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## Clinical paper

# Association between regional cerebral oxygen saturation and outcome of patients with out-of-hospital cardiac arrest: An observational study

Takeshi Kawaguchi<sup>a</sup>, Jumpei Tsukuda<sup>a</sup>, Rika Onoe<sup>a</sup>, Kenichiro Morisawa<sup>a</sup>,  
Toru Yoshida<sup>a</sup>, Koichi Hayashi<sup>b</sup>, Shigeki Fujitani<sup>a,\*</sup>

### Abstract

**Aim:** This study aimed to evaluate the association between cerebral oxygen saturation (StO<sub>2</sub>) and return of spontaneous circulation (ROSC) in patients with out-of-hospital cardiac arrest (OHCA).

**Methods:** We retrospectively evaluated the data of patients with OHCA to determine the association between ROSC and various StO<sub>2</sub> parameters (initial\_StO<sub>2</sub>, final\_StO<sub>2</sub>, mean\_StO<sub>2</sub>, and Δ\_StO<sub>2</sub> [=final\_StO<sub>2</sub>-initial\_StO<sub>2</sub>]). Time-domain near-infrared spectroscopy was used to determine absolute StO<sub>2</sub> values.

**Results:** Of the 108 patients with OHCA, 23 achieved ROSC. Although initial\_StO<sub>2</sub> values did not differ between the groups, final\_StO<sub>2</sub>, mean\_StO<sub>2</sub>, and Δ\_StO<sub>2</sub> were higher in the ROSC group than in the non-ROSC group. The cut-off values for initial\_StO<sub>2</sub>, mean\_StO<sub>2</sub>, and Δ\_StO<sub>2</sub> as predictors of ROSC were 35%, 30%, and 5%, respectively. The odds ratio for ROSC had markedly increased in the Δ\_StO<sub>2</sub> ≥ 5% subgroup (19.70 [6.06–64.11], *p* < 0.001). When the change in StO<sub>2</sub> (=d\_StO<sub>2</sub>) at 8 min from the initiation of StO<sub>2</sub> measurement was assessed, the d\_StO<sub>2</sub> ≥ 5% subgroup had a higher odds ratio for ROSC than the d\_StO<sub>2</sub> < 5% subgroup (5.8 [1.78–18.85], *p* = 0.002), and this tendency was maintained until 20 min. In the evaluation using a two-by-two contingency table with initial\_StO<sub>2</sub> and Δ\_StO<sub>2</sub> as two parameters, 61.9% of the patients fell under the categories of initial\_StO<sub>2</sub> < 35% and Δ\_StO<sub>2</sub> < 5% and had the lowest rate of ROSC achievement (4.6%). In the Δ\_StO<sub>2</sub> ≥ 5% subgroup, approximately two-thirds of the patients achieved ROSC irrespective of the initial\_StO<sub>2</sub> (initial\_StO<sub>2</sub> ≥ 35%, 66.7%; initial\_StO<sub>2</sub> < 35%, 60.0%).

**Conclusions:** Initial\_StO<sub>2</sub> and Δ\_StO<sub>2</sub> were associated with the achievement of ROSC.

**Keywords:** Near-infrared spectroscopy, Cerebral oxygen saturation, Cardiopulmonary resuscitation, Return of spontaneous circulation, Discriminant analysis

## Introduction

Out-of-hospital cardiac arrest (OHCA) is associated with high morbidity and mortality rates and is a major challenge in the field of emergency and critical care medicine.<sup>1</sup> Although neurological damage resulting from hypoxic-ischaemic brain injury is one of the main determinants of the prognosis of patients with OHCA,<sup>2–3</sup> the transition from OHCA to return of spontaneous circulation (ROSC) is the

initial step to survival to hospital discharge and favourable outcomes. The association between ROSC and end tidal CO<sub>2</sub> (ETCO<sub>2</sub>) has been demonstrated,<sup>4</sup> but it remains unclear whether other parameters are involved in the achievement of ROSC.

Near-infrared spectroscopy (NIRS) is a non-invasive modality that can continuously provide information on the oxygen saturation of various tissues, including the brain and kidney.<sup>5</sup> Measurement of regional cerebral oxygen saturation (StO<sub>2</sub>) using NIRS is a topic of particular interest as NIRS can determine the StO<sub>2</sub> level through

**Abbreviations:** OHCA, out-of-hospital cardiac arrest, NIRS, near-infrared spectroscopy, TOI, tissue oxygenation index, StO<sub>2</sub>, regional cerebral oxygen saturation, CPR, cardiopulmonary resuscitation

\* Corresponding author at: Department of Emergency and Critical Care Medicine St. Marianna University School of Medicine 2-16-1 Sugao, Miyamae-ku, Kawasaki, Kanagawa 216-8511, Japan.

E-mail address: [shigekifujitani@gmail.com](mailto:shigekifujitani@gmail.com) (S. Fujitani).

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forehead detectors, and the feasibility of this method for patients with OHCA has been established.<sup>6–9</sup> We recently demonstrated that high StO<sub>2</sub> (i.e., tissue oxygenation index [TOI],  $\geq 40\%$ ), recorded at the start of the observation, was associated with an increased rate of ROSC, thus indicating the contributory role of high initial StO<sub>2</sub> (initial\_StO<sub>2</sub>) in the achievement of ROSC.<sup>10</sup> Furthermore, in previous studies, initial StO<sub>2</sub>, mean StO<sub>2</sub> (mean\_StO<sub>2</sub>), and changes in StO<sub>2</sub> were associated with ROSC.<sup>9,11–13</sup> Although these studies demonstrate a close association between StO<sub>2</sub> and ROSC, the most reliable StO<sub>2</sub> parameter (i.e., initial\_StO<sub>2</sub>, mean\_StO<sub>2</sub>, or changes in StO<sub>2</sub>) is yet to be determined.

Several types of NIRS devices that can record StO<sub>2</sub> levels are currently available, such as continuous wave, frequency-domain, and time-domain NIRS.<sup>14</sup> As opposed to other NIRS systems that measure relative changes in StO<sub>2</sub>, the time-domain NIRS system measures the absolute StO<sub>2</sub> with low intraindividual variability of measurements, thus enabling direct and quantitative comparison of StO<sub>2</sub> among patients with a high reproducibility.<sup>14</sup> To the best of our knowledge, however, this system has not been applied to the assessment of StO<sub>2</sub> in patients with OHCA. We attempted to evaluate the association between StO<sub>2</sub> and the achievement of ROSC among patients with OHCA admitted to our emergency department. Furthermore, we aimed to identify the StO<sub>2</sub> parameters that were associated with ROSC, either separately or in combination.

## Methods

### Study design

This retrospective, single-centre, observational study was conducted at St. Marianna University Hospital (Kawasaki, Kanagawa, Japan), which is a tertiary hospital with 1200 beds. Patient enrolment in this study started from August 2019 to March 2022, with an interruption because of the COVID-19 pandemic (May 2020 to September 2021). The study was approved by the Institutional Review Board and Ethics Committee of St. Marianna University School of Medicine (approval No. 5659) and was conducted in accordance with the Declaration of Helsinki. The need for patient consent was waived because of the observational nature of this study. The study was registered at UMIN (UMIN 000048249).

Patients aged 18 years or older with OHCA who were transferred to our emergency department were included (Supplementary Fig. 1). Patients who had achieved ROSC before hospital arrival or experienced NIRS probe attachment failure were excluded. The StO<sub>2</sub> evaluation was performed by a group of specialised staff who were well versed in NIRS; the patients transferred during the time when the staff was off duty were excluded. Each patient's clinical information was collected from the pre-hospital records, including medical history, initial cardiac rhythm of cardiac arrest (CA), and presence/absence of witness and bystander cardiopulmonary resuscitation (CPR). The causes of CA and laboratory data were also evaluated.

### Measurements

We used the tNIRS-1 (Hamamatsu Photonics, Shizuoka, Japan) to determine the StO<sub>2</sub>; the values were obtained non-invasively and continuously with each probe placed on either side of the patient's forehead separately upon arrival. A characteristic feature of this instrument is that it measures absolute StO<sub>2</sub> values of the superficial cerebral cortex, thus allowing direct quantitative analysis of StO<sub>2</sub>.<sup>14</sup> The device probes were attached by our emergency medical

technicians. The attending staff was not blinded to the StO<sub>2</sub> values during patient care, and they were instructed to follow the latest AHA guidelines for resuscitation care irrespective of the StO<sub>2</sub> values to minimise the effect of NIRS monitoring on patient care. Sustained ROSC was defined as sustained circulation for more than 20 min after CPR.

The StO<sub>2</sub> values obtained from each probe were evaluated (and averaged) at various time points, including the start (i.e., when the probes were attached upon arrival) and end of the measurements (i.e., when patients achieved ROSC or when the resuscitation was terminated)—the data obtained at these time points were defined as initial\_StO<sub>2</sub> and final\_StO<sub>2</sub>, respectively. The difference in StO<sub>2</sub> values between initial\_StO<sub>2</sub> and final\_StO<sub>2</sub> or between initial\_StO<sub>2</sub> and StO<sub>2</sub> at specific time points was defined as  $\Delta$ \_StO<sub>2</sub> or d\_StO<sub>2</sub>, respectively. The average StO<sub>2</sub> during the evaluation period was also assessed (mean\_StO<sub>2</sub>).

### Statistical analysis

Continuous variables were expressed as mean (standard deviation [SD]) and median [Q1–Q3], and categorical variables as number and percentage. Data were compared using Student's t-test or Mann–Whitney U test. Chi-square test or Fisher's exact test was used for the analysis of categorical variables. Receiver operating characteristic (ROC) analysis was conducted to determine the respective (i.e., initial\_StO<sub>2</sub>, mean\_StO<sub>2</sub>,  $\Delta$ \_StO<sub>2</sub>) cut-off values for ROSC. Patients were divided into ROSC and non-ROSC groups based on their initial\_StO<sub>2</sub> and  $\Delta$ \_StO<sub>2</sub> values using the linear discriminant analysis method. The John Macintosh Project (JMP) statistical software (version 16, SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses. Statistical significance was set at  $p < 0.05$ .

## Results

### Demographic characteristics

During the study period, 689 patients with OHCA were transferred to our emergency department, of which 84.3% were unable to receive StO<sub>2</sub> evaluation because of age restrictions, absence of research staff, or probe attachment failure (Supplementary Fig. 1). A total of 108 OHCA patients were finally enrolled; among them, 23 achieved sustained ROSCs and 6 survived to hospital admission.

There were no differences in age and sex distributions between the ROSC and non-ROSC-groups (Table 1). Approximately one-third of the patients experienced witnessed CA or received bystander CPR, and the proportions of witnessed CA (69.6% vs 30.1%,  $p < 0.001$ ) and bystander CPR (52.4% vs 28.2%,  $p = 0.04$ ) were higher in the ROSC group. The ROSC group also had more frequent occurrences of shockable rhythm and suspected cardiac causes of CA. Blood gas analysis showed higher pH and bicarbonate concentration and lower lactate and potassium concentration in the ROSC group.

In 42 patients with witnessed CA, we were able to assess the time between OHCA and the initiation of StO<sub>2</sub> measurement (i.e., 36 [25–45] min, Supplementary Table 1). This group had higher initial\_StO<sub>2</sub> values than the group with non-witnessed CA (32.0 [11.5]% vs 27.2 [11.1]%,  $p = 0.036$ ). Alternatively, the group with initial\_StO<sub>2</sub>  $\geq 35\%$  had higher proportion of witnessed CA than of non-witnessed CA (odds ratio [OR] = 2.79 [95%CI: 1.07–7.29]). Furthermore, in the witnessed CA group, 16 patients achieved ROSC

**Table 1 – Patients' characteristics.**

	Total (n = 108)	ROSC group (n = 23)	Non-ROSC group (n = 85)	p value	Odds ratio for ROSC
Age (years), mean (SD)	73.1 (15.6)	71.6 (13.8)	73.6 (16.0)	0.56	
Male, n (%)	57 (52.8%)	11 (47.8%)	46 (54.1%)	0.59	0.78 [0.31-1.96]
Shockable rhythm, n (%)	8 (7.7%)	7 (31.8%)	1 (1.2%)	<0.001	36.75 [4.22-319.45]
Witness, n (%)	42 (38.9%)	16 (69.6%)	26 (30.1%)	<0.001	5.18 [1.91-14.11]
Bystander CPR, n (%)	33 (33.3%)	11 (52.4%)	22 (28.2%)	0.04	2.63 [1.01-6.80]
Suspected cardiac cause of CA, n (%)	11 (10.2%)	5 (21.7%)	6 (7.1%)	0.04	3.66 [1.01-13.32]
Initial_StO2 (%), mean (SD)	29.4 (12.0)	33.8 (15.3)	28.2 (10.6)	0.12	
Final_StO2 (%), mean (SD)	30.6 (12.0)*	41.8 (12.6)**	27.6 (10.2)	<0.001	
Time during NIRS monitoring (min), median [Q1-Q3]	16 [11.0-23.0]	27 [19.0-40.0]	15 [11.0-21.0]	<0.001	
<b>Blood gas analysis</b>					
pH, mean (SD)	6.83 (0.17)	6.93 (0.16)	6.79 (0.16)	0.003	
PaCO2 (torr), mean (SD)	90.3 (30.0)	86.0 (28.7)	92.2 (30.6)	0.43	
PaO2 (torr), mean (SD)	59.3 (62.3)	81.2 (90.0)	49.6 (40.0)	0.14	
HCO3 <sup>-</sup> (mmol/L), mean (SD)	14.6 (4.8)	16.5 (4.3)	13.8 (4.8)	0.02	
Lactate (mmol/L), mean (SD)	10.97 (4.45)	8.15 (2.65)	12.26 (4.51)	<0.001	
Potassium (mmol/L), mean (SD)	6.2 (1.8)	5.6 (1.4)	6.7 (1.9)	0.02	

ROSC; return of spontaneous circulation, CPR; cardiopulmonary resuscitation, CA; cardiac arrest, NIRS; near-infrared spectroscopy, StO2; cerebral oxygen saturation.

\*; p = 0.06, \*\*; p < 0.001 vs initial\_StO2 in respective groups.

and had a shorter interval between CA and NIRS initiation than those who did not achieve ROSC (28 [17–40] min vs 37 [29–48] min, respectively, p = 0.039). Bystander CPR was not associated with initial\_StO2 (32.3 [13.6]% vs 28.2 [10.9]%, respectively, p = 0.136); the number of patients with initial\_StO2 ≥ 35% was similar between the bystander CPR and no bystander CPR groups (OR = 1.57 [95%CI: 0.56–4.39], p = 0.386).

### NIRS results

StO2 did not increase significantly during the CPR procedures (p = 0.06, Table 1). Although initial\_StO2 values were nearly the same between the ROSC and non-ROSC groups (p = 0.12), the final\_StO2 and subsequently Δ\_StO2 and mean\_StO2 values were significantly higher in the ROSC group (Fig. 1).

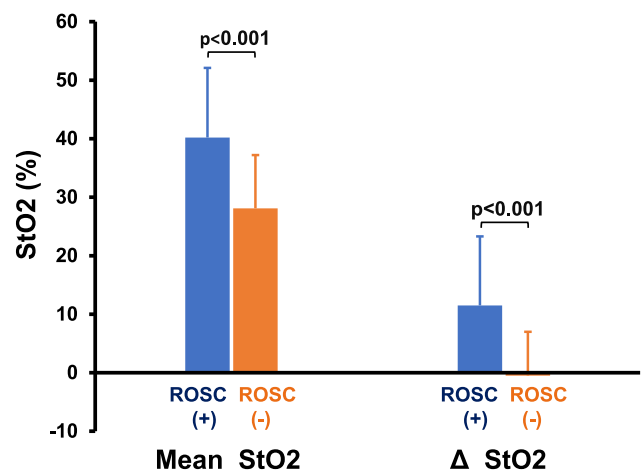
ROC analysis showed cut-off values of 35%, 30%, and 5% for initial\_StO2, mean\_StO2, and Δ\_StO2, respectively (Supplementary Fig. 2A-2C). The OR for ROSC was not significantly high for initial\_StO2 ≥ 35%, but was markedly high for mean\_StO2 ≥ 30% and Δ\_StO2 ≥ 5% (Fig. 2).

### Temporal changes in StO2 difference and association with ROSC

Because the final values when NIRS measurements were discontinued were required to determine the Δ\_StO2, we further evaluated the changes in StO2 from the start of measurement to specific time points (d\_StO2 at 4, 8, 12, 16, and 20 min) and assessed the association between ROSC and d\_StO2. The temporal courses of d\_StO2 showed higher values in the ROSC group than in the non-ROSC group at 8, 16, and 20 min (Fig. 3A). Notably, in the ROSC group, the d\_StO2 at 4 min was lower than Δ\_StO2 (p = 0.02). Likewise, d\_StO2 at 4 min did not affect the OR for ROSC, but the ORs were high at 8 min and later (Fig. 3B).

### ROSC evaluation using two-by-two contingency table

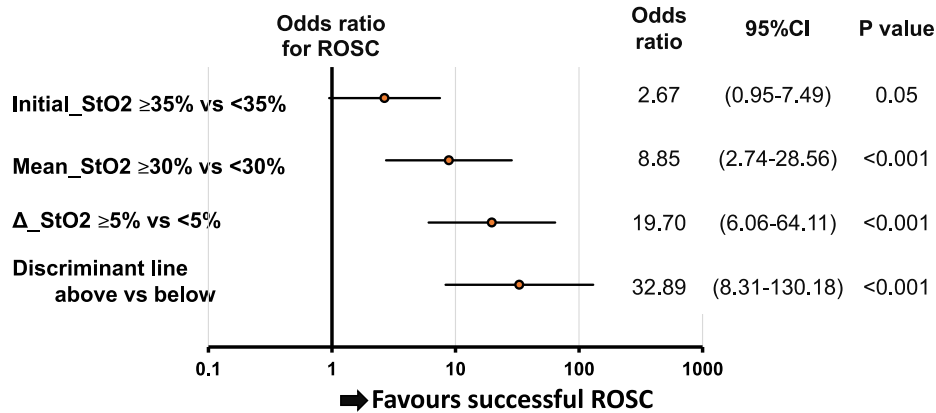
We observed divergent StO2 profiles/responses, depending on the types of categorisation (initial\_StO2 vs mean\_StO2 or Δ\_StO2,



**Fig. 1 – StO2 parameters in ROSC and no ROSC patients. ROSC, return of spontaneous circulation.**

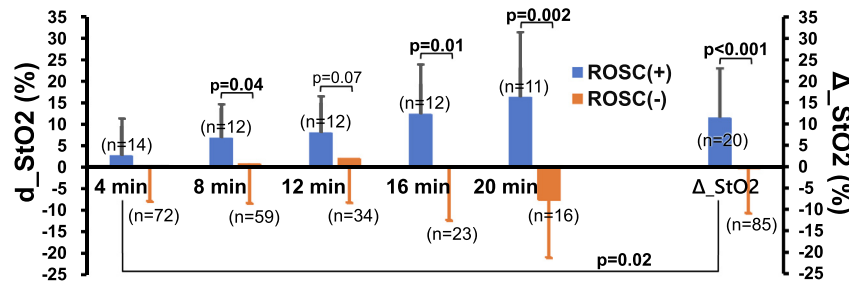
Supplementary Fig. 3A). Furthermore, initial\_StO2 data were strongly correlated with mean\_StO2 ( $r^2 = 0.66$ ) but only modestly correlated with Δ\_StO2 ( $r^2 = 0.12$ , Supplementary Fig. 3B). We, therefore, evaluated how StO2 affected the incidence of ROSC using initial\_StO2 and Δ\_StO2 as static and dynamic parameters, respectively. Approximately-two-thirds (i.e., 61.9%) of the patients had low values for both parameters (i.e., initial\_StO2 < 35% and Δ\_StO2 < 5%) as well as the lowest rate of ROSC (4.6%, Table 2). In the subgroup with Δ\_StO2 ≥ 5%, approximately-two-thirds of the patients achieved ROSC irrespective of the initial\_StO2 (initial\_StO2 ≥ 35%; 66.7%, initial\_StO2 < 35%; 60.0%). In contrast, in the subgroup with Δ\_StO2 < 5%, more patients with initial\_StO2 ≥ 35% tended to achieve ROSC than those with initial\_StO2 < 35% (p = 0.07).

To further characterise the profiles of ROSC with reference to the association between initial\_StO2 and Δ\_StO2, the data were plotted

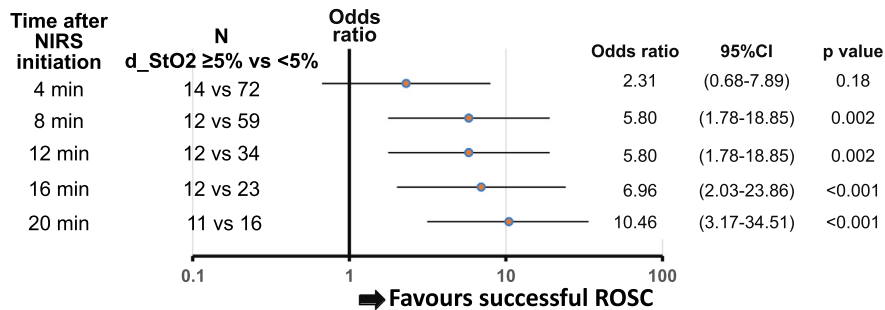


**Fig. 2 – Odds ratios for ROSC and survival. Odds ratios for ROSC were significantly associated with mean\_StO2, D\_StO2 and linear discriminant line. ROSC, return of spontaneous circulation.**

**A) Changes in d\_StO2 in ROSC(+) and ROSC(-) group**



**B) Odds ratios for ROSC in association with d\_StO2 ≥5% at various time points**



**Fig. 3 – Temporal changes in StO2 from baseline (0 min: d\_StO2) and its association with ROSC. d\_StO2 denotes the difference between initial\_StO2 and St\_O2 at specific time points. The d\_StO2 was higher in the ROSC group than in the no ROSC group when based on the early time points (A). The odds ratio for ROSC in association with d\_StO2 ≥ 5% vs <5% increased with time, reaching 10.457 in the period over 20 min (B). ROSC, return of spontaneous circulation.**

as a function of two-dimensional parameters of StO2 (Fig. 4). The groups with and without ROSC were distributed widely in the spectrum of initial\_StO2 versus Δ\_StO2 axis, with a slight overlap between the groups. When linear discriminant analysis was applied to these populations, a relatively distinct separation was found, with a coefficient of determination of 84.8%. The OR for ROSC in patients assigned to the plot area above the linear discriminant line was 32.89 (95%CI: 8.31–130.18) compared with those assigned to the area below the line (p < 0.001, Fig. 2).

Because the negative slope coefficient of the discriminant line favoured a low cut-off value for Δ\_StO2 (i.e., 0%), rather than 5%, over the range of initial\_StO2 ≥ 35% (Supplementary Table 2), this population assigned to this area was divided *de novo* into a subgroup

with Δ\_StO2 ≥ 0% (category A) and a subgroup with Δ\_StO2 < 0% (category B; Fig. 4). Thus, the high Δ\_StO2 (≥0%) subgroup (category A) tended to have a higher rate of ROSC (62.5%) than the low Δ\_StO2 subgroup (category B, 21.4%, p = 0.05). We observed a lower rate of ROSC in category D (4.6%; initial\_StO2 < 35% and Δ\_StO2 < 5%) than in category B (p = 0.03).

**Discussion**

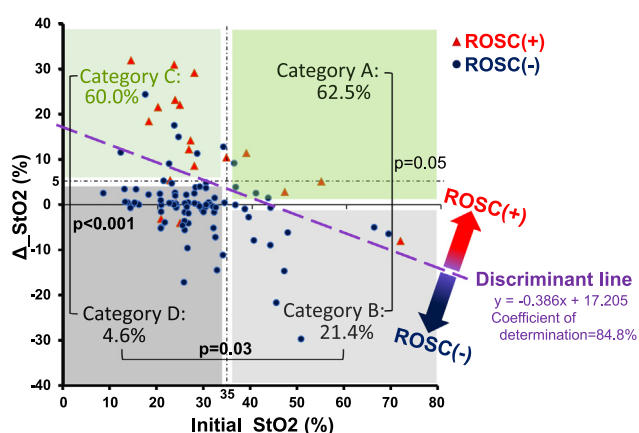
ROSC after OHCA offers favourable outcomes that might lead to survival to hospital discharge. As part of our armamentarium for treating patients with OHCA, we have obtained a new technology

**Table 2 – Number of patients and ratio of ROSC/survival among subgroups based on  $\Delta$ \_StO2 and initial\_StO2 categorisation.**

A)	Number of patients [1]	i_StO2 < 35% n (%)	i_StO2 $\geq$ 35% n (%)	p value
	$\Delta$ _StO2 $\geq$ 5%	20 (19.0%)	3 (2.9%)	0.55
	$\Delta$ _StO2 < 5%	65 (61.9%)	17 (16.2%)	
B)	Number of ROSC [2]	i_StO2 < 35% n ([2]/[1], %)	i_StO2 $\geq$ 35% n ([2]/[1], %)	
	$\Delta$ _StO2 $\geq$ 5%	12 (60.0%) <sup>a)</sup>	2 (66.7%) <sup>b)</sup>	
	$\Delta$ _StO2 < 5%	3 (4.6%) <sup>c)</sup>	3 (18.8%) <sup>d)</sup>	

a) vs b); p = 1.00, a) vs c); p < 0.001, b) vs c); p = 0.01, b) vs d); p = 0.14, c) vs d); p = 0.07.

ROSC; return of spontaneous circulation, i\_StO2; initial\_StO2.



**Fig. 4 – Patient distribution based on two StO2 parameters and discriminant analysis between ROSC and non-ROSC groups. Percentage in each category box indicates the number of patients who achieved ROSC/[ROSC + non-ROSC]. ROSC, return of spontaneous circulation.**

for monitoring cerebral oxygen supply, i.e., NIRS, and there is increasing evidence on the contributory role of this system in the management of patients with OHCA.<sup>7–13,15</sup> Because continuous assessment of StO2 yields multiple evaluation markers, including initial\_StO2, mean\_StO2, and  $\Delta$ \_StO2, many studies suggest a close association between ROSC and one of these parameters.<sup>6,10–13,16</sup> Nevertheless, the StO2 parameter that most clearly reflects the achievement of ROSC is still unclear.

Evaluation of cerebral oxygen supply offers critical information regarding the survivability and brain function of patients with OHCA. Numerous studies that adopted various NIRS systems for non-invasive evaluation of cerebral oxygen supply have shown the association between ROSC and StO2, including initial\_StO2,<sup>8–11</sup> mean\_StO2,<sup>6,8–9</sup> and  $\Delta$ \_StO2.<sup>12–13,16</sup> We previously demonstrated that both initial\_StO2 and  $\Delta$ \_StO2 were associated with ROSC using a conventional NIRS (NIRO-200NX, Hamamatsu Photonics, Shizuoka, Japan), which evaluated relative changes in StO2, and suggested these parameters as useful markers for ROSC.<sup>10,16</sup> In this study, we provided direct evidence that the patients with ROSC have higher final\_StO2, mean\_StO2 and  $\Delta$ \_StO2 (Table 1, Fig. 1) using a new type of time-domain NIRS, which is characterised by measurement

of absolute StO2 values with high reproducibility and brain-depth sensitivity.<sup>14</sup> Furthermore, the subgroup with higher mean\_StO2 or  $\Delta$ \_StO2 had elevated ORs for ROSC (Fig. 2), suggesting that elevated StO2 values are required for ROSC after OHCA.<sup>17–18</sup>

There are inconsistent results regarding StO2 and its association with ROSC. Several studies, including our previous study, demonstrated that high initial\_StO2 contributed to the increased occurrence of ROSC.<sup>8–11</sup> In contrast, this study failed to show a significant difference in initial\_StO2 between the ROSC and non-ROSC groups (Table 1). Furthermore, subgroups emerged with markedly elevated ORs for ROSC when the patients were categorised by mean\_StO2 (8.85, p < 0.001) or  $\Delta$ \_StO2 (19.70, p < 0.001, Fig. 2). Consistently, the temporal changes in StO2 in response to CPR differed, depending on the type of categorisation (initial\_StO2 vs mean\_StO2 or  $\Delta$ \_StO2, Supplementary Fig. 3A). The divergent StO2 responses and different rates of ROSC between the subgroups indicate the need for additional approaches to address these issues.

We also evaluated the occurrence of ROSC from a two-dimensional view of StO2. Initial\_StO2 is a static parameter affecting the whole clinical profile of patients while  $\Delta$ \_StO2 is presumed to be a dynamic factor reflecting treatment efficacy. Because of the strong correlation between initial\_StO2 and mean\_StO2 (Supplementary Fig. 3B), we assessed the occurrence of ROSC using initial\_StO2 and  $\Delta$ \_StO2 in a two-by-two factorial model (Table 2). Thus,  $\Delta$ \_StO2 is a principal determinant of the achievement of ROSC in patients with OHCA. Furthermore, even though the contribution of  $\Delta$ \_StO2 was low (i.e., <5%), high initial\_StO2 (i.e.,  $\geq$ 35%) might contribute to increased rates of ROSC. Indeed, a new categorisation based on linear discriminant analysis showed a significantly higher rate of ROSC in the subgroup with initial\_StO2  $\geq$  35% than in the subgroups with initial\_StO2 < 35% (i.e., category B vs D, p = 0.03, Fig. 4). In this regard, Takegawa et al.<sup>19</sup> demonstrated that a combination of baseline StO2 and the amount of maximum rise from baseline was an adequate index for predicting ROSC. Our observations are consistent with their findings showing that both static and dynamic StO2 parameters are required for a detailed evaluation of the prognostication of OHCA. Moreover, our study using a tNIRS-1, which measures absolute StO2, could offer direct evidence of the role of StO2 in the achievement of ROSC.

Although this study demonstrates an association between StO2 and ROSC, caution is needed when our results are interpreted in clinical practice. Because  $\Delta$ \_StO2 is based on initial\_StO2 and final\_StO2 measurements, we were unable to determine the proba-



bility of ROSC until the CPR procedure was discontinued. Therefore, we assessed the StO<sub>2</sub> at specific time points and calculated the changes from baseline (i.e., d\_StO<sub>2</sub>). We found no difference between  $\Delta$ \_StO<sub>2</sub> and the d\_StO<sub>2</sub> evaluated at 8 min or later in the ROSC group (Fig. 3A). Furthermore, the rate of ROSC was high when d\_StO<sub>2</sub> was measured at 8 min or later up to 20 min (Fig. 3B). However, it remains to be determined whether the d\_StO<sub>2</sub> data obtained during 20 min reflect the  $\Delta$ \_StO<sub>2</sub> as alternative values for evaluating the occurrence of ROSC. Finally, categorisation into four groups reduced the population size in each StO<sub>2</sub> category. Further evaluation is required to address these important issues.

Although several studies demonstrate that initial\_StO<sub>2</sub> is closely associated with ROSC,<sup>9–11</sup> pre-hospital characteristics and/or milieu may affect this parameter, including CPR and flow time. This study shows that patients with witnessed OHCA have higher initial\_StO<sub>2</sub> than those with no witness (Supplementary Table 1). We previously found that the changes in StO<sub>2</sub> during ambulance transportation were associated with chest compression rate and StO<sub>2</sub> on hospital arrival.<sup>16</sup> Thus, pre-hospital care at the scene or during transportation may affect the initial\_StO<sub>2</sub> measured on hospital arrival. The reason why bystander CPR does not elevate initial\_StO<sub>2</sub> (32.3% vs 28.02%,  $p = 0.136$ ) nor modify the number of patients with initial\_StO<sub>2</sub>  $\geq 35\%$  (OR = 1.57,  $p = 0.386$ ) needs to be clarified.

Regarding  $\Delta$ \_StO<sub>2</sub>, when initial\_StO<sub>2</sub> is already high, the rise in  $\Delta$ \_StO<sub>2</sub> is modest (Fig. 4, Supplementary Fig. 3). In contrast, when initial\_StO<sub>2</sub> is low, high  $\Delta$ \_StO<sub>2</sub> tends to be associated with high rates of ROSC (Fig. 4). Perhaps, high  $\Delta$ \_StO<sub>2</sub> reflects viability during CPR. Previous studies, but not all, showed that high initial\_StO<sub>2</sub> was associated with ROSC.<sup>8–11</sup> Thus, comprehensive evaluations are needed to explain the relationship between ROSC and StO<sub>2</sub>.

### Limitations

Because of the nature of this study, the sample size was not sufficiently large to extrapolate our results to well-established indicators such as end-tidal CO<sub>2</sub><sup>4,20</sup>; hence, the results should be interpreted with caution. Furthermore, the enrolment was reduced because of the COVID-19 pandemic. Second, the attachment of the NIRS probes and the activation of this system were performed by emergency medical technicians, whose work shifts were fixed during the daytime of weekdays in our hospital. Moreover, the average age of the patients enrolled was 73.1 years. Because younger patients retain higher possibility to be resuscitated from CA, it is reasonably inferred that prioritisation of CPR deters emergency medical staff from implementing NIRS monitoring. These selection biases might distort the results associated with ROSC. Furthermore, because of the retrospective study, we were unable to evaluate the exact time between OHCA and the initiation of StO<sub>2</sub> measurement. This pre-hospital OHCA period might affect the StO<sub>2</sub> and ROSC. Finally, OHCA not only disrupts the StO<sub>2</sub> but also modifies many other parameters related to ROSC. Thus, additional studies are required on this topic.

### Conclusions

Using the time-domain NIRS, we found that initial\_StO<sub>2</sub> and  $\Delta$ \_StO<sub>2</sub> were associated with the achievement of ROSC in OHCA patients. While our study indicates an association between StO<sub>2</sub> and ROSC, further studies are required to confirm this association.

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### Conflicts of interest

None.

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### Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.resplu.2022.100343>.

### Author details

<sup>a</sup>Department of Emergency and Critical Care Medicine, St. Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki, Kanagawa 216-8511, Japan <sup>b</sup>Department of Emergency and Critical Care Medicine, St. Marianna University, Yokohama City Seibu Hospital, 1197-1 Yasashi-cho, Asahi-ku, Yokohama, Kanagawa 241-0811, Japan

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