that high rSO_2 was independently associated with good neurologic outcomes (odds ratio = 14.07, $P < 0.001$). Patients with high rSO_2 showed favourable neurologic prognoses if they had undergone therapeutic hypothermia or coronary angiography (CPC1/2, 69% [54/78]). However, 24% (25/103) of those with high rSO_2 did not undergo these procedures and exhibited unfavourable neurologic prognoses (CPC1/2, 4% [1/25]).

Conclusion: rSO_2 is a good indicator of 90-day neurologic outcomes for post-cardiac arrest intervention patients.

Introduction

The advent of systematic bundled post-cardiac arrest interventions (PCAI) has increased the likelihood of patients surviving with good neurologic function after out-of-hospital cardiac arrests (OHCA).[1,2] In particular, therapeutic hypothermia (TH) and percutaneous coronary intervention (PCI) with emergent coronary angiography (CAG) have been reported to improve the prognoses of patients following OHCA of presumed cardiac cause.[2–4]

On the other hand, recent studies have shown that TH does not provide a beneficial effect following OHCA.[5,6] In fact, brain damage severity estimations and outcome prognoses for OHCA patients were found to be inaccurate,[7,8] implying that stratification before or imbalance corrections after randomisation might have been problematic in many previous studies. Additionally, the absence of appropriate measurements for brain damage severity estimations and prognosis determinations might make it difficult to perform stratified randomisations in clinical trials involving patients experiencing OHCA of presumed cardiac cause.[9] Thus, better prognostic factors are needed to elucidate 'true indications' of PCAI outcomes following such events.

Regional cerebral oxygen saturation (rSO_2) is a measure of cerebral perfusion that is obtained noninvasively via near-infrared spectroscopy and monitored in patients during cardiac arrest since the instrument does not require vascular pulsation.[10,11] We previously reported that rSO_2, measured upon arrival at the hospital, might help predict neurologic outcomes in patients following OHCA.[12] However, few studies have focused on whether rSO_2 measurements are effective for estimating brain damage severity, for determining prognoses, or in the decision-making process for PCAI in patients who have experienced OHCA of presumed cardiac cause.[13] Therefore, this study aimed to evaluate the clinical usefulness of rSO_2 monitoring to estimate the severity of brain damage and determine the prognoses of patients following OHCA of presumed cardiac causes.

Methods

Study design and setting

The Japan-Prediction of Neurological Outcomes in Patients Post-cardiac Arrest (J-POP) Registry is a prospective multicentre cohort study, and 15 Japanese tertiary emergency care hospitals participated in the J-POP during the study period (15 May 2011 to 30 August 2013). The inclusion criterion was unresponsiveness during and after resuscitation upon arrival at the hospital following an OHCA. The exclusion criteria included (1) trauma, (2) accidental hypothermia, (3) age <18 years, (4) completion of the 'Do Not Attempt Resuscitation' form, and (5) a Glasgow coma scale (GCS) score >8 upon arrival at the hospital. The details of the J-POP registry design and main outcomes have been published elsewhere.[12]

To identify the value of emergency room rSO_2 measurements in the PCAI (including TH and CAG) decision-making process, we analysed 1195 consecutive patients with OHCA of presumed cardiac cause from the J-POP registry.

Emergency medical care in Japan

In Japan, emergency lifesaving technicians are permitted to insert tracheal tubes and administer intravenous adrenaline (epinephrine).[14] All emergency medical service providers perform cardiopulmonary resuscitation (CPR) according to the current CPR guidelines.[15,16] However, the providers are not permitted to terminate CPR in the field.

Procedures after arrival at the hospital

All patients received advanced life support in accordance with national guidelines. If sustained return of spontaneous circulation (ROSC), i.e. the restoration of a palpable pulse that is sustained for at least 20 min, was not obtained using standard advanced life support, patients with initially documented ventricular fibrillation or pulseless ventricular tachycardia received extracorporeal CPR and extracorporeal circulatory support or a cardiopulmonary bypass. If patients obtained sustained ROSC, TH was induced once their systolic blood pressure exceeded 90 mmHg and their GCS score was 3–8.[5,17,18] All procedural (e.g., extracorporeal CPR, CAG, PCI, and TH) and diagnostic decisions were made at the discretion of the attending physician(s).

Data collection

Data were prospectively collected according to the Utstein style.[19,20] Baseline patient characteristics and in-hospital data were collected from medical records and databases.

Cardiac arrest was defined as the absence of spontaneous respiration, a palpable pulse, and stimuli responsiveness.[19] The arrest was presumed to be of cardiac origin unless it was due to cerebrovascular disease, respiratory disease, external factors (e.g., drug overdose or asphyxia), or other non-cardiac factors.

Near-infrared spectroscopy

Upon arrival at the hospital, 2 disposable near-infrared spectrometer (INVOS™ 5100C; Covidien, Boulder, CO, USA) probes were carefully applied to both sides of the patient's forehead. After several seconds of stabilisation, rSO_2 was monitored using the probes for at least 1 min, and the lowest rSO_2 reading was recorded.[11,12,21]

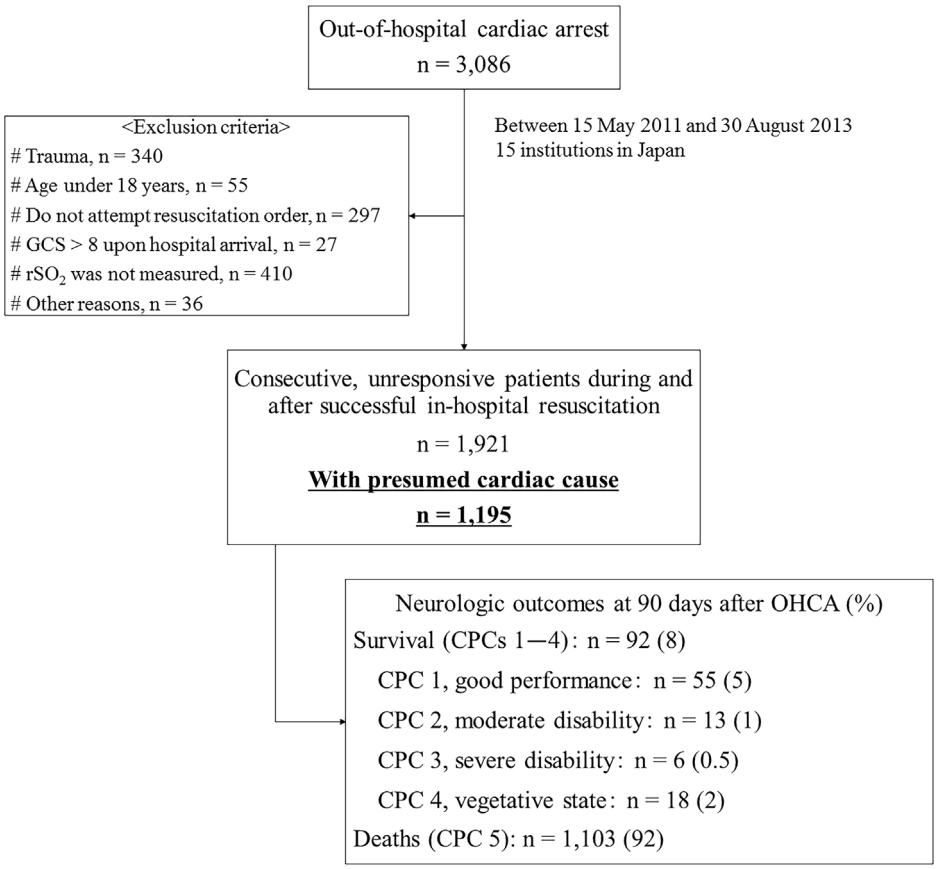


Fig. 1. Study flow. CPC, Glasgow–Pittsburgh cerebral performance category; GCS, Glasgow Coma Scale; OHCA, out-of-hospital cardiac arrest; rSO_2, regional cerebral oxygen saturation.

Study endpoints

The primary endpoint was the patients' 90-day neurologic outcomes, categorised according to the Glasgow–Pittsburgh cerebral performance categories (CPC), described in the Utstein style guidelines.[19] The guidelines categorise CPC 1 (good performance) and CPC 2 (moderate disability) as 'good neurologic outcomes', whereas CPC 3 (severe disability), CPC 4 (vegetative state), and CPC 5 (brain death or death) are defined as 'poor neurologic outcomes'. Individual patient CPC were determined by at least 2 physicians-in-charge who were blinded to the rSO_2 readings determined upon arrival at the hospital.

Statistical analyses

Unpaired *t*-tests or Mann–Whitney *U*-tests were conducted for unpaired comparisons. A χ^2 or Fischer's exact test was conducted to examine differences between categorical variables. Receiver operating characteristic curve (ROC) analysis was performed to evaluate the accuracy of predicted post-event good neurologic outcomes at 90 days. To analyse the effects of rSO_2 on neurologic outcomes, we developed logistic regression models that were adjusted for a pulse detectable upon arrival at the hospital, defibrillation before arrival at the hospital, bystander-initiated CPR, age, male sex, use of an advanced airway device before arrival at the hospital, and intravenous epinephrine administration before arrival at the hospital, in addition to rSO_2 upon arrival at the hospital. The JMP (version 10.0.0, SAS Institute, Cary, NC, USA) and STATA (version 11.1, Stata, College Station, TX, USA) software were used for all statistical analyses. All reported probability values are 2-tailed, and $P < 0.05$ was considered statically significant.

Ethical considerations

This study complied with the Declaration of Helsinki and conformed to the Guidelines for Epidemiologic Studies issued by the Ministry of Health, Labour, and Welfare of Japan. The study protocol was approved by the institutional review board or ethics committee of each participating medical institution, which also waived the requirement for informed consent.

Results

General patient characteristics and outcomes

During the study period, the registry accumulated data on 3086 consecutive OHCA patients who were referred to the 15 participating hospitals. In accordance with the study protocol, 1921 consecutive patients were enrolled, and 1195 patients with OHCA of presumed cardiac cause were included in the analysis (Fig. 1).

Table 1 shows the characteristics and neurologic outcomes of all patients. Among all patients, 880 (74%) were pronounced dead in the emergency department. Of the remaining 315 patients, 223 (19%) died after admission to the hospital, whereas 92 (8%) survived for at least 90 days. After 90 days, 55 (5%), 13 (1%), 6 (0.5%), and 18 (2%) patients were classified as CPC 1, 2, 3, and 4, respectively. Accordingly, 68 patients (6%) were considered to have good neurologic outcomes (CPC 1 or 2).

Table 1
Patient characteristics and neurologic outcomes of all patients, patients with regional cerebral oxygen saturation ≥40%, and <40% upon arrival at the hospital.

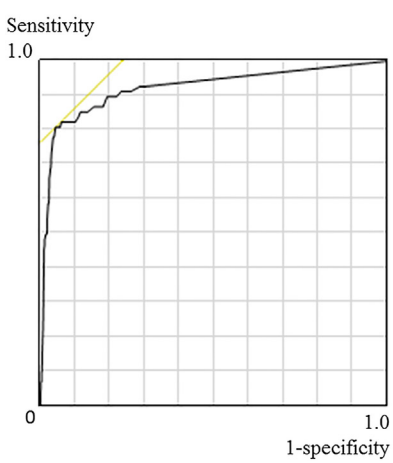
Characteristics	All patients (n = 1195)	Patients with rSO_2 <40% upon arrival at the hospital (n = 1092)	Patients with rSO_2 ≥40% upon arrival at the hospital (n = 103)	P-value*
rSO_2 at arrival at the hospital, mean (SD)	21 (13)	18 (5)	58 (12)	<0.001
Age, years, mean (SD)	72 (15)	73 (15)	65 (17)	<0.001
Male sex, n (%)	756 (63)	674 (62)	82 (80)	<0.001
Location of cardiac arrest, n (%)				
Home	813 (68)	771 (71)	42 (41)	<0.001
Nursing home/Assisted living	104 (9)	93 (9)	11 (11)	
Public building	55 (5)	42 (4)	13 (13)	
Street	94 (8)	76 (7)	18 (17)	
Other	129 (11)	110 (10)	19 (18)	
Type of bystander-witness status, n (%)				
No witness	641 (54)	621 (57)	20 (19)	<0.001
Family members	297 (25)	255 (23)	42 (41)	
EMS	63 (5)	53 (5)	10 (10)	
Other	194 (16)	163 (15)	31 (30)	
Bystander-initiated CPR, n (%)	292 (24)	236 (22)	56 (54)	<0.001
Initially documented rhythms on the scene of cardiac arrest, n (%)				<0.001
VF/pulseless VT	189 (16)	137 (13)	52 (50)	
PEA	257 (22)	237 (22)	20 (19)	
Asystole/unknown	749 (63)	718 (66)	31 (30)	
Pre-hospital procedures, n (%)				
Advanced airway devices	703 (59)	655 (60)	48 (47)	0.008
Intravenous adrenaline administration	341 (29)	314 (29)	27 (26)	0.59
Defibrillation	225 (19)	161 (15)	64 (62)	<0.001
Emergency call to arrival at the hospital, min, mean (SD)	35 (13)	35 (12)	33 (19)	<0.001
Rhythms at rSO_2 measurement, n (%)				
VF/pulseless VT	75 (6)	67 (6)	8 (8)	<0.001
PEA	214 (18)	203 (19)	11 (11)	
Asystole	817 (68)	806 (74)	11 (11)	
Others (pulse detectable upon arrival at the hospital)	89 (7)	16 (1)	73 (71)	
Procedures after arrival at the hospital, n (%)				
Extracorporeal CPR	95 (8)	84 (8)	11 (11)	0.28
Therapeutic hypothermia	154 (13)	86 (8)	68 (66)	<0.001
Coronary angiography	135 (11)	78 (7)	57 (55)	<0.001
Primary percutaneous coronary intervention	64 (5)	43 (4)	21 (20)	<0.001
CPC 1 or 2 at 90 days, n (%)	68 (6)	13 (1)	55 (53)	<0.001

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.
* Comparing patients with rSO_2 ≥40% and those with rSO_2 <40% upon arrival at the hospital.

Regional cerebral oxygen saturation upon arrival at the hospital

We observed a mean (±standard deviation) rSO_2 of 21 ± 13% upon arrival at the hospital (Table 1). According to the ROC curve analysis, the optimal cut-off for predicting good 90-day neurologic outcomes was an rSO_2 ≥40% (sensitivity 0.81, 95% confidence interval [CI] 0.70–0.89; specificity 0.96, 95% CI 0.94–0.97; area under the curve [AUC] 0.92, 95% CI 0.91–0.934; P < 0.001; Fig. 2).

The characteristics and neurologic outcomes of patients with rSO_2 ≥40% (n = 103) and <40% (n = 1092) upon arrival at the hospital



ROC analyses	
AUC (95% CI)	0.92 (0.91 – 0.94)
p-value	<0.001
Optimal cut-off	≥40%
Sensitivity (95% CI)	0.81 (0.70 – 0.89)
Specificity (95% CI)	0.96 (0.94 – 0.97)

CPC 1/2 at 90 days (%)			
	rSO2≥40%	rSO2<40%	p-value
Overall	55/103 (53)	13/1,092 (1)	<0.001
With ROSC upon hospital arrival	46/73 (63)	0/16 (0)	<0.001
Without ROSC upon hospital arrival	9/30 (30)	13/1,076 (1)	<0.001

Fig. 2. Receiver operating characteristic curve analysis of regional cerebral oxygen saturation upon arrival at the hospital as a predictor of good 90-day neurologic outcomes and neurologic outcomes according to regional cerebral oxygen saturation cut-off values. AUC, area under the curve; CI, confidence interval; CPC, Glasgow–Pittsburgh cerebral performance category; ROC, receiver operating characteristic; ROSC, return of spontaneous circulation; rSO_2, regional cerebral oxygen saturation.

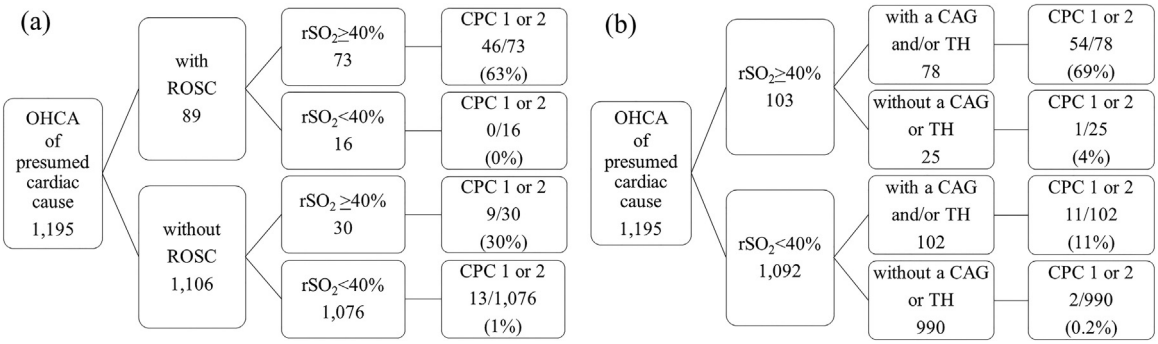


Fig. 3. Neurologic outcomes at 90 days, based on regional cerebral oxygen saturation cut-off values upon arrival at the hospital, in patients with an undetectable pulse or comatose patients with a detectable pulse upon arrival at the hospital, and in those undergoing or not undergoing therapeutic hypothermia and/or an emergent coronary angiography. (a) Neurologic outcomes (based on regional cerebral oxygen saturation cut-off values upon arrival at the hospital) in patients with an undetectable pulse or comatose patients with a detectable pulse upon arrival at the hospital; (b) neurologic outcomes at 90 days (based on regional cerebral oxygen saturation cut-off values upon arrival) at the hospital in patients undergoing or not undergoing therapeutic hypothermia and/or an emergent coronary angiography. CAG, coronary angiography, CPC, Glasgow–Pittsburgh cerebral performance category; OHCA, out-of-hospital cardiac arrest; rSO_2, regional cerebral oxygen saturation; TH, therapeutic hypothermia.

are shown in Table 1. Good neurologic outcomes were observed for 53% (55/103) and 1% (13/1092) of the patients with rSO_2 ≥40% and <40%, respectively (P < 0.001, Fig. 2).

Of the 89 comatose patients whose pulse could be detected upon arrival at the hospital, 73 had rSO_2 ≥40% and 16 had rSO_2 <40% (Fig. 3). Among these patients, 46 (63%) patients with high rSO_2 measures had good neurologic outcomes. None of these patients had low rSO_2 (P < 0.001). Of the 1106 patients whose pulse could not be detected upon arrival at the hospital, 30 had rSO_2 ≥40% and 1076 had rSO_2 <40% (Fig. 3). Among these patients, good neurologic outcomes were observed for 9 (30%) patients with high rSO_2 measures and 13 (1%) with low rSO_2 (P < 0.001).

Multivariate analyses for good neurologic outcomes

Multivariate analyses (adjusted for prehospital patient characteristics that showed a significant univariate association with outcomes) for good neurologic outcomes associated with prehospital variables and high (≥40%) rSO_2 indicated that high rSO_2 was independently associated with good neurologic outcomes (odds ratio 14.07, 95% CI 5.01–39.86, P < 0.001, AUC 0.96; Table 2).

Post-cardiac arrest interventions

Extracorporeal CPR, TH, CAG, and PCI were performed in 95 (8%), 154 (13%), 135 (11%), and 64 (5%) patients, respectively.

A higher proportion of patients who underwent TH had good neurologic outcomes (CPC1/2; 36%) than those not undergoing TH (CPC1/2; 1%, P < 0.001). Similarly, a higher proportion of patients who underwent a CAG had good neurologic outcomes (CPC1/2; 41%) than those who did not (CPC1/2; 1%, P < 0.001). Last, patients who underwent TH or a CAG showed significantly more favourable characteristics (Table 1).

Furthermore, more than two thirds of patients with rSO_2 ≥40% who underwent TH or a CAG showed good neurologic outcomes (CPC1/2; 69%; Fig. 3), and this rate of good neurologic outcomes rate was significantly higher than in patients with rSO_2 <40% who underwent the same procedures (CPC1/2; 11%; P < 0.001). However, among patients with rSO_2 ≥40%, 24% (25/103) did not undergo TH or a CAG. These patients exhibited a significantly lower rate of good neurologic outcomes than those undergoing TH or a CAG (CPC1/2; 4% vs. 69%, respectively; P < 0.001; Fig. 3). Many of these patients had other unfavourable characteristics such as older age, OHCA at home, no witnesses, no bystander-initiated CPR, no

Table 2
Multivariate analysis for good neurologic outcomes, adjusted for prehospital variables and regional cerebral oxygen saturation >40%.

	rSO_2 ≥40% upon arrival at the hospital	Good neurologic outcome 90 days after OHCA				
	n/total *n* (%)	*n*/total *n* (%)	Odds ratio (not adjusted) (95% CI)	*P* value	Odds ratio (adjusted for prehospital variables)* (95% CI)	*P*-value
rSO_2 ≥40% upon arrival at the hospital	N/A	55/103 (53)	95.1 48.66–185.86	<0.001	14.07 5.04–39.86	<0.001
Defibrillation before arrival at the hospital	64/225 (28)	53/225 (24)	19.62 10.81–35.60	<0.001	4.18 1.86–9.62	<0.001
Pulse detectable upon arrival at the hospital	73/89 (82)	46/89 (52)	52.71 29.15–95.32	<0.001	5.05 1.78–14.72	0.002
Bystander-initiated CPR	56/292 (19)	45/292 (15)	6.97 4.14–11.75	<0.001	3.20 1.52–6.88	0.002
Age (1 year older)	N/A	59/560 (11)	0.95 0.94–0.96	<0.001	0.97 0.95–0.99	0.01
Intravenous adrenaline administration before arrival at the hospital	27/341 (8)	12/341 (7)	0.52 0.26–0.95	0.032	0.52 0.19–1.31	0.17
Male sex	82/756 (11)	58/756 (8)	3.56 1.80–7.05	<0.001	2.01 0.75–5.94	0.17
Advanced airway devices before arrival at the hospital	48/703 (7)	24/703 (3)	0.36 0.22–0.60	<0.001	0.68 0.61–1.52	0.35

CI, confidence interval; CPR, cardiopulmonary resuscitation; N/A, not applicable; OHCA, out-of-hospital cardiac arrest.

* Adjusted for the following variables: pulse detectable at arrival at the hospital, defibrillation before arrival at the hospital, bystander-initiated CPR, age, male sex, use of advanced airway devices before arrival at the hospital, and intravenous adrenaline administration before arrival at the hospital.

Table 3
Characteristics of patients with high regional cerebral oxygen saturation (>40%) upon arrival at the hospital undergoing or not undergoing therapeutic hypothermia and/or an emergent coronary angiography.

Characteristics	Underwent therapeutic hypothermia and/or an emergent coronary angiography (n = 78)	Did not undergo therapeutic hypothermia and/or an emergent coronary angiography (n = 25)	P-value
rSO_2 upon arrival at the hospital, mean (SD)	60 (12)	51 (8)	<0.001
Age, years, mean (SD)	61 (15)	76 (18)	<0.001
Male sex, n (%)	65 (83)	17 (68)	0.15
Location of cardiac arrest, n (%)			<0.001
Home	26 (3)	16 (64)	
Nursing home/assisted living	5 (6)	6 (24)	
Public building	13 (17)	0 (0)	
Street	17 (22)	1 (4)	
Others	17 (22)	2 (8)	
Type of bystander-witness status, n (%)			<0.001
No witness	9 (12)	11 (44)	
Family members	31 (40)	11 (44)	
EMS	8 (10)	2 (8)	
Others	30 (38)	1 (4)	
Bystander-initiated CPR, n (%)	48 (61)	8 (32)	0.012
Initially documented rhythms on the scene of cardiac arrest, n (%)			<0.001
VF/pulseless VT	48 (62)	4 (16)	
PEA	10 (13)	10 (40)	
Asystole/unknown	20 (26)	11 (44)	
Pre-hospital procedures, n (%)			
Advanced airway devices	33 (42)	15 (60)	0.17
Intravenous adrenaline administration	15 (19)	12 (48)	0.008
Defibrillation	59 (76)	5 (20)	<0.001
Emergency call to arrival at the hospital, min, mean (SD)	32 (20)	36 (13)	0.01
Rhythms at rSO_2 measurement, n (%)			
VF/pulseless VT	6 (8)	2 (8)	
PEA	6 (8)	5 (20)	
Asystole	4 (5)	7 (28)	
Others (pulses detectable at arrival at the hospital)	62 (79)	11 (44)	
CPC 1 or 2 at 90 days, n (%)	54 (69)	1 (4)	<0.001

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

shockable rhythms, and no detectable pulse upon arrival at the hospital (Table 3).

Discussion

Our results show that high rSO_2 upon arrival at the hospital predicted good 90-day neurologic outcomes with high sensitivity, specificity, and AUC (optimal cut-off, $rSO_2 \geq 40\%$) in patients experiencing OHCA of presumed cardiac cause. These data are consistent with our previous report on all non-trauma OHCA patients in the J-POP Registry.[12] Half of the patients (55/108, 51%) with $rSO_2 \geq 40\%$ upon arrival at the hospital had good neurologic outcomes. Surprisingly, even if a pulse was not detectable upon arrival at the hospital, 30% of patients (9/30) with high rSO_2 demonstrated good neurologic outcomes. In contrast, none of the patients (0/19) with low rSO_2 had good neurologic outcomes, even if a pulse was detected upon arrival at the hospital. These compelling results show that rSO_2 monitoring is a promising method for selecting good candidates for PCAI (including TH, CAG, and PCI). To the best of our knowledge, this is the first report demonstrating the clinical usefulness of rSO_2 measurements for estimating brain damage severity and predicting outcomes in patients with OHCA of presumed cardiac origin.

As reported by Ito et al. 2/446 (0.4%) patients demonstrated good 90-day neurologic outcomes despite having low rSO_2 (15%) upon arrival at the hospital, implying that rSO_2 values alone cannot be used to determine whether resuscitative efforts should be terminated. Therefore, rSO_2 monitoring is useful for determining which patients will likely have good neurologic outcomes following OHCA of presumed cardiac cause (i.e. which patients are good PCAI candidates).[12]

Many studies have shown strong positive effects of bundled PCAI for improving post-cardiac arrest outcomes.[1,2,22] Another multicentre registry study in Japan reported that 55% of OHCA patients had good neurologic prognoses after PCAI.[23] In the present study, up to 69% of patients with $rSO_2 \geq 40\%$ showed good neurologic prognoses if they underwent PCAI. Thus, monitoring rSO_2 in the emergency room, following OHCA of presumed cardiac cause, provides a good indication of the 90-day neurologic outcomes following PCAI. However, in the present study, approximately 25% patients with high rSO_2 did not undergo TH or a CAG and these patients exhibited a significantly lower rate of good neurologic outcomes than those undergoing TH or a CAG (CPC1/2; 4% vs. 69%, respectively; $P < 0.001$; Fig. 3). High rSO_2 values upon hospital arrival indicated that the patients did not suffer from severe hypoxic cerebral damage. Thus, we hypothesised that rSO_2 was an intermediate factor in the process of cerebral damage formation after OHCA, and that high rSO_2 values upon hospital arrival indicated that the patients might be good candidates for PCAI even if they had unfavourable characteristics. In fact, as unfavourable characteristics were relatively common among these patients, PCAI might have been underutilised in these individuals. Further studies are needed to determine whether patients in this group are good candidates for PCAI.

TH at a target temperature of 33 °C was recently reported to not confer a benefit over TH at a target temperature of 36 °C,[6] implying the overuse of PCAI. Rittenberger et al.[24] remarked that future studies should continue to define patient subgroups that would benefit from specific therapies and clarify protocols for such interventions, based on each patient's illness, including a mandatory estimation of brain damage severity. Further studies are needed to clarify whether rSO_2 monitoring in the emergency room is useful for

predicting brain damage severity and making decisions regarding PCAI administration.

This study has several limitations. Although we previously reported that continuous rSO_2 monitoring would be desirable prior to arrival at the hospital, the absence of portable near-infrared spectroscopy devices makes this impossible.[12] Second, near-infrared spectroscopy rSO_2 measurements reflect only cerebral perfusion in the superficial layers of limited frontal lobe areas, and rSO_2 is not a reliable marker of brain tissue oxygen partial pressure.[10–12] Third, we could not blind the investigators to the rSO_2 values because rSO_2 monitoring requires real-time visual confirmation. As per a pre-specified protocol, all patients received the best available therapy, regardless of their rSO_2[12]; however, we could not eliminate the possibility that low rSO_2 might have influenced the decision to terminate resuscitation. Fourth, as emergency medical service providers in Japan are not permitted to terminate CPR, most OHCA patients who are treated by these personnel are transported to emergency departments. Thus, a very small proportion of patients with documented rhythms at the scene of cardiac arrest demonstrated ventricular tachycardia/fibrillation and had very poor 90-day neurologic outcomes. Hence, the international validity of this study might be limited. Finally, this study was not randomised, and to assess the predictive value of a clinical tool, precise validation cohorts are needed to verify our observations.

Conclusions

In conclusion, our study shows that $rSO_2 \geq 40\%$ upon arrival at the hospital predicted good 90-day neurologic outcomes in patients suffering OHCA of presumed cardiac cause, even if a pulse was undetectable upon arrival at the hospital. Patients with $rSO_2 \geq 40\%$ upon arrival at the hospital who underwent PCAI showed remarkably favourable neurologic prognoses. Thus, rSO_2 monitoring following OHCA of presumed cardiac cause is an indicator of 90-day neurologic outcomes following PCAI. However, about 25% of patients with $rSO_2 \geq 40\%$ in our study did not undergo TH or a CAG and had quite poor neurologic outcomes, implying that PCAI might be underutilised in these cases. Future studies are necessary to evaluate the efficiency of rSO_2 monitoring during the PCAI decision-making process following OHCA of presumed cardiac cause.

Conflict of interest statement

Dr. Nishiyama conducted an investigator-sponsored study (Covidien, Japan) entitled 'Pre-hospital Resuscitation for Sustaining Cerebral Oxidation: Observational Cohort Study'. The other authors declare no conflicts of interest.

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