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Clinical paper

Regional cerebral oxygen saturation in cardiac arrest survivors undergoing targeted temperature management 36 °C versus 33 °C: A randomized clinical trial

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Abstract

Aim of study: To investigate whether regional cerebral oxygen saturation (rSO_2) diers in out-of-hospital cardiac arrest (OHCA) survivors undergoing targeted temperature management (TTM) 36 °C versus 33 °C.

Methods: A randomized clinical trial was conducted at intensive care units in two referral hospitals. Fifty-seven comatose OHCA survivors were randomized into either a 36 °C or 33 °C group. Patients were cooled and maintained at an oesophageal temperature of either 36 °C or 33 °C for 24 hours, rewarmed at a rate of 0.25 °C/hour, and maintained at <37.5 °C until 72 hours. During 72 hours of TTM, rSO_2 was continuously monitored on the left forehead using near-infrared spectroscopy (INVOS^{TM} 5100C). The rSO_2 level at 72 hours was compared between the two groups. Next, serial rSO_2 levels for 72 hours were compared using mixed eects regression. The association between rSO_2 levels and 6-month neurological outcomes was also evaluated.

Results: There were no significant dierences in the rSO_2 level at 72 hours between the 36 °C and 33 °C groups ($p = 0.372$). Furthermore, serial rSO_2 levels for 72 hours of TTM were not dierent between the two groups ($p = 0.733$). However, low rSO_2 levels, particularly at 24 hours of TTM, were significantly associated with poor 6-month neurological outcomes (odds ratio = 0.899, 95% confidence interval: 0.831–0.974). The area under the receiver operating characteristic curve of the rSO_2 level at 24 hours for poor neurological outcomes was 0.800.

Conclusions: Regardless of target temperatures, low rSO_2 levels during TTM were significantly associated with poor 6-month neurological outcomes in OHCA survivors.

Keywords: Out-of-hospital cardiac arrest Brain Oximetry Spectroscopy Near-Infrared Hypothermia Induced Prognosis

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Introduction

After achieving a return of spontaneous circulation (ROSC) following cardiopulmonary resuscitation (CPR) after cardiac arrest, cerebral ischaemia–reperfusion injury occurs.[1] Cerebral reperfusion injury is partly mediated by an imbalance between cerebral oxygen delivery and consumption.[2] Increased oxygen metabolism causes excessive oxygen consumption and an oxygen debt in brain tissues.[3] To attenuate reperfusion injury, current guidelines recommend providing targeted temperature management (TTM) between 32 °C and 36 °C for 24 hours after ROSC.[4]

In recent years, the feasibility of regional cerebral oxygen saturation (rSO_2), measured by near-infrared spectroscopy (NIRS), has been studied for assessing the cerebral oxygen metabolic status and predicting neurological outcomes in cardiac arrest survivors, but there is controversy. Several studies have reported that rSO_2 may represent the cerebral oxygen metabolic status and have prognostic value.[5–8] However, other studies have failed to demonstrate a correlation between rSO_2 levels and neurological outcomes.[9–12] RSO_2 depends on arterial oxygen saturation (SaO_2), cerebral oxygen metabolic ratio ($CMRO_2$), haemoglobin concentration, and cerebral blood flow (CBF).[13,14] Of these, the $CMRO_2$ depends on body temperature and brain injury severity.[15] CBF depends on mean arterial pressure (MAP), intracranial pressure (ICP), and cerebral vessel diameter which is regulated in part by the arterial partial pressure of carbon dioxide ($PaCO_2$).[13,14] In a variety of clinical conditions, potential influences of these factors can alter the rSO_2 level and make it difficult to establish the usefulness of rSO_2 monitoring in cardiac arrest survivors.[13–16] In particular, the effects of induced hypothermia on the rSO_2 level remain uncertain.

Therefore, we designed this randomized clinical study. We hypothesized that if MAP, haemoglobin, SaO_2, and $PaCO_2$ are kept in target therapeutic ranges during TTM, rSO_2 levels would differ in OHCA survivors undergoing TTM 36 °C versus 33 °C because of a difference in the cerebral oxygen metabolic status.

Materials and methods

Patients

This open-labelled randomized clinical trial was conducted in two referral hospitals. The study protocol was registered at ClinicalTrials.gov (NCT02889744). This study was approved by the Institutional Review Boards of Seoul National University Hospital (SNUH)/Seoul National University College of Medicine (SNUMC) (IRB No., 1601–127-739) and Seoul Metropolitan Government Seoul National University Boramae Medical Center (IRB No., 26–2017-37). Written informed consent was obtained from each participant's legally authorized representatives (LARs).

We enrolled consecutive comatose OHCA survivors who were admitted to intensive care units (ICUs), from August 2016 to December 2019. We defined coma as lacking meaningful responses to verbal commands. Exclusion criteria were non-cardiac causes including trauma, drowning, hanging, and intoxication; predicted death within 72 hours; contraindications to TTM including haemorrhage, fatal arrhythmia, and sepsis; baseline cerebral performance category (CPC) score $\geq$ 3; presence of an advanced directive to withhold or withdraw life-sustaining treatment; or lack of informed consent.[4,17] We defined 'predicted death within 72 hours' as follows: (1) serum lactate level > 15 mmol/L, despite 30 mL/kg initial crystalloid infusion, and (2–1) mean arterial pressure (MAP) < 65 mmHg, despite administration of 1 μg/kg/minute norepinephrine, or (2–2) PaO_2 < 60 mmHg, despite 100% oxygen supplementation. Patients who withdrew consent after randomization, and patients with inappropriate or ineligible consent obtained from relatives without legal authority were also excluded.

Study protocol

All of the patients were treated with standardized care, including crystalloid infusion (30 mL/kg), and vasopressor infusion to maintain a MAP > 65 mmHg monitored through an arterial catheter.[4,18] Next, they were blindly randomized in parallel at a 1:1 ratio into the 36 °C group or the 33 °C group, and were provided TTM within 1 hour after ROSC. For TTM, patients were cooled and maintained at an oesophageal temperature of either 36 °C or 33 °C for 24 hours, rewarmed at a rate of 0.25 °C/hour, and then maintained at <37.5 °C until 72 hours using an external cooling device (Artic Sun® Temperature Management System, Bard, Murray Hill, NJ).[19,20] Sedatives and neuromuscular blocking agents (NMBAs) were continuously or intermittently administered to avoid shivering. Within 24 hours after ICU admission, electroencephalography (EEG) was performed to detect the presence of seizures. Between 48 and 72 hours, follow-up EEG was performed once more. If epileptiform discharges were detected, anti-epileptic drugs were immediately administered upon consultation of neurologists. For 72 hours of TTM, we maintained a MAP $\geq$ 65 mmHg, end-tidal CO_2 ($EtCO_2$) 35–40 mmHg, peripheral oxygen saturation (SpO_2) 94–98%, and haemoglobin levels $\geq$ 8.0 g/dL (in patients with coronary artery diseases $\geq$ 10.0 g/dL).[4,8,21,22] Furthermore, rSO_2 was continuously monitored for 72 hours of TTM using INVOS™ 5100C (Medtronic, Dublin, Ireland) and INVOS™ Cerebral/Somatic Oximetry Adult Sensors (Medtronic), which were placed on the left forehead.[13] Haemodynamic and laboratory data were collected at the initiation of TTM (0 h), 24 hours (24 h), and 72 hours (72 h). Serum neuron specific enolase (NSE) levels were measured by electrochemiluminescence immunoassay (ECLIA). Since August 2017, Korean law has allowed a withdrawal of life-sustaining therapies. In patients who had no pupillary reflex and no EEG waveform after 14 days of intensive care, life-sustaining therapies were withdrawn under written permission from LARs and the approval of the Medical Ethics Committee of our institute.

The primary outcome was a difference in the rSO_2 level at 72 h between the 36 °C and 33 °C groups. The secondary outcome was a difference in serial rSO_2 levels for 72 hours of TTM between the two groups. Post hoc analysis evaluated a difference in rSO_2 levels for 72 hours between the patients who had good and poor 6-month neurological outcomes. Good neurological outcomes were defined as cerebral performance category (CPC) 1 and 2, and poor neurological outcomes CPC between 3 and 5.[23] CPC 5 includes all cause of mortality. Six-month neurological outcomes were assessed by an investigator blinded to the patients' data via telephone interview or medical record review.

Sample size calculation and randomization

From the results of previous studies, we assumed that the mean difference in the absolute rSO_2 level at 72 h between the 36 °C and 33 °C groups would be 3% with 4% standard deviation.[6,15] By referral to the Medical Research Collaborating Center (MRCC) of SNUH/SNUMC (2015–0207), a sample size of at least 58 (29 per group)

was calculated with a power of 0.8 and a significance level of 0.05 by using Power Analysis and Sample Size Software (http://www.ncss.com). Considering 15% unexpected loss, 66 participants were initially randomized by the 4, 6-block randomization method at the MRCC SNUH/SNUMC website (http://mrcc.snu.ac.kr).

Statistics

Demographic and laboratory data were analysed using Student's *t*-test or chi-square test. A difference in the rSO_2 level at 72 h between the 36 °C and 33 °C groups was analysed using Student's *t*-test. Cumulative survival was compared using Kaplan-Meier survival analysis with the log-rank post hoc test. Serial rSO_2 levels for 72 hours of TTM between the 36 °C and 33 °C groups and between the patients who had good and poor 6-month neurological outcomes were compared using the generalized linear mixed effect model with an identity link. For this test, we analysed the data with time as a continuous variable. To explore the relationships between time points and rSO_2 levels, we plotted rSO_2 levels at each time point (hour) by each group and patient. The plots did not show any nonlinear relationship. Thus, the mixed effect model including fixed effects (group, time, and group-time interaction) and random effects (patient-level random intercepts and slopes) were applied. Missing values due to unexpected death within 72 hours were not included in this analysis.

Next, the time-related effects of rSO_2 levels at 0 h, 24 h, and 72 h on poor 6-month neurological outcomes were analysed using stepwise logistic regression analysis (with an entry level of 0.05 and a stay level of 0.05). The diagnostic abilities of rSO_2 and NSE levels for 6-month neurological outcomes were calculated by the area under the curves (ACUs) for the receiver operating characteristic (ROC) curves, and their cut-off values were selected at levels with a specificity $\geq$ 99.9%.[4] Correlations between rSO_2 levels and parameters representing neuronal and systemic ischaemia–reperfusion injuries (serum NSE and lactate levels) and influencing rSO_2 levels

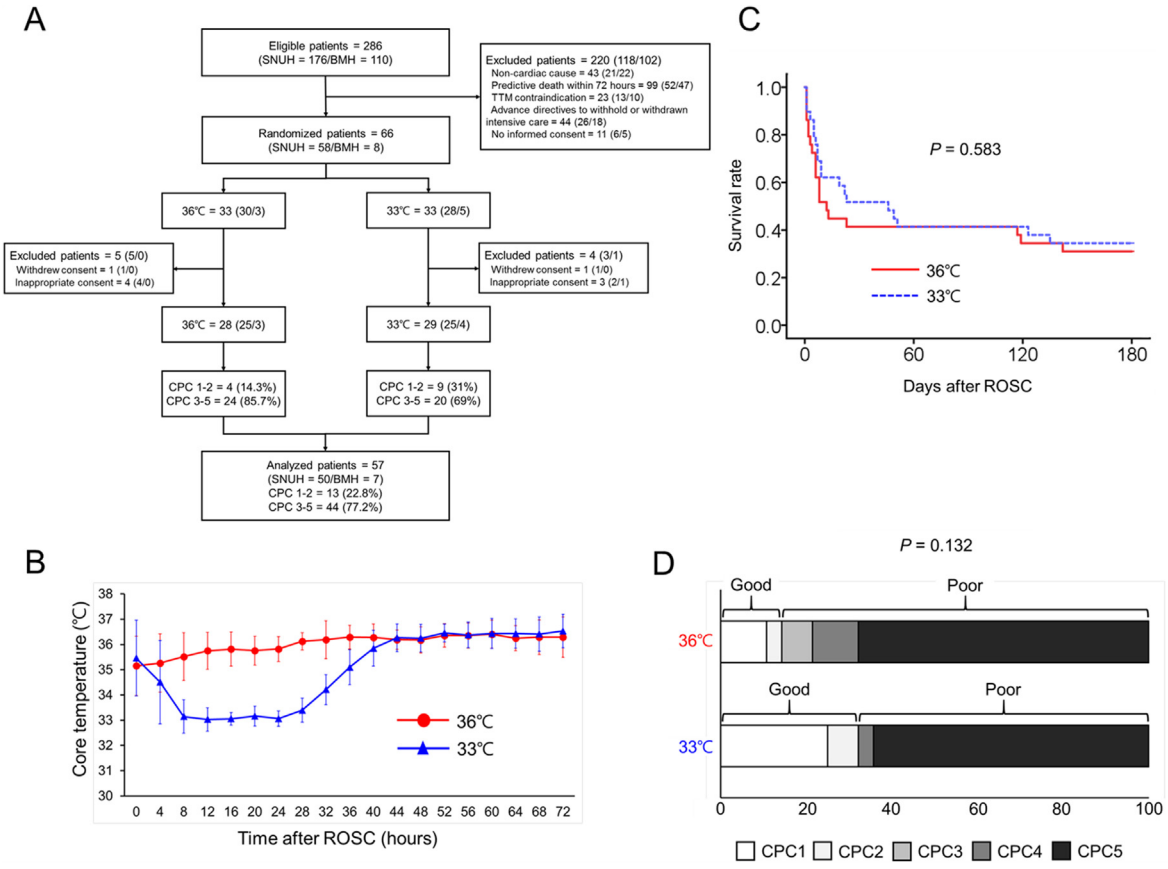

Fig. 1 – Patients' characteristics and clinical outcomes. (A) CONSORT diagram. Among the 286 comatose out-of-hospital cardiac arrest (OHCA) survivors who were admitted to the intensive care units (ICUs) of two referral hospitals, 66 provided written informed consent and were initially randomized. However, informed consents of 2 patients were withdrawn and those of 7 patients were obtained from ineligible relatives. Therefore, 57 patients were finally enrolled. Twenty-eight patients underwent targeted temperature management (TTM) 36 °C for 24 hours (the 36 °C group) and 29 patients underwent TTM 33 °C for 24 hours (the 33 °C group). Then, the patients were rewarmed at a rate of 0.25 °C/hour and were maintained at less than 37.5 °C until 72 hours. (B) Serial oesophageal temperatures for 72 hours of TTM in the 36 °C and 33 °C groups. (C) Cumulative survival. (D) Six-month neurological outcomes. Good neurological outcomes were defined as cerebral performance category (CPC) 1 and 2, and poor neurological outcomes were defined as CPC between 3 and 5. No differences were observed in cumulative survival and 6-month neurological outcomes between the 36 °C and 33 °C groups.

Table 1 – Characteristics of enrolled patients.

	Mean ± standard deviation (SD)					
	Total (n = 57)		TTM 36 °C (n = 28)		TTM 33 °C (n = 29)	
	N	%	N	%	N	%
Male gender	47	(82.5)	22	(78.6)	25	(86.2)
Age, years	69.02 ± 13.15		69.39 ± 11.48		68.66 ± 14.78	
Basal CPC	1.47 ± 0.71		1.32 ± 0.61		1.62 ± 0.78	
Underlying diseases						
DM	29	(50.9)	15	(53.6)	14	(48.3)
HT	42	(73.7)	20	(71.4)	22	(75.9)
Witnessed arrest	46	(80.7)	25	(89.3)	21	(72.4)
Bystander CPR	24	(42.1)	9	(32.1)	15	(51.7)
No flow time, minutes	4.35 ± 4.22		4.96 ± 4.22		3.76 ± 4.21	
Total collapse time, minutes	29.02 ± 17.92		32.36 ± 18.31		25.79 ± 17.25	
Initial shockable rhythm	12	(21.1)	6	(21.4)	6	(20.7)
Underwent CAG	20	(35.1)	8	(28.6)	12	(41.4)
APACHE II score	26.19 ± 5.63		27.42 ± 4.98		25.00 ± 6.05	
SOFA score	10.61 ± 3.96		10.46 ± 3.82		10.76 ± 4.15	
Brain rSO_2, %						
0 h	55.57 ± 13.21		53.75 ± 12.81		57.33 ± 13.60	
24 h	54.85 ± 13.06		55.29 ± 13.33		54.46 ± 13.06	
48 h	54.82 ± 15.86		54.93 ± 17.40		54.72 ± 14.67	
72 h	55.88 ± 13.35		57.83 ± 13.73		54.10 ± 13.06	
NSE, ng/mL						
0 h	80.38 ± 99.57		95.39 ± 103.75		65.36 ± 95.00	
24 h	130.55 ± 136.93		166.55 ± 140.72		97.54 ± 127.39	
72 h	153.51 ± 147.55		170.75 ± 147.51		137.91 ± 149.44	
Lactate, mmol/L						
0 h*	8.53 ± 4.76		9.95 ± 5.26		7.16 ± 3.85	
24 h	4.55 ± 5.16		5.46 ± 6.34		3.67 ± 3.60	
72 h	3.06 ± 3.93		2.44 ± 3.10		3.60 ± 4.52	
MAP, mmHg						
0 h	96.54 ± 32.53		91.89 ± 33.63		101.03 ± 31.36	
24 h	83.30 ± 21.89		79.08 ± 20.24		87.07 ± 22.97	
72 h	84.13 ± 21.25		81.73 ± 22.44		86.15 ± 20.41	
Hemoglobin, g/dL						
0 h	11.61 ± 2.58		11.59 ± 2.70		11.63 ± 2.51	
24 h	11.15 ± 2.82		11.06 ± 2.95		11.22 ± 2.74	
72 h	11.83 ± 6.70		11.65 ± 5.66		11.99 ± 7.54	
$PaCO_2$, mmHg						
0 h	49.69 ± 24.61		52.96 ± 29.36		46.53 ± 18.94	
24 h	37.00 ± 9.30		36.67 ± 11.20		37.30 ± 7.30	
72 h	37.46 ± 9.07		38.26 ± 10.27		36.79 ± 8.08	
PaO_2, mmHg						
0 h	194.98 ± 141.79		179.82 ± 138.69		209.61 ± 145.63	
24 h	128.63 ± 101.09		130.47 ± 137.59		126.92 ± 50.26	
72 h	108.53 ± 78.98		116.26 ± 108.05		102.04 ± 43.24	

TTM, targeted temperature management; CPC, cerebral performance category; DM, diabetes mellitus; HT, hypertension; CPR, cardiopulmonary resuscitation; CAG, coronary angiography; APACHE II score, Acute Physiology And Chronic Health Evaluation II score; SOFA score, Sequential Organ Failure Assessment score; rSO_2, regional cerebral oxygen saturation; NSE, neuron specific enolase; MAP, mean arterial pressure; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen.

(MAP, haemoglobin, $PaCO_2$, and PaO_2 levels) were evaluated using Spearman correlation analysis. *P*-values < 0.05 were considered statistically significant, and the significance levels quoted are two-sided. Statistical analyses were conducted by using SPSS version 23.0 (SPSS, Chicago, IL) and SAS version 9.4 (SAS, Cary, NC).

Results

Enrolled patients

During the study period, 286 comatose OHCA survivors were admitted to the ICUs of the two referral hospitals. Among them, 220

patients were excluded, and 66 patients whose LARs provided written informed consent were initially randomized. However, after randomization, 9 patients were excluded. Informed consents of 2 patients were withdrawn, and informed consents of 7 patients were obtained from relatives without legal authority. Therefore, in the modified intention-to-treat analysis, 57 patients were finally enrolled (Fig. 1A). Among them, 28 patients underwent TTM 36 °C and 29 patients TTM 33 °C. Thirteen (22.8%) and 44 (77.2%) patients had good (CPC, 1 and 2) and poor (CPC, 3–5) 6-month neurological outcomes, respectively (Fig. 1A). Serial oesophageal temperatures in both the 36 °C and 33 °C groups are shown in Fig. 1B.

Between the 36 °C and 33 °C groups, there were no significant differences in demographic and laboratory findings (Table 1). Furthermore, no significant differences were observed in rSO_2, MAP, haemoglobin, serum NSE, $PaCO_2$, PaO_2, or serum lactate levels between the 36 °C and 33 °C groups (Table 1). In cumulative survival and 6-month neurological outcomes, there were no differences between the two groups (Fig. 1C and 1D).

Primary outcome

There was no significant difference in the rSO_2 level at 72 h between the 36 °C and 33 °C groups. The mean difference in the rSO_2 level at 72 h was 3.74% (95% confidence interval [CI]: −4.6% to 12.1%, $p = 0.372$).

Secondary outcome

For 72 hours of TTM, no significant differences were observed in serial rSO_2 levels between the 36 °C and 33 °C groups (Fig. 2A). The mean group difference was −1.3% (95% CI: −8.573% to 6.061%, $p = 0.737$). For the mixed effect model analysis, a total of 4,104 values were read, 3,538 were used, and 566 were not used.

Post hoc analysis

When we compared the patients who had good and poor 6-month neurological outcomes, patients who had poor outcomes were older and had higher basal CPC, longer intervals from collapse to CPR and from collapse to ROSC, fewer coronary angiography procedures, and higher initial Acute Physiology And Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores than patients who had good outcomes (Table 2). Moreover, in patients who had poor outcomes, rSO_2 levels at 24 h and 48 h, MAP at 72 h, and haemoglobin levels at 0 h were lower, but serum NSE levels at 24 h and 72 h and serum lactate levels at 0 h were higher than in patients who had good outcomes (Table 2).

Serial rSO_2 levels for 72 hours of TTM were significantly lower in patients who had poor outcomes compared to those in patients who had good outcomes (Fig. 2B). The mean group difference was 13.4% (95% CI: 5.474%–21.392%, $p < 0.001$). In particular, the low rSO_2 level at 24 h was most significantly associated with poor outcomes (odds ratio = 0.899, 95% CI: 0.831–0.974, $p = 0.009$) (Supplement 1).

In ROC curve analyses, the AUC of the rSO_2 level at 24 h for poor 6-month neurological outcomes was 0.800, with a cut-off level $\leq$ 48.8% (sensitivity 44.7% and specificity 100.0%, 95% CI for specificity: 75.3%–100.0%) (Fig. 3A), and the AUC of the serum NSE level at 24 h was 0.824, with a cut-off level $\geq$ 93.0 ng/mL (sensitivity 52.9% and specificity 100.0%, 95% CI for specificity: 73.5%–100.0%) (Fig. 3B).

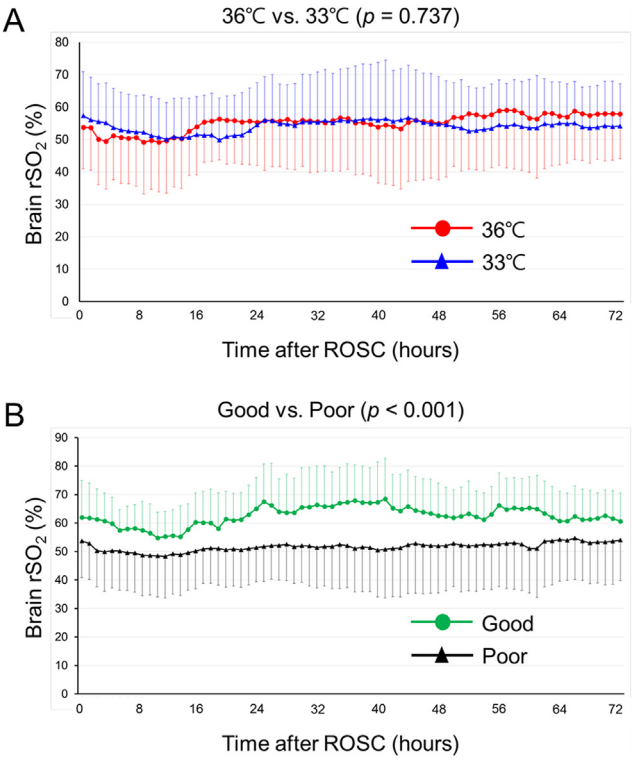

Fig. 2 – Serial regional cerebral oxygen saturation (rSO_2) levels for 72 hours of TTM. (A) Comparison of rSO_2 levels between the 36 °C and 33 °C groups. (B) Comparison of rSO_2 levels between patients who had good and poor neurological outcomes. For 72 hours of TTM, no significant differences in serial rSO_2 levels were observed between the 36 °C and 33 °C groups. However, rSO_2 levels were significantly lower in patients who had poor 6-month neurological outcomes compared to those in patients who had good outcomes. Data are presented as the mean ± standard deviation.

Correlations between rSO_2 and related parameters

At 24 h, the rSO_2 level negatively correlated with the NSE ($r = -0.420$, 95% CI: −0.635 to −0.144, $p = 0.004$) and lactate levels ($r = -0.426$, 95% CI: −0.632 to −0.165, $p = 0.002$) (Fig. 4A). Among the parameters known to affect rSO_2 levels, only MAP positively correlated with the rSO_2 level ($r = 0.491$, 95% CI: 0.250–0.676, $p < 0.001$) (Fig. 4B).

Discussions

In this randomized controlled trial, the rSO_2 level at 72 h was not significantly different between the 36 °C and 33 °C groups. Serial rSO_2 levels for 72 hours of TTM also did not differ between the two groups.

In both the 36 °C and 33 °C groups, rSO_2 levels appeared to decrease within the first few hours, and then, slowly increase up to 24 hours, as in previous studies.[6,15] A decrease in rSO_2 levels during the early period of TTM might be due to cerebral hypoperfusion occurring immediately after ROSC, no-reflow, rather than low body temperatures.[24]

Table 2 – Patients who had good versus poor 6-month neurological outcomes.

	Mean ± standard deviation (SD)						
	Total (n = 57)		Good (n = 13)		Poor (n = 44)		
	N	%	N	%	N	%	*P*
Male gender	47	(82.5)	12	(92.3)	35	(79.5)	0.426
Age, years	69.02 ± 13.15		62.23 ± 17.90		71.02 ± 10.84		0.033
Basal CPC	1.47 ± 0.71		1.08 ± 0.28		1.59 ± 0.76		0.020
Underlying diseases							
DM	29	(50.9)	4	(30.8)	25	(56.8)	0.123
HT	42	(73.7)	8	(61.5)	34	(77.3)	0.258
Witnessed arrest	46	(80.7)	11	(84.6)	35	(79.5)	1.000
Bystander CPR	24	(42.1)	9	(69.2)	15	(34.1)	0.052
No flow time, minutes	4.35 ± 4.22		1.15 ± 1.34		5.30 ± 4.33		0.001
Total collapse time, minutes	29.02 ± 17.92		16.54 ± 13.51		32.70 ± 17.51		0.002
Initial shockable rhythm	12	(21.1)	8	(61.5)	4	(9.1)	< 0.001
Underwent CAG	20	(35.1)	11	(84.6)	9	(20.5)	< 0.001
APACHE II score	26.19 ± 5.63		20.69 ± 4.52		27.82 ± 4.88		< 0.001
SOFA score	10.61 ± 3.96		8.00 ± 3.14		11.39 ± 3.87		0.004
Brain rSO_2, %							
0 h	55.57 ± 13.21		61.97 ± 13.02		53.68 ± 12.81		0.057
24 h	54.85 ± 13.06		65.03 ± 10.89		51.37 ± 11.97		0.001
48 h	54.82 ± 15.86		62.63 ± 11.40		51.92 ± 16.43		0.016
72 h	55.88 ± 13.35		60.64 ± 9.88		53.97 ± 14.21		0.094
NSE, ng/mL							
0 h	80.38 ± 99.57		53.49 ± 50.73		89.34 ± 110.33		0.135
24 h	130.55 ± 136.93		35.47 ± 20.63		164.10 ± 144.84		0.004
72 h	153.51 ± 147.55		18.28 ± 9.16		204.81 ± 142.77		< 0.001
Lactate, mmol/L							
0 h	8.53 ± 4.76		5.79 ± 4.16		9.37 ± 4.66		0.015
24 h	4.55 ± 5.16		2.54 ± 2.71		5.17 ± 5.58		0.124
72 h	3.06 ± 3.93		1.27 ± 0.52		3.67 ± 4.39		0.080
MAP, mmHg							
0 h	96.54 ± 32.53		111.69 ± 32.08		92.07 ± 31.64		0.067
24 h	83.30 ± 21.89		91.08 ± 23.91		80.78 ± 20.89		0.181
72 h	84.13 ± 21.25		96.54 ± 16.06		79.51 ± 21.27		0.006
Hemoglobin, g/dL							
0 h	11.61 ± 2.58		13.02 ± 2.30		11.18 ± 2.52		0.022
24 h	11.15 ± 2.82		12.34 ± 2.28		10.76 ± 2.89		0.053
72 h	11.83 ± 6.70		14.65 ± 10.02		10.84 ± 4.84		0.090
$PaCO_2$, mmHg							
0 h	49.69 ± 24.61		38.78 ± 11.54		52.91 ± 26.55		0.068
24 h	37.00 ± 9.30		38.13 ± 5.78		36.64 ± 10.20		0.513
72 h	37.46 ± 9.07		36.05 ± 5.23		37.96 ± 10.10		0.412
PaO_2, mmHg							
0 h	194.98 ± 141.79		169.18 ± 98.14		202.60 ± 152.43		0.355
24 h	128.63 ± 101.09		126.45 ± 69.91		129.32 ± 109.87		0.912
72 h	108.53 ± 78.98		99.41 ± 70.35		111.76 ± 82.55		0.623

CPC, cerebral performance category; DM, diabetes mellitus; HT, hypertension; CPR, cardiopulmonary resuscitation; CAG, coronary angiography; APACHE II score, Acute Physiology And Chronic Health Evaluation II score; SOFA score, Sequential Organ Failure Assessment score; rSO_2, regional cerebral oxygen saturation; NSE, neuron specific enolase; MAP, mean arterial pressure; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen.

Although no statistically significant differences were observed, the MAP in the 33 °C group seemed to be higher than that in the 36 °C group, and neurological outcomes in the 33 °C group also seemed to be better than those in the 36 °C group. These findings suggest two mechanistic possibilities. First, TTM 33 °C may not reduce cerebral oxygen metabolism when compared to TTM 36 °C. These results are consistent with previous clinical studies of neurological outcomes in cardiac arrest survivors who underwent TTM 36 °C versus 33 °C.[21] Second, TTM 33 °C may be more neuroprotective by reducing cerebral oxygen metabolism than TTM 36 °C, but rSO_2 levels might not be able to directly indicate the neuroprotective mechanism of TTM because of other mitigating factors.

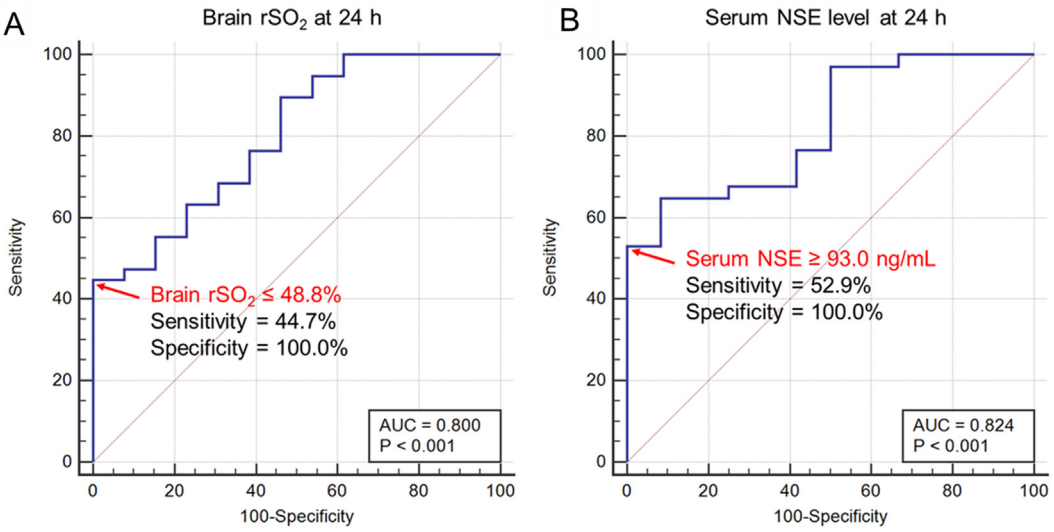

Fig. 3 – Receiver operating characteristic (ROC) curve analysis. (A) Diagnostic abilities of rSO_2 and (B) neuron specific enolase (NSE) levels for 6-month neurological outcomes. At 24 hours of TTM (24 h), the rSO_2 level was most significantly associated with poor 6-month neurological outcomes, and thus, we evaluated the diagnostic ability of the rSO_2 level at 24 h. The area under the curve (AUC) of the rSO_2 level at 24 h was 0.800, and its cut-off level for predicting poor 6-month neurological outcomes was equal to or less than 48.8% (sensitivity 44.7% and specificity 100.0%, 95% confidence interval [CI] for specificity: 75.3%–100.0%). The AUC of the serum NSE level at 24 h was 0.824, and its cut-off level was equal to or greater than 93.0 ng/mL (sensitivity 52.9% and specificity 100.0%, 95% CI for specificity: 73.5%–100.0%).

Because MAP positively correlated with rSO_2 levels, rSO_2 levels should have tended to be higher in the 33 °C group than in the 36 °C group (but they were not). This might be due to a decrease in cerebral oxygen metabolism by TTM 33 °C.

In patients who had poor neurological outcomes, a significant reduction in rSO_2 levels was observed. This sustained rSO_2 reduction might be due to more severe brain injury. In addition, a decrease in oxygen supplementation induced by global ischaemia–reperfusion injury after cardiac arrest might contribute to this reduction.[4,21,22] Our data also showed that rSO_2 levels negatively correlated with serum NSE and lactate levels, which have been known to represent neuronal injury and systemic circulatory dysfunction, respectively.[25–27] We found that the rSO_2 level at 24 h predicted 6-month neurological outcomes well and that all of the patients whose rSO_2 levels at 24 h were less than 49% had poor neurological outcomes. Until now, except for EEG, there have been no real-time monitoring tools during TTM used for predicting neurological outcomes.[28,29] We suggest that rSO_2 may be considered a potential adjunctive real-time monitoring tool for assessing brain injury severity and predicting neurological outcomes in OHCA survivors undergoing both TTM 36 °C and TTM 33 °C.

Previous studies have reported that the prognostic value of rSO_2 levels in cardiac arrest survivors is limited because of their wide range, particularly in patients with severe brain injury.[9,12] In our previous study, increases in soluble markers representing blood–brain-barrier (BBB) breakdown were associated with poor neurological outcomes in OHCA survivors.[30] When BBB breakdown occurs, cerebral oxygen supplementation depends on CBF, which is influenced by MAP, ICP, $PaCO_2$, and haemoglobin levels, rather than cerebrovascular autoregulation.[13,31–34] In the present study, to narrow the rSO_2 range, we kept influencing factors including $PaCO_2$, PaO_2, and haemoglobin levels within target ranges for 72 hours of TTM. As a result, we found that rSO_2 levels could acquire a significant prognostic value for predicting neurological outcomes.

Although no significant differences were observed in MAP between the patients who had good and poor neurological outcomes except at 72 h, rSO_2 levels positively correlated with MAP. When $PaCO_2$, PaO_2, and haemoglobin levels are kept in target ranges, CBF is mainly determined by MAP and ICP.[13,14,35] However, there have been no noninvasive ICP monitoring tools, and no routine therapies to decrease ICP in cardiac arrest survivors. In the clinical setting, only increasing MAP targets may help increase CBF.[36,37] A previous study showed that increased MAP targets were associated with improved neurological outcomes.[38] However, a routine MAP target increase using vasopressors may induce adverse events, such as increased ICP, increased myocardial oxygen consumption, and mesenteric or limb ischaemia.[14] Therefore, individualized CBF-guided optimal MAP identification is needed.[39] Until now, there have been no studies investigating whether rSO_2-guided identification of optimal MAP can improve neurological outcomes. A recent study showed that the same directional movements of MAP and rSO_2 were observed in patients with severely compromised cerebral autoregulation.[40] These data suggest that rSO_2 may be considered to be a guiding tool to identify optimal MAP in cardiac arrest survivors with severe brain injury.

This study has several limitations. First, care providers were not blinded to the patients' data including core body temperatures and rSO_2 levels. Instead, 6-month neurological outcomes were assessed by an investigator blinded to patients' data. Second, to monitor rSO_2 for 72 hours of TTM, we excluded patients who seemed to be more likely to die within 72 hours. Therefore, there were limitations in generalizing our findings to all cardiac arrest survivors. Third, there have been no previous studies that compared rSO_2 levels between cardiac arrest survivors undergoing TTM 36 °C and 33 °C, and thus,

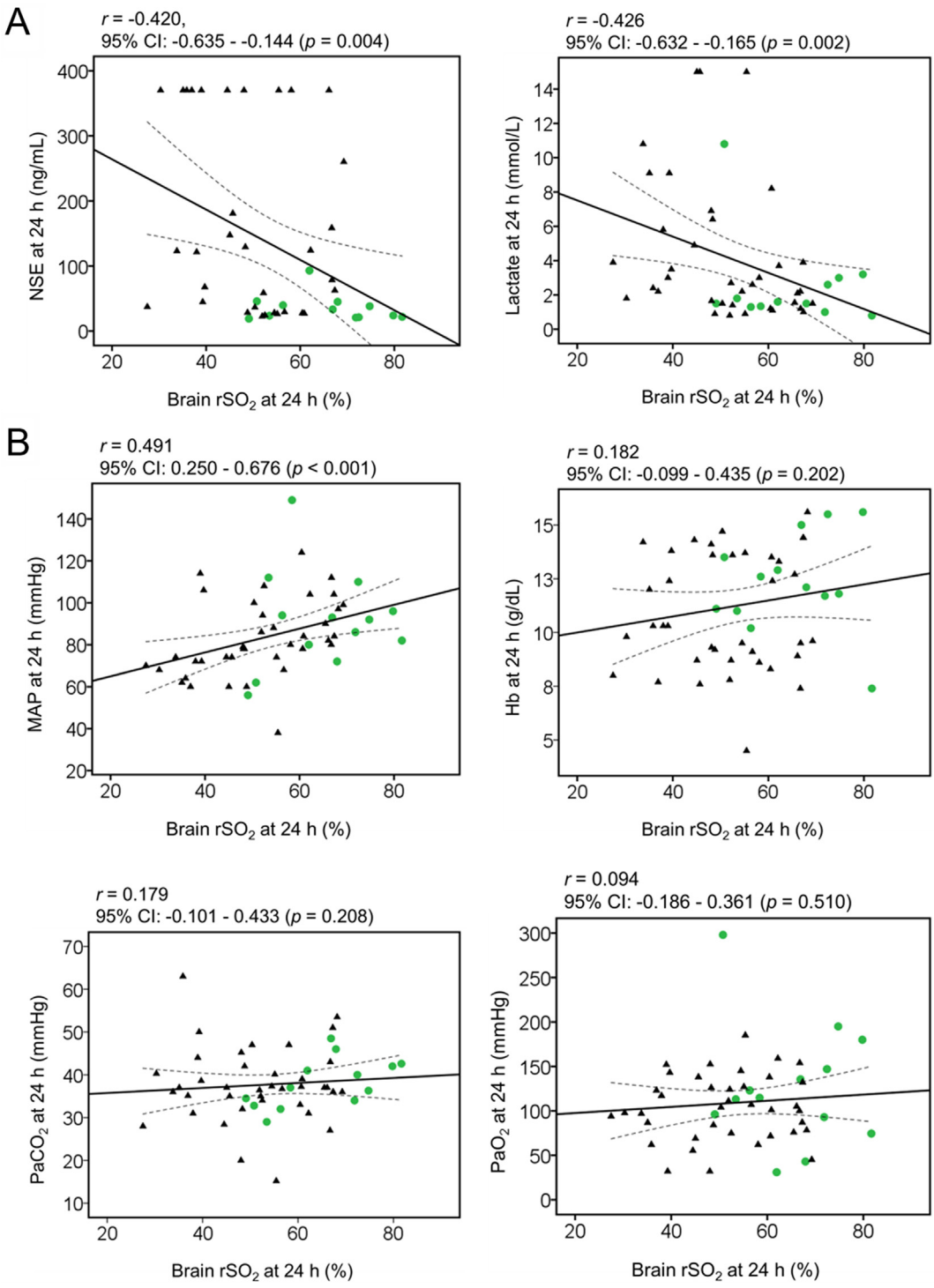

Fig. 4 – Correlations between rSO_2 levels and related parameters. (A) Correlations between rSO_2 and parameters representing neuronal injury (serum NSE) and circulatory shock (serum lactate). (B) Correlations between rSO_2 and parameters known to affect rSO_2 levels. At 24 h, the rSO_2 level negatively correlated with the serum NSE and lactate levels. Among the parameters known to affect rSO_2 levels, mean arterial pressure (MAP) was positively correlated with the rSO_2 level. However, haemoglobin, arterial partial pressure of carbon dioxide ($PaCO_2$), and arterial partial pressure of oxygen (PaO_2) levels did not correlate with the rSO_2 level. Green round markers denote good 6-month neurological outcomes and black triangles denote poor 6-month neurological outcomes. Data are presented as Spearman's rho (r) with 95% confidence interval (CI).

we estimated the sample size from previous results of rSO_2 levels changing from normothermia to induced hypothermia.[6,15] Fourth, we did not measure cerebral perfusion pressure and/or CBF, and did not analyse other mitigating parameters that could potentially influence rSO_2 levels during TTM, such as left ventricle ejection fraction; required and used doses of vasopressor/inotrope, sedatives, and neuromuscular blocking agents; sedation scales; prevalence of seizures; and antiepileptic drugs.[14,35] Furthermore, we did not routinely collect neurological examination and brain imaging data. Incorporating these parameters may help to better understand the mechanistic link between cerebral oxygen metabolism and rSO_2, and the impact of rSO_2 on neurological outcomes. In the future, the prognostic value of rSO_2 during TTM for predicting neurological outcomes, and the clinical impact of rSO_2-guided optimal MAP targets on neurological outcomes in cardiac arrest survivors should be confirmed through large-scale clinical trials.

Conclusions

Between the 36 °C and 33 °C groups, rSO_2 levels were not significantly different. Regardless of target temperatures, low rSO_2 levels during TTM were associated with poor 6-month neurological outcomes. Our findings suggest that rSO_2 may be considered a potential adjunctive real-time monitoring tool for assessing brain injuries and predicting long-term neurological outcomes in OHCA survivors undergoing TTM.

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Dataset

The study protocol was registered at ClinicalTrials.gov (NCT02889744), and all study data are included in the article and in Supplement 2.

CRediT authorship contribution statement

Woon Yong Kwon: Conceptualization, Methodology, Formal analysis, Writing – original draft, Visualization, Project administration. **Yoon Sun Jung:** Conceptualization, Methodology, Investigation, Writing – original draft, Visualization. **Gil Joon Suh:** Conceptualization, Methodology, Writing - review & editing, Project administration, Funding acquisition. **Taekyun Kim:** Formal analysis, Investigation, Data curation. **Hyeongkyu Kwak:** Investigation. **Taekwon Kim:** Investigation. **Jeong Yeon Kim:** Investigation, Data curation. **Min Sung Lee:** Investigation. **Kyung Su Kim:** Investigation, Writing - review & editing. **Jonghwan Shin:** Conceptualization, Investigation. **Hui Jai Lee:** Investigation. **Kyung Min You:** Investigation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2021.07.026.

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