Parameters Influencing Brain Oxygen Measurement by Regional Oxygen Saturation in Postcardiac Arrest Patients with Targeted Temperature Management

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In several studies, regional cerebral oxygen saturation (rSO2) has been measured in patients with postcardiac arrest syndrome (PCAS) to analyze the brain’s metabolic status. However, the significance of rSO2 in PCAS patients remains unclear. In the present study, we investigated the relationship between rSO2 and physiological parameters. Comatose survivors of out-of-hospital PCAS with targeted temperature management (TTM) at 34°C for 24 hours were included. All patients were monitored for their rSO2 and additional parameters (arterial oxygen saturation \([\text{SaO}_2]\), hemoglobin \([\text{Hb}]\), mean arterial pressure \([\text{MAP}]\), arterial carbon dioxide pressure \([\text{PaCO}_2]\), and body temperature) measured at the start of monitoring and 24 and 48 hours after return of spontaneous circulation (ROSC). Patients were divided into favorable and unfavorable groups, and the correlation between rSO2 and these physiological parameters was evaluated by multiple regression analysis. Forty-nine patients were included in the study, with 15 in the favorable group and 34 in the unfavorable group. There was no significant difference in the rSO2 value between the two groups at any time point. The multiple regression analysis of the favorable group revealed a moderate correlation between rSO2 and \SaO_2, Hb, and \PaCO_2 only at 24 hours (coefficients: 0.482, 0.422, and 0.531, respectively), whereas that of the unfavorable group revealed moderate correlations between rSO2 and Hb values at all time points, \PaCO_2 at 24 hours and \MAP at 24 and 48 hours. rSO2 was moderately correlated to MAP in unfavorable patients. To optimize brain oxygen metabolic balance for PCAS patients with TTM measuring rSO2, we suggest total evaluation of each parameters of \SaO_2, Hb, MAP, and \PaCO_2.

Keywords: regional cerebral oxygen saturation (rSO2), postarrest brain injury, cerebrovascular autoregulation, targeted temperature management (TTM)

Introduction

In several studies, near-infrared spectroscopy (NIRS) has been used to measure regional cerebral oxygen saturation (rSO2) in patients with postcardiac arrest syndrome (PCAS) to predict the outcome and analyze the brain’s metabolic status (Meex et al., 2013; Ahn et al., 2014; Storm et al., 2014; Ibrahim et al., 2015). In these studies of PCAS patients in the intensive care unit (ICU), rSO2 was significantly lower in nonsurviving (Meex et al., 2013; Ahn et al., 2014) and poor neurological outcome patients (Storm et al., 2014) than in surviving or good neurological outcome patients. In contrast, Ibrahim et al. (2015) reported that there was no difference between the rSO2 of survivors and non-survivors in the ICU setting. Recently, Ihara et al. (2019) showed that there was no difference in the rSO2 value between severely brain-injured PCAS patients with abnormal amplitude-integrated electroencephalography (aEEG) and mildly brain-injured patients with continuous aEEG wave. This was because the rSO2 of patients with abnormal aEEG had a dramatically wider range than that of patients with normal aEEG. It was concluded that this variation in rSO2 in patients with severe brain injury may indicate the pathophysiology of postcardiac arrest brain injury owing to impaired cerebrovascular autoregulation (CVAR) and cerebral blood flow (CBF) (Ihara et al., 2019).

Generally, brain oxygenation, measured by rSO2, will depend on Fick’s principle: \[\text{rSO}_2 = \frac{\text{SaO}_2 - \text{CMRO}_2}{1.34 \times \text{Hb} \times \text{CBF}}\] (SaO2: arterial oxygen saturation, CMRO2: cerebral oxygen metabolic ratio, Hb: hemoglobin). CMRO2
changes depending on the body temperature (BT) (Ehrlich et al., 2002) and severity of whole-brain ischemic injury (Tichauer et al., 2009). CBF is described by the Hagen-Poiseuille’s equation: 

\[
\text{CBF} = \frac{k \times (\text{MAP} \times \text{ICP}) \times d^4}{(L \times \mu)}
\]

(k: physical constant, MAP: mean arterial pressure, ICP: intracranial pressure, d: cerebral vessel diameter, \( \mu \): blood viscosity, L: length of vessel). Cerebral vessel diameter is regulated by arterial carbon dioxide pressure (PaCO2) and \( \mu \) is influenced by Hb (Nakashima et al., 2017). In the standard ICU setting for PCAS patients, parameters such as SaO2, Hb, MAP, BT, and PaCO2 are usually evaluated. Therefore, by investigating the relationship between rSO2 and these parameters, we could indirectly estimate brain oxygenation in the injured brain. This study is a post hoc analysis of our previous investigation (Ihara et al., 2019) estimating the relationship between rSO2 and parameters such as SaO2, Hb, PaCO2, MAP, and BT.

**Methods**

This observational study was performed at the intensive care unit at Nihon University Itabashi Hospital. Approval was obtained from the Clinical Research Institutional Review Board (IRB) of the Nihon University School of Medicine Itabashi Hospital (RK-121109-1). Participants of this study were comatose survivors of out-of-hospital PCAS, aged 20 years or older, and treated with targeted-temperature management (TTM) from July 1, 2012 to June 31, 2015. This study included consecutive patients treated with TTM; however, patients were excluded if (1) they died abruptly within 72 hours after cardiac arrest without sufficient evaluation of brain function or (2) they had a history of neurological diseases or brain injury.

The details of the TTM protocol have been described in our previous study (Ihara et al., 2019). In brief, patients who remained comatose after return of spontaneous circulation (ROSC) were treated with TTM at 34°C for 24 hours. After patients with ROSC were sedated (midazolam, 0.08 mg/kg intravenously) and paralyzed (rocuronium bromide, 0.8 mg/kg intravenously) to control shivering, the conditions were maintained with a continuous infusion of midazolam (0.05–0.1 mg/kg/h), fentanyl (1 μg/kg/h), and rocuronium (0.3–0.6 mg/kg/h). The parameters were measured and recorded as follows: mean blood pressure (BP) >65 mmHg, SpO2 94–97%, PaCO2 35–45 mmHg, and Hb <7 g/dL. All patients were monitored for rSO2 (INVOS 5100 C; Covidien, Boulder, CO) immediately after the patient’s arrival in the ICU. The NIRS probe was placed on the left forehead to detect frontal cerebral oxygen saturation. rSO2 and the other parameters (MAP, SaO2, PaCO2, and Hb) were evaluated at the start of monitoring and 24 and 48 hours after ROSC. The neurological outcome was assessed using the Cerebral Performance Category (CPC) scale (Cummins et al., 1991) during discharge from the hospital. Patients were divided into two groups according to the outcome: favorable neurological outcome (favorable group) was defined as patients with a CPC score of 1 or 2, and unfavorable outcome (unfavorable group) was defined as patients with a CPC score of 3–5.

Statistical analysis was performed using IBM SPSS Version 22. The Fisher’s exact probability test, t test, and Mann–Whitney U test were used to assess statistical significance of characteristics and parameters between favorable group and unfavorable group. Relationships between rSO2 and each parameter were examined with the Spearman’s rank correlation coefficient and multiple regression analysis. A p-value <0.05 was considered statistically significant.

The ratio of variation to mean value at rSO2 and each parameter between favorable groups was evaluated by the coefficient of variation (CV = [standard deviation/mean] × 100). The significant difference in CV between the two groups was calculated using the likelihood ratio test with the hypothesis that k normally distributed populations share the same CV. The web program that we used to statistically analyze CV is www1.fpl.fs.fed.us/covtestk.html. This method was mentioned in a previous study (Ihara et al., 2019). A p-value <0.05 was also considered statistically significant.

**Results**

The details of patients flow has been described in detail in our previous study (Ihara et al., 2019). In addition, 2 patients died within 72 hours during TTM and they were excluded in the subsequent studies and analysis as was the case in the previous study (Ihara et al., 2019). Forty-nine patients were included in this study, with 15 patients in the favorable group (CPC1: 11 cases, CPC2: 4) and 34 in the unfavorable group (CPC3: 3, CPC4: 11, CPC5: 20). Patient characteristics are presented in Table 1. There were significant differences between the favorable and unfavorable groups with respect to gender male (80% vs. 50%), proportion with shockable rhythm (60% vs 27%), and time from arrest to ROSC (20.9 ± 19.1 vs. 36.4 ± 18.2; minutes). The rSO2 value was compared between the two groups, and there was no significant difference at any time point. Hb was significantly larger

**Table 1. Comparison of Characteristics Between Patients in the Favorable and Unfavorable Groups**

|                          | Favorable group n = 15 | Unfavorable group n = 34 | p value |
|--------------------------|------------------------|--------------------------|---------|
| Age, years, mean ± SD    | 57.8 ± 18.2            | 67.7 ± 14.2              | 0.068   |
| Male, n (%)              | 12 (80)                | 17 (50)                  | 0.049   |
| Cardiac cause, n (%)     | 10 (67)                | 18 (53)                  | 0.371   |
| Witnessed, n (%)         | 13 (87)                | 24 (71)                  | 0.228   |
| Shockable rhythm, n (%)  | 9 (60)                 | 9 (27)                   | 0.025   |
| Bystander CPR, n (%)     | 10 (67)                | 15 (42)                  | 0.146   |
| Time from arrest to ROSC, min, mean ± SD | 20.9 ± 19.1 | 36.4 ± 18.2 | 0.010   |
| Time from ROSC to rSO2 application, min, mean ± SD | 351.9 ± 199.4 | 350.6 ± 177.5 | 0.845   |

CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; rSO2, regional cerebral oxygen saturation.
The CV of rSO2 at 48 hours and SaO2, Hb, PaCO2, MAP, or BT at any time point between the two groups.

The correlation coefficient between rSO2 and each parameter at every time point is given in Table 3 for both groups. Table 4 shows the results of the multiple regression analysis between rSO2 and each parameter at every time point in the favorable and unfavorable group. In the favorable group, SaO2, Hb, and PaCO2 had moderate correlations with rSO2 at 24 hours, and the standardized partial regression coefficients were 0.482, 0.422, and 0.531, respectively. In the unfavorable group, rSO2 was moderately correlated with Hb at all time points, PaCO2 at 24 hours and MAP at 24 and 48 hours.

Discussion

In the present study, there was no significant difference in rSO2 values between the two groups at any time point after resuscitation from CA. The value of rSO2 in the unfavorable group had a significantly larger variation than that in the favorable group in early stages after ROSC; although there were no significant differences in the variation of the other parameters between the two groups. In the favorable group, SaO2, Hb, and PaCO2 had moderate correlations with rSO2 only at 24 hours. In the unfavorable group, moderate correlations existed between rSO2 and Hb at all time points, PaCO2 at 24 hours, and MAP at 24 and 48 hours.

In theory, the concentration of Hb must have a binary effect on brain oxygenation. According to Fick’s principle, as Hb concentration increases, brain oxygenation will also increase because of the increase in oxygen carrier. On the contrary, based on Hagen–Poiseuille’s law, as Hb concentration increases, brain oxygen will decrease as CBF decreases with augmented blood viscosity owing to Hb. However, practically, the relationship between rSO2 and Hb concentration obeys Fick’s principle, with rSO2 having a positive correlation with Hb concentration in cardiac surgical and neurosurgical patients (Yoshitani et al., 2007). In the present study, Hb concentration was significantly positively correlated with rSO2 at all time points in the unfavorable group and at 24 hours in the favorable group. This indicates that brain oxygenation based on Hb concentration obeys Fick’s principle. Storm et al. reported that rSO2 was significantly lower in patients with poor outcomes; however, Hb concentration was

Table 2. Comparing of Patient Parameters Between the Favorable and Unfavorable Groups for Every Time Point

| Parameter          | Favorable group | Unfavorable group | p value |
|--------------------|-----------------|-------------------|---------|
| Start of monitoring|                 |                   |         |
| rSO2 (%)           | 55.5 ± 5.9      | 57.1 ± 14.0       | 0.587   |
| SaO2 (%)           | 97.5 ± 2.0      | 97.1 ± 2.5        | 0.494   |
| Hb (g/dL)          | 14.4 ± 2.8      | 12.1 ± 2.9        | 0.008   |
| PaCO2 (mmHg)       | 34.9 ± 6.7      | 35.1 ± 7.8        | 0.803   |
| MAP (mmHg)         | 101.2 ± 18.4    | 87.1 ± 16.6       | 0.015   |
| Body temperature   | 34.3 ± 0.8      | 33.9 ± 0.6        | 0.112   |

After 24 hours

| Parameter          | Favorable group | Unfavorable group | p value |
|--------------------|-----------------|-------------------|---------|
| rSO2 (%)           | 62.9 ± 9.1      | 57.6 ± 15.8       | 0.615   |
| SaO2 (%)           | 96.4 ± 3.0      | 97.0 ± 2.1        | 0.730   |
| Hb (g/dL)          | 13.7 ± 3.3      | 11.7 ± 2.7        | 0.039   |
| PaCO2 (mmHg)       | 36.5 ± 6.1      | 36.6 ± 9.4        | 0.879   |
| MAP (mmHg)         | 104.3 ± 15.9    | 85.9 ± 18.2       | 0.001   |
| Body temperature   | 34.5 ± 1.0      | 34.3 ± 1.0        | 0.806   |

After 48 hours

| Parameter          | Favorable group | Unfavorable group | p value |
|--------------------|-----------------|-------------------|---------|
| rSO2 (%)           | 68.9 ± 10.9     | 64.5 ± 13.3       | 0.275   |
| SaO2 (%)           | 96.3 ± 2.2      | 96.1 ± 3.3        | 0.654   |
| Hb (g/dL)          | 13.4 ± 3.1      | 10.8 ± 2.3        | 0.012   |
| PaCO2 (mmHg)       | 40.0 ± 6.1      | 37.4 ± 6.9        | 0.341   |
| MAP (mmHg)         | 97.5 ± 20.4     | 85.9 ± 23.0       | 0.123   |
| Body temperature   | 36.3 ± 0.8      | 35.9 ± 0.8        | 0.076   |

Mean ± SD

rSO2, regional cerebral oxygen saturation; SaO2, arterial oxygen saturation; Hb, hemoglobin; PaCO2, arterial carbon dioxide pressure; MAP, mean arterial pressure.

Table 3. Correlation Coefficient Between rSO2 and Each Parameter at Every Time Point in the Favorable and Unfavorable Groups

| Parameter | SaO2 | Hb  | PaCO2 | MAP  | BT   |
|-----------|------|-----|-------|------|------|
| Start of monitoring |      |     |       |      |      |
| Favorable group | 0.329 | 0.667* | 0.653* | 0.428 | BT  |
| Unfavorable group | 0.329 | 0.488* | 0.013 | 0.107 |      |
| 24 hours after ROSC |      |     |       |      |      |
| Favorable group | 0.409 | 0.697* | 0.460 | 0.421 | -0.110 |
| Unfavorable group | -0.026 | 0.524* | 0.259 | 0.558* | 0.088 |
| 48 hours after ROSC |      |     |       |      |      |
| Favorable group | -0.056 | 0.621* | 0.558 | 0.435 | -0.080 |
| Unfavorable group | -0.102 | 0.622* | 0.276 | 0.529* | 0.485 |

Correlation coefficient: *p < 0.05.

rSO2, regional cerebral oxygen saturation; ROSC, return of spontaneous circulation; SaO2, arterial oxygen saturation; Hb, hemoglobin; PaCO2, arterial carbon dioxide pressure; MAP, mean arterial pressure; BT, body temperature.
also significantly lower in those patients (Storm et al., 2014). As they pointed out in their discussion, low rSO2 in their study may be due to a low Hb concentration, rather than the severity of brain injury.

In an experimental study of piglets with hypoxia-ischemia, CMRO2 decreased after resuscitation (Tichauer et al., 2009). Clinically, Edgren et al. (2003) using positron emission tomography study reported that the initial CMRO2 of PCAS patients was commonly low, irrespective of whether their outcome was favorable or not. CMRO2 depends on body temperature and decreases during hypothermia (Ehrlich et al., 2002), and there was no difference in body temperature between the favorable and unfavorable groups in the present study. Therefore, low CMRO2 may not influence the difference in rSO2 between groups.

It was reported that in the majority of PCAS patients in their acute phase after cardiac arrest, the CBF and rCBF were either absent or right shifted (Sundgreen et al., 2001). In addition, during the evaluation of rSO2 for PCAS patients after ROSC, the impairment of CBF following CA is associated with poor outcome (Brady et al., 2007; Ameloot et al., 2015; Pham et al., 2015). If CBF is sustained because of mild brain injury in PCAS patients, rSO2 may not change depending on MAP and may change on SaO2, Hb, and PaCO2 as per the Fick’s principle. In this study rSO2 moderately correlated with SaO2, Hb, and PaCO2 and had no correlation with MAP in the favorable group at 24 hours. It indicates that the favorable group may have mild brain injury and CBF is sustained. Conversely, if PCAS patients with severe brain injury are completely impaired in CBF and CBF, rSO2 and MAP may not be positively correlated. This pattern might explain the patient’s situation of the unfavorable group at the start of monitoring. If CBF is right-shifted, change in CBF depending on MAP and rSO2 may positively correlate with MAP. This was observed in patients of the unfavorable group at 24 and 48 hours after ROSC. Ihara et al. (2019) reported that the CV of rSO2 in PCAS patients with abnormal EEG was significantly larger than those with normal EEG and suggested that it resulted in an impaired CVAR. This hypothesis may not contraindicate the results of this study. Patients with unfavorable outcome should have severe brain injury and the impairment of CVAR. It may indicate wide variation of CBF and wide variation of rSO2 in patients of unfavorable group, compared with those of favorable group. There is no standard value of MAP that would be appropriate for all hemodynamic targets (Ameloot et al., 2015). Due to an impaired CVAR, we could control MAP by measuring rSO2 to avoid brain ischemia for PCAS management (Sekhon et al., 2016).

The cerebral vasculature constricts by decreasing PaCO2, and this CO2 reactivity results in a reduction of CBF (Kontos et al., 1977). If CO2 reactivity is preserved without brain damage, then rSO2 and PaCO2 are positively correlated (Booth et al., 2011). In the present study, rSO2 and PaCO2 were positively correlated in the favorable and unfavorable groups, which suggests that the reactivity of PaCO2 was preserved in these patients. On the contrary, there was no significant correlation between rSO2 and PaCO2 in other conditions. In PCAS patients, CO2 reactivity was reported to be preserved, although they had severe brain injury owing to CA (Buunk et al., 1997; Bisschops et al., 2010). As mentioned above, CVAR is impaired in certain brain injuries by CA, and CBF may change depending on MAP. In such a situation, we may not evaluate PaCO2 reactivity by this method. We need to measure the response of rSO2 value individually in PCAS patients, thus changing PaCO2 by controlling the ventilator.

This study, however, has its limitations. If rSO2 is measured in patients with a normal or mildly injured brain, rSO2 should be correlated with SaO2, Hb, and PaCO2 and not with MAP. This could explain Fick’s formula (Nakashima et al., 2017) and display normal CVAR (Sundgreen et al., 2001; Brady et al., 2007; Pham et al., 2015). In this study, only patients in the favorable group at 24 hours were followed with this hypothesis. Although we could not explain this phenomenon exactly, it may be due to the following reasons: (1) the number of patients may be too small; (2) each parameter was managed within a narrow range, causing the variation range to be narrow; and (3) an unstable brain situation immediately after resuscitation at the start of monitoring and due to change in brain metabolism during the rewarming stage at 48 hours.

Pham et al. (2015) reported that early impairment of CVAR following cardiac arrest is independently associated with mortality. Our results suggest that rSO2 was moderately correlated with MAP and CVAR and could be impaired in PCAS patients with unfavorable outcome. Ehara et al. (2017) showed that in the unfavorable patients, the cerebral rSO2

|                  | SaO2  | Hb    | PaCO2 | MAP   | BT    | R²   |
|------------------|-------|-------|-------|-------|-------|------|
| **Start of monitoring** |       |       |       |       |       |      |
| Favorable group  | 0.119 | 0.345 | 0.356 | 0.123 | 0.222 | 0.485 |
| Unfavorable group| 0.269 | 0.579*| 0.023 | −0.150| 0.078 | 0.424 |
| **24 hours after ROSC** |       |       |       |       |       |      |
| Favorable group  | 0.482*| 0.422*| 0.531*| 0.004 | −0.031| 0.911 |
| Unfavorable group| 0.124 | 0.555*| 0.269*| 0.328*| 0.223 | 0.526 |
| **48 hours after ROSC** |       |       |       |       |       |      |
| Favorable group  | 0.669 | 0.559 | 1.052 | −0.336| 0.003 | 0.758 |
| Unfavorable group| 0.037 | 0.550*| 0.205 | 0.408*| 0.111 | 0.647 |

Standardized partial regression coefficients; *p < 0.05.

rSO2, regional cerebral oxygen saturation; ROSC, return of spontaneous circulation; SaO2, arterial oxygen saturation; Hb, hemoglobin; PaCO2, arterial carbon dioxide pressure; MAP, mean arterial pressure; BT, body temperature.
values increased significantly just after the start of ECPR. Taken together, we could predict the outcome for PCAS patients at a very early stage of ROSC by evaluating the relationship between rSO2 and blood pressure. Ameloot et al. (2015) suggested that there is no “one-size-fits-all” hemodynamic target for the PCAS patients because of impaired CVAR. In this study, rSO2 was changed by MAP, SaO2, Hb, and PaCO2, depending on patient’s brain severity. By evaluation of rSO2 in PCAS patients, we could optimize brain oxygen metabolic balance through management of the parameters influencing brain oxygen balance such as SaO2, Hb, MAP, and PaCO2.

Conclusion

In this study, variation of rSO2 was widely dependent on MAP in unfavorable patients, maybe because of impaired CVAR. It will be difficult to predict the outcome by absolute values of rSO2 in the case of PCAS patients. To evaluate brain injury in those patients by rSO2, we should focus on the relationship between rSO2 and blood pressure. Furthermore, in the management of PCAS patients with TTM by rSO2, we would suggest total evaluation for each parameter of SaO2, Hb, MAP, and PaCO2 to optimize brain oxygen metabolic balance.

Author Disclosure Statement

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