Effects of therapeutic hypothermia on cerebral tissue oxygen saturation in a swine model of post-cardiac arrest

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Abstract. Since the introduction of therapeutic hypothermia (TH), trends have changed in the monitoring indicators used during and after cardiac arrest. During hypothermia, the cerebral metabolic rate of oxygen is reduced, which leads to uncertainty in regional cerebral tissue oxygen saturation ($S_{ct}O_2$). The aim of the present study was to evaluate the effect of TH on changes in $S_{ct}O_2$ using near-infrared spectroscopy. A total of 23 male domestic pigs were randomized into three groups: TH (n=9), normothermia (NT; n=9) and control (n=5). Animals in the control group underwent surgical preparation only. The animal models were established using 8 min of ventricular fibrillation and 5 min of cardiopulmonary resuscitation. In the TH group, at 5 min after resuscitation, the animals were cooled with a cooling blanket and ice packs for 24 h. $S_{ct}O_2$ was recorded throughout the experiment. In all groups, The mean arterial pressure, arterial carbon dioxide partial pressure, arterial oxygen partial pressure, lactate, neuron-specific enolase (NSE) and S100B were measured at baseline and at 1, 3, 6, 12, 24 and 30 h after resuscitation. $S_{ct}O_2$ significantly decreased after ventricular fibrillation, compared with the baseline. Following resuscitation, the $S_{ct}O_2$ values gradually increased to 55.6±3.8% of baseline in the TH group and 51.2±3.5% in the NT group (P=0.039). Significant differences between the two groups were observed, starting at 6 h after cardiac arrest. Throughout the hypothermic period, NSE and S100B showed an increasing trend, then decreased during rewarming in the TH and NT groups. NSE and S100B showed greater improvement in the TH group compared with the NT group at 6 and 24 h after resuscitation. Following cardiac arrest, therapeutic hypothermia could increase $S_{ct}O_2$ after resuscitation and could improve neurological outcome. In conclusion, $S_{ct}O_2$ may be a feasible marker for use in the early assessment of brain damage during and after cardiac arrest.

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Abbreviations: CPR, cardiopulmonary resuscitation; MAP, mean arterial pressure; NIRS, near-infrared spectroscopy; NSE, neuron-specific enolase; NT, normothermia; PaO_2, arterial oxygen partial pressure; $PaCO_2$, arterial carbon dioxide partial pressure; ROSC, return of spontaneous circulation; $S_{ct}O_2$, cerebral tissue oxygen saturation; TH, therapeutic hypothermia

Key words: cardiac arrest, post cardiac arrest syndrome, hypothermia, cerebral tissue oxygen saturation, near infrared spectroscopy

Introduction

Among patients who exhibit the return of spontaneous circulation (ROSC) upon arrival at emergency departments, and who do not survive until hospital discharge, ~70% succumb to post-anoxic neurological injury (1). There is an urgent requirement for early assessment and monitoring of brain damage following cardiac arrest. Monitoring approaches, including neurological evaluation, cranial CT, electroencephalography and somatosensory evoked potentials, have been designed to assess brain damage after cardiac arrest (2). In addition, serum markers [neuron-specific enolase (NSE) and S100B] are easily available, observer-independent and have been indicated to reflect the severity of brain damage accurately, as well as improve early evaluation and the quantification of post-cardiac arrest brain damage (3). However, these serum markers require collection of blood samples, which is invasive and unsustainable for continued monitoring (4). Furthermore, the results are not available in real time.

Regional cerebral tissue oxygen saturation ($S_{ct}O_2$), which is monitored in a non-invasive manner using near-infrared spectroscopy (NIRS), constitutes a potentially feasible marker for the early assessment of brain damage following cardiac arrest (5). Examinations of the role of $S_{ct}O_2$ during and after cardiac arrest have revealed that $S_{ct}O_2$ levels increase with high-quality cardiopulmonary resuscitation (CPR) during cardiac arrest, and that $S_{ct}O_2$ levels are correlated with outcomes, including ROSC and survival (6-8). However, there is variability in $S_{ct}O_2$ based on the oxygen penetration of arteries, veins, capillaries and

nonvascular tissue, such that baseline values among subjects vary by ~10% (9). Therefore, cerebral and tissue oximetry values are more appropriate for monitoring trends than for use as absolute indices of tissue oxygenation.

Due to the absence of baseline measurements and uncontrolled experiments, as well as the generally limited numbers of samples, there has been minimal discussion regarding sequential changes in $S_{ct}O_2$ following ROSC (10). Hypothermic therapy is the only treatment with proven efficacy in terms of neurological outcome after cardiac arrest (11,12). $S_{ct}O_2$ remains uncertain due to hypothermic reduction of the cerebral metabolic rate of oxygen (10). Although NIRS monitoring is growing in popularity, definitive data regarding the benefits of its use remain sparse. Therefore, further research is required. The aim of the present study was to elucidate variations in $S_{ct}O_2$ from the time of cardiac arrest until 30 h after resuscitation in an animal model of hypothermia, to establish the usefulness of $S_{ct}O_2$ monitoring during and after cardiac arrest.

Table I. Selected signs of the moribund state[a] (14).

Impaired mobility (unable to reach food and water)
Inability to maintain upright position
Prolonged lack of activity (2-3 days in duration)
Labored breathing and cyanosis
Prolonged decreased food and water intake
Extreme or prolonged weight loss/emaciation
Prolonged diarrhea or constipation
Biochemical or physical evidence of organ failure
Bleeding from an orifice
Unconsciousness

[a]Any one of the signs may be criteria for euthanasia.

Materials and methods

Ethics. This was a prospective, randomized, controlled experimental study, using a porcine model of cardiac arrest and resuscitation. The protocol of the current study was approved by the Animal Care and Use Committee of the Medical School of Zhejiang University. Animal care and experiments were conducted in accordance with the guidelines of the Institutional Animal Care and Use Committee (13).

Animal preparation. A total of 23 healthy male domestic pigs (4-6 months; 36.5±2 kg) were supplied by Shanghai Jiagan Biological Technology Co., Ltd. The research animals were maintained in standard atmospheric pressure, a 12/12-h light/dark cycle, room temperature (20-25˚C), and 60-80% humidity. Animals had access to food and water *ad libitum*. Animals were fasted overnight with free access to water prior to the commencing of experiments. Anesthesia induction was initiated by intramuscular injection of ketamine (20 mg/kg) and completed via an ear vein injection of sodium pentobarbital (30 mg/kg). Tracheal intubation was performed and mechanical ventilation was applied at a rate of 25 breaths/min, with peak inspiratory pressure of 25 cm H_2O and positive end-expiratory pressure of 5 cm H_2O. After central vascular access was achieved, hydration was maintained with 5% dextrose and 0.9% NaCl and anesthesia was maintained with sodium pentobarbital (8 mg/kg/h) and fentanyl (2 μg/kg/h). Ventilation rate and airway pressure were adjusted to maintain arterial carbon dioxide partial pressure ($PaCO_2$) at 35-45 mmHg. Femoral arteries and veins were cannulated for the measurement of aortic pressure and core temperature, and for the collection of blood samples. All catheters were flushed intermittently with saline containing bovine heparin (5 IU/ml). Ventricular fibrillation (VF) was induced by advancing a 5-Fr pacing catheter (EP Technologies, Inc.) from the right external jugular vein into the right ventricle. Catheter position was confirmed by characteristic pressure morphology and fluoroscopy. For all animals, body temperature was maintained at 36-38˚C during the preparation.

NIRS, concept and device. Prior to the induction of VF, NIRS probes were placed on the supraorbital region above the eyebrows, ~4 cm apart, over the frontoparietal cortex and covered to prevent ambient light interference. $S_{ct}O_2$ was continuously monitored with a Tissue Oxygenation Monitor (EGOS-600A; Suzhou Engin Bio-medical Electronics Co., Ltd.), which measured the difference between oxygenated and deoxygenated hemoglobin in venous, arterial and capillary blood. This also served as an assessment of cerebral perfusion and delivery, as well as uptake of oxygen. $S_{ct}O_2$ indicates adequate blood flow and oxygen delivery in relation to oxygen consumption, rather than directly measuring cerebral blood flow or tissue oxygenation. Since ~70% of the sampled blood is venous, normal $S_{ct}O_2$ is approximately 60-80%. Thus, $S_{ct}O_2$ decreases when oxygen supply falls relative to oxygen uptake and requirements and increases when oxygen supply increases relative to uptake and requirements (5).

Experimental protocol. Baseline measurements were obtained 15 min prior to the induction of VF in all groups. The animals were randomized into three groups, using the sealed envelope method: i) Therapeutic hypothermia (TH) group; ii) Normothermia (NT) group; and iii) Control group. Control animals only underwent surgical preparation, including endotracheal intubation and all venous and arterial catheterizations, without cardiac arrest and resuscitation. In the NT and TH groups, VF was induced via the application of a 1 mA alternating current through the 5-Fr pacing catheter, delivered to the right ventricular endocardium. Mechanical ventilation was discontinued after onset of VF. After 8 min of untreated VF, CPR was manually performed at a ratio of 30:2 (compression to ventilation). Compression quality was continuously monitored using the ZOLL feedback device (ZOLL Medical Corporation) to guarantee optimal compressions (depth of 50-60 mm and rate of 100-120/min). Ventilation was performed using a CPR simple respirator with room air. After 2.5 min of CPR, the first bolus of epinephrine (procaine and adrenaline injection, Fuzhou Neptunus Fuyao Pharmaceutical Co., Ltd.; 20 g/kg) was administered. After 5 min of CPR, defibrillation was attempted by the delivery of a single 150-J biphasic waveform electrical shock. ROSC was defined as an unassisted HR >100/min demonstrated by arterial blood pressure wave forms. Following ROSC, the $SctO_2$, mean arterial pressure, arterial carbon dioxide partial pressure,

Table II. Baseline characteristics.

Variables	TH group (n=9)	NT group (n=9)	Control group (n=5)	P-value
Body weight, kg	36.3 (3.1)	36.9 (2.7)	36.2 (3.0)	0.901
Heart rate, beats/min	108.6 (11.0)	105.4 (13.4)	104.4 (5.0)	0.762
Mean aortic pressure, mmHg	113.6 (12.0)	121.4 (12.4)	119.8 (7.8)	0.395
End-tidal CO_2, mmHg	39.4 (3.3)	40.1 (2.9)	39.6 (1.7)	0.872
Core temperature, ˚C	37.9 (0.3)	38.0 (0.3)	37.9 (0.4)	0.891
ROSC	8/9	7/9	5/5	0.172

Data are presented as mean (standard deviation). TH, therapeutic hypothermia; NT, normothermia; ROSC, return of spontaneous circulation.

arterial oxygen partial pressure, lactate, NSE and S100B were observed in all groups for 30 h after ROSC, then all the catheters were removed, the wounds closed, the animals taken off the ventilator when awakened and then returned to their cages in the laboratory. For 2 weeks, one researcher took daily measurements of several objective parameters (food/water consumption, body weight and body surface temperature). Animals were immediately euthanized with an intravenous injection of 150 mg/kg sodium pentobarbital upon reaching the moribund state/humane endpoints to reduce the amount of animal suffering (Table I; 14).

Following ROSC, mechanical ventilation was continued with FiO_2 of 0.21 for 30 h. In the TH group, TH was implemented at 5 min after resuscitation via surface cooling with a cooling blanket and ice packs, to reach a temperature of 32-34˚C as quickly as possible; this was maintained for 24 h, and was followed by a rewarming rate of 1˚C/h for 5 h. In the NT and control groups, the temperature was maintained at approximately 36-38˚C during the 30 h observation period.

Venous blood samples were collected through a central venous catheter and the first 10 ml of blood was discarded to ensure that the sample was not mixed with normal saline and heparin diluent. Immediately after sampling, the blood in the tubes was mixed by manually spinning and inverting to prevent coagulation, carefully avoiding the formation of foam, then placed on a mixture of water and ice to ensure a constant temperature of ≤4˚C, and monitored using a thermometer. The tubes were centrifuged within 1 h of collection at 1,500 x g for 15 min at 4˚C. The plasma was then separated and stored as aliquots in plastic tubes at -70˚C until assayed. Arterial blood samples were analyzed within 1 min of collection. The experimental pipeline was summarized in Fig. 1.

Measurement. Hemodynamics, electrocardiogram data and blood temperature were continuously recorded using a patient monitoring system (BeneView T6; Shenzhen Mindray Bio-Medical Electronics Co., Ltd.). Coronary perfusion was calculated as the difference between decompression diastolic aortic and time-coincident right atrial pressure, which was measured at the end of each minute of precordial compression. $S_{ct}O_2$ was continuously monitored at baseline and at 1, 3, 6, 12, 24 and 30 h after ROSC. Venous and arterial blood samples were collected at the same time points. Serum concentrations of NSE and S100B were measured using ELISA assay kits (MEXN-R0832, Shanghai Meixuan Biotechnology Co., Ltd.). Arterial blood gas and lactate were measured using a Blood Gas/Electrolyte Analyzer (Model 5700; Instrumentation Laboratory). All assays were performed in a blinded manner by an independent member of the laboratory staff.

Statistical analysis. Statistical analysis was performed using SPSS software (version 19.0, IBM Corp.). Changes in $S_{ct}O_2$ hemodynamic measurements over time were compared using the one-sample Wilcoxon signed rank test. The results are presented as the median (interquartile range), mean (standard deviation), or percent (%), as indicated. Comparisons between time-based measurements within each group were performed using a repeated-measurement ANOVA. If there was a significant difference in the overall comparison of groups, comparisons between any other 2 groups were performed using a Bonferroni test. $P<0.05$ was considered to indicate a statistically significant difference.

Results

During the study period, 20/23 pigs were successfully resuscitated after cardiac arrest and were observed for 30 h (8/9 pigs in the TH group, 8/9 pigs in the NT group and 4/5 pigs in the control group). One pig in NT group was successfully resuscitated, then succumbed 12 h later. There were no significant differences in baseline characteristics, including hemodynamics and body temperature, among the three groups (Table II). Throughout CPR, no differences were observed in the duration of CPR, epinephrine dosage, hemodynamics, number of shocks required to establish ROSC, or subsequent incidence of recurrent VF between the TH and NT groups (Table III). Following ROSC, mean arterial pressure (MAP) was initially 117.9±11.3 mmHg, then remained >100 mmHg throughout the 30 h observation period.

In the TH group, body temperature was rapidly reduced from 37.9±0.3˚C to 34.9±0.9˚C within 2 h after ROSC. Thereafter, a temperature of 32-34˚C was maintained until 24 h after ROSC, followed by rewarming at a rate of 1˚C/h for 5 h (Fig. 2). The temperature of animals in the control and NT groups were maintained at 37-38˚C throughout the experiment.

Fig. 3 indicated the course of MAP, arterial oxygen partial pressure (PaO_2), $PaCO_2$ and lactate throughout the 30 h following ROSC in the three groups. After ROSC, MAP decreased but remained at a normal physiological level of >98 mmHg in all animals. In the TH group, post-resuscitation $PaCO_2$ gradually increased and was significantly greater

Table III. Characteristics during cardiopulmonary resuscitation.

Variables	TH group (n=8)	NT group (n=7)	P-value
Duration of CPR, min	5 (0)	5.6 (1)	0.158
Number of shocks to ROSC	1.7 (1.4)	3.29 (2.5)	0.084
Epinephrine dosage, mg	71.5 (71.5)	1025.7 (395.6)	0.345
Prevalence of recurrent VF	0.8 (1.4)	1.7 (2.4)	0.762
CPP in PC_1, mmHg	17.8 (2.6)	17.4 (3.2)	0.379
CPP in PC_2, mmHg	22.8 (3.4)	21.9 (2.4)	0.591
CPP in PC_3, mmHg	28.6 (5.1)	28.7 (3.2)	0.115
CPP in PC_4, mmHg	37.8 (4.4)	37.1 (3.9)	0.892
CPP in PC_5, mmHg	27.9 (5.2)	27.1 (4.7)	0.691

Data are presented as mean (standard deviation). TH, therapeutic hypothermia; NT, normothermia; CPR, cardiopulmonary resuscitation; VF, ventricular fibrillation; CPP, coronary perfusion pressure; PC_n, n min after precordial compression.

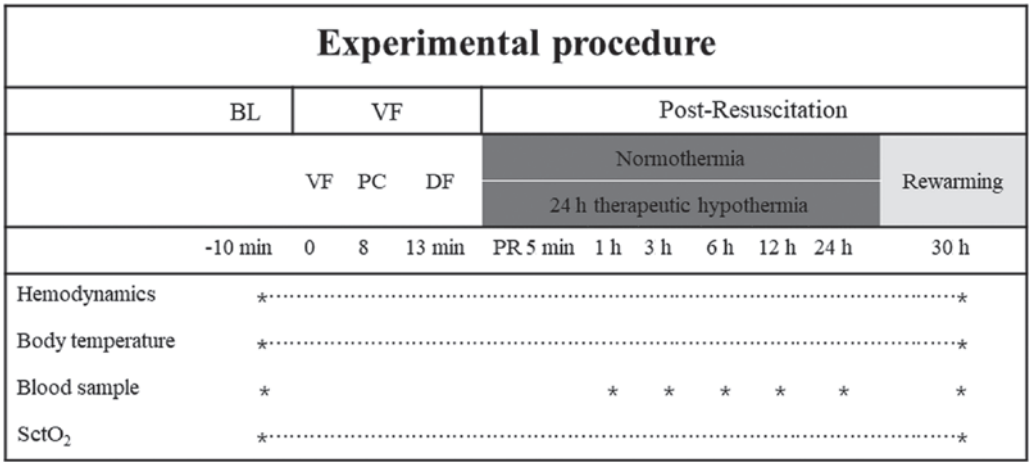

Figure 1. Experimental pipeline and procedure. BL, baseline; DF, defibrillation; PC, precordial compression; PR, post resuscitation; VF, ventricular fibrillation; $S_{ct}O_2$, cerebral tissue oxygen saturation.

compared with the NT group at 6, 12 and 24 h (P<0.05), then decreased during the rewarming period. There no significant differences were observed in arterial PaO_2 or lactate between the NT and TH groups.

Biomarkers of brain damage (NSE, S100B) by blood samples. Following ROSC, serum levels of NSE were significantly increased to 40.00±3.78 ng/ml and 45.29±2.69 ng/ml in all resuscitated animals in the TH and NT groups during the hypothermic period, then decreased to 31.50±2.73 ng/ml and 35.29±2.75 ng/ml at rewarming time (all P<0.05; Fig. 4). Serum levels of S100B were significantly increased to 3640.75±162.93 pg/ml and 4067.86±154.07 pg/ml in all resuscitated animals in the TH and NT groups during the hypothermic period, then decreased to 3282.75±205.42 pg/ml and 3914.86±177.64 pg/ml at rewarming time (all P<0.05; Fig. 4). Throughout the experiment, serum levels of NSE and S100B increased after VF and resuscitation, then declined at rewarming time in both TH and NT groups. However, NSE and S100B were lower in the TH group compared with the NT group after ROSC; these differences were significant at 12 and 6 h after ROSC (all P<0.05; Fig. 4).

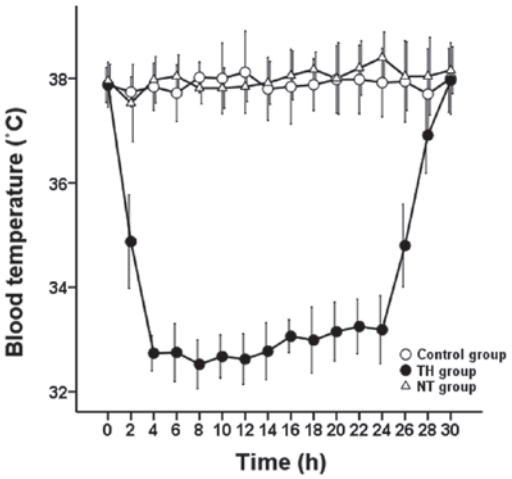

Figure 2. Blood temperature (˚C) after resuscitation. TH, therapeutic hypothermia; NT, normothermia; BL, baseline.

$S_{ct}O_2$ obtained by NIRS. Mean $S_{ct}O_2$ was monitored from the initiation of VF (baseline) until 30 h following ROSC, and the

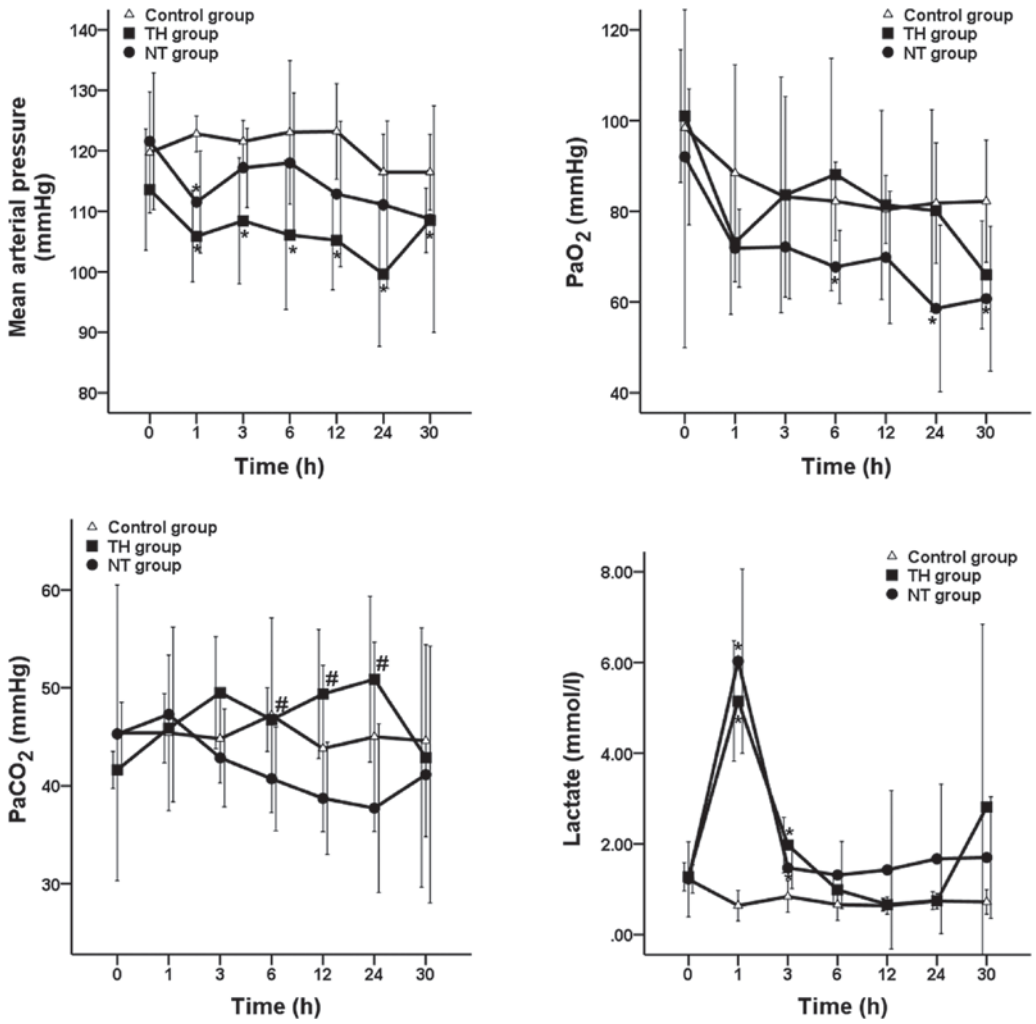

Figure 3. Course of hemodynamic parameters, mean arterial pressure, arterial carbon dioxide pressure, arterial oxygen pressure and lactate. *P<0.05, vs. control group; #P<0.05, vs. NT group. MAP, mean arterial pressure; $PaCO_2$, arterial carbon dioxide tension; PaO_2, arterial oxygen tension.

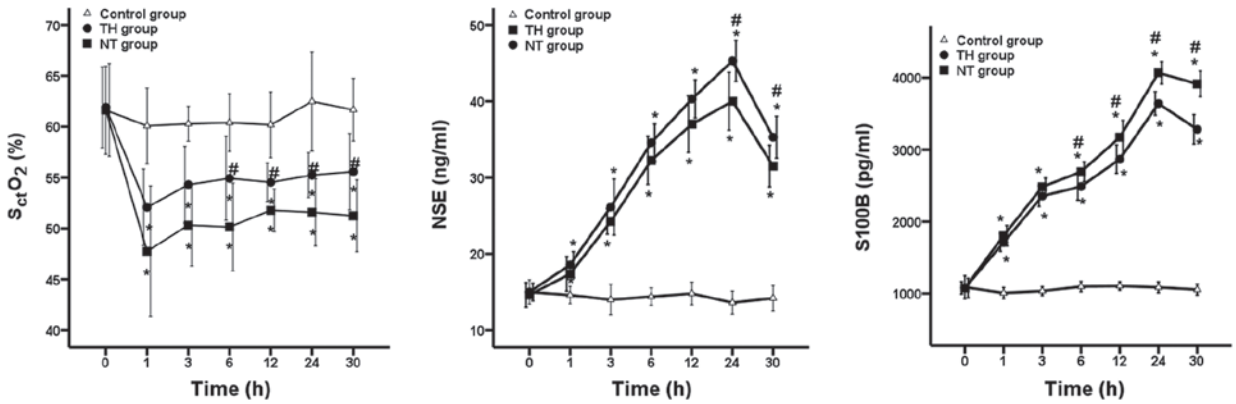

Figure 4. Dynamic changes of $S_{ct}O_2$, NSE and SB100 in three groups after CPR. *P<0.05, vs. control group; #P<0.05, vs. NT group; TH, therapeutic hypothermia; NT, normothermia.

mean $S_{ct}O_2$ values at baseline were 61.9% (4.0%) in the TH group and 61.6% (4.5%) in the NT group (P=0.155). The mean $S_{ct}O_2$ values after 8 min of VF were 41.6% (3.5%) and 41.2% (3.6%) (P=0.664) in the TH and NT groups, respectively (Fig. 5). The mean $S_{ct}O_2$ significantly decreased after 8 min of VF in the two groups, compared with $S_{ct}O_2$ at baseline (P<0.001 and P<0.001). During 5 min of CPR, the mean $S_{ct}O_2$ values gradually increased to 48.3% (2.74%) and 47.0% (2.40%), but there were no significant differences between the TH and NT groups (P=0.524). Following ROSC, a progressive increase in mean $S_{ct}O_2$ was observed in both groups, such that stable values were reached at approximately 12 h after ROSC

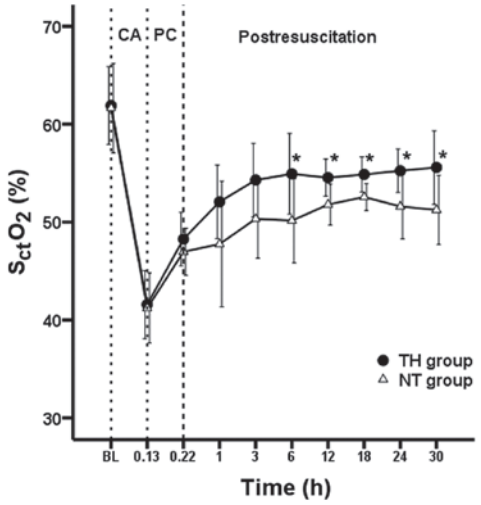

Figure 5. Dynamic changes of $S_{ct}O_2$ during the whole experiment. *P<0.05, vs. NT group. $S_{ct}O_2$, cerebral tissue oxygen saturation; TH, therapeutic hypothermia; NT, normothermia; BL, baseline; CA, cardiac arrest; PC, precordial compression.

in the two groups. $S_{ct}O_2$ values increased to 55.2% (2.2%) in the TH group and 51.2% (3.5%) in NT group at 24 h after ROSC (P=0.024). Finally, $S_{ct}O_2$ values further increased to 55.6% (3.8%) in the TH group and 51.2% (3.5%) in the NT group during the rewarming period (P=0.039; Fig. 5). Throughout the experiment, $S_{ct}O_2$ declined after VF, then increased following ROSC in the TH and NT groups. However, $S_{ct}O_2$ values in the TH group were greater compared with the NT group at 6 h after ROSC (54.9% vs. 50.1%; P=0.047).

Discussion

The present study monitored $S_{ct}O_2$ and biomarkers of brain injury in the overall course from the time of cardiac arrest until 30 h after ROSC in the TH and NT groups. Hemodynamics and PaO_2 were similar in both treatment groups. $S_{ct}O_2$ declined after VF, then increased in both treatment groups. NSE and S100B began to show differences from 6 h onwards, when values were compared between the TH and NT groups. $S_{ct}O_2$ was significantly greater in the TH group compared with the NT group at 6 h after ROSC. Therefore, the results of the present study indicated that therapeutic hypothermia could increase $S_{ct}O_2$.

The current study used a model of out-of-hospital cardiac arrest (OHCA), which comprised 8 min of untreated VF, followed by CPR at a ratio of 30:2. Earlier studies (15,16) have demonstrated that this model is feasible to explore monitoring of and protection against multiple organ injuries after resuscitation (for example in brain injuries). Furthermore, OHCA is associated with increased levels of morbidity and mortality worldwide and the majority of patients who attain ROSC often exhibit poorer neurologic outcomes, compared with those who experience in-hospital cardiac arrest (17). Therefore, it was hypothesized that it might be useful to evaluate the values and dynamics of continuous $S_{ct}O_2$ measurements during OHCA, particularly around the time of ROSC (18).

The biomarkers NSE and S100B are associated with the neurological outcomes and serve important roles in prognostication because they are nearly universally accessible and are inexpensive (3). In the present study, a consistent trend between S100B and NSE in NT and TH groups was observed throughout the 30 h observation period. Furthermore, the levels of S100B and NSE were higher in NT and TH groups compared with the control group, which indicated the presence of brain damage after cardiac arrest in the two groups. The level of S100B in TH group was lower compared with the NT group from 6 h after ROSC, while the NSE level was lower in TH group beginning at 24 h after ROSC compared with NT group. These finding were consistent with those of previous studies (19,20). NSE levels have indicated promising results only at later stages (>24 h after cardiac arrest) (21). S100B serum levels can assess overall cerebral outcome and survival following cardiac arrest at earlier points than other methods (22). However, these markers require the collection of blood samples, which is invasive and unsustainable for continued monitoring. Furthermore, the results are not available in real time.

To maximize the effectiveness of CPR and increase the likelihood that victims will survive without major neurological deficits, continuous monitoring is required to determine the balance between cerebral oxygen demand and delivery (11,23). NIRS is a noninvasive optical technique that uses near-infrared spectrum photons (700-1,300 nm) to calculate hemoglobin saturation (24,25). At these wavelengths, oxyhemoglobin and deoxyhemoglobin exhibit different absorption properties. A tissue oximeter could calculate the total concentrations of oxyhemoglobin and deoxyhemoglobin, thus enabling assessments of mixed oxygen saturation in tissues. As NIRS measures the oxygen saturation in all vessels <1 mm diameter (including arteries, capillaries and venules) (26), it can provide readings in instances of low blood flow, independently of pulsatile flow, including the flow exhibited during cardiac arrest. Its prognostic value has been validated in recent studies (5,27). NIRS could offer a large clinical benefit in that it alerts clinicians promptly, enabling implementation of corrective interventions. A meta-analysis indicated clinicians should consider NIRS saturation trends during resuscitative efforts (5,28).

The present study investigated sequential changes and the physiological significance of $S_{ct}O_2$ during therapeutic hypothermia and normal temperature immediately following ROSC (29-31). After cardiac arrest, $S_{ct}O_2$ decreased, then progressively increased in the TH and NT groups. This decrease could be explained by the onset of different pathophysiological mechanisms after cardiac arrest. During 5 min of CPR, a steep increase in $S_{ct}O_2$ was observed, which is likely to be related the initiation of CPR, as described in a previous study (32).

Within the first few hours after ROSC, the NT group showed a significant decrease in cerebral oxygenation, compared with baseline levels. Low $S_{ct}O_2$ in this context might be related to an inadequate oxygen supply to meet cerebral oxygen demand, and may indicate cerebral ischemia caused by unstable hemodynamics, hypoxia or reduced $PaCO_2$, rather than a cerebral metabolic suppression. Another cause of the reduction in $S_{ct}O_2$ values is the continuation of a no-reflow phenomenon exhibited by the brain, which can be caused by post-ischemic hypoperfusion, increased blood viscosity, reduced small-vessel caliber, or impaired microvascular perfusion. As a result, cerebral blood flow might be reduced, regardless of normal blood pressure. Some studies have shown that severe brain damage might cause metabolic depression and hyperemia and that increased

$S_{ct}O_2$ may occur in the very early stage of post-cardiac arrest syndrome (8,27). Therefore, the significance of higher or lower $S_{ct}O_2$ in the early post-resuscitation phase remains to be elucidated. In the present study, the overall trend following ROSC demonstrated a progressive increase, which reached stable values after ~6 h in both groups.

Significant increases in $S_{ct}O_2$ were observed at 6 h after ROSC in the TH group, compared with the NT group, which is consistent with the findings of a previous study (7). TH reduces cerebral oxygen consumption (33,34) and suppresses cerebral reperfusion injury, which is characterized by increased intracellular levels of glutamate and oxygen free-radical reactions; both of these phenomena occurring when cerebral blood flow is restored after resuscitation (35,36). Experimental studies and previous clinical trials have demonstrated that mild hypothermia may be superior to NT for the maintenance of cerebral oxygenation and neurological function (37,38). However, no significate differences were observed in $SctO_2$ between NT and TH groups at the early stages (1, 3 h) of post-resuscitation. In the TH group, the body temperature decreased and only reached a stable level at 3 h after ROSC. Perhaps the unstable temperature affected the protective outcome of hypothermia and caused the no significant P-values, similar to a previous study (15).

The present study possessed several limitations. One potential limitation was that the sample size of animals was small, but all the tests suggested that there was a difference between groups. Focusing on the $S_{ct}O_2$ in a larger sample clinical study should be performed in the future. Additionally, cerebral hemodynamic parameters (transcranial doppler or jugular bulb oxygenation) were not assessed in conjunction with changes in $S_{ct}O_2$, although a combination of assessment with these parameters could improve understanding of cerebral hemodynamic disturbances. However, jugular bulb oxygenation is an invasive technique that is difficult to perform in post-cardiac arrest animals. In addition, its use in such animals is difficult to justify. NIRS is feasible for use in monitoring the oxygen saturation in all vessels <1 mm diameter within the human brain, but anatomical differences in the thickness of the forehead between pigs and humans might limit detection capabilities. A higher rate of rewarming of 1˚C/h was also applied, based on the finding in a previous study (39). However, current guidelines indicate that patients should be rewarmed at a rate of 0.25-0.5˚C/h (11). Additionally, although all animals were continuously monitored under anesthesia throughout the experiment, post-resuscitation neurologic function was not evaluated. Lastly, one approach alone is unlikely to reflect the brain injury accurately after cardiac arrest. A multimodal approach for neurologic assessment has been demonstrated to be effective and the optimal sequential combination of tests requires further investigation (40).

The finding of the present study indicated that, following cardiac arrest, therapeutic hypothermia could increase $S_{ct}O_2$ following ROSC and it was demonstrated that it could improve overall neurological outcome. Additionally, $S_{ct}O_2$ was feasible for use as an early marker of brain damage during and after cardiac arrest.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

MZ and ZL designed the study, CW and JX analyzed and summarized the literature and were responsible for writing the manuscript. XJ and QC analyzed the data. XL, AQ, MW performed the experiments. MZ, ZL, AQ, CW and JX assisted in providing constructive analysis and interpreted the data. All authors read and approve the final manuscript.

Ethics approval and consent to participate

The protocol of the current study was approved by the Animal Care and Use Committee of the Medical School of Zhejiang University. Animal care and experiments were conducted according to Institutional Animal Care and Use Committee guidelines.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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