TRANSLATIONAL RESEARCH

Effects of Mild Hypothermia on Cerebral Large and Small Microvessels Blood Flow in a Porcine Model of Cardiac Arrest

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Abstract

Background The effect of mild hypothermia (MH) on microcirculation after resuscitation from cardiac arrest is controversial. The aim of this study was to determine whether MH improves or aggravates the disturbance of cerebral microcirculation.

Methods Twenty domestic male pigs were randomized into the MH group ($n = 8$), non-hypothermia (NH) group ($n = 8$) or sham operation group ($n = 4$). In the MH group, the animals were initiated rapid intravascular cooling at 1 h after return of spontaneous circulation (ROSC) from 8 min ventricular fibrillation, and the core temperature was reduced to 33 °C for 12 h and then rewarmed to 37 °C. In the NH group, animals did not receive hypothermia treatment after ROSC. In the sham operation group, the same surgical procedure was performed, but without inducing ventricular fibrillation and hypothermia treatment. The cerebral microvascular flow index (MFI) of large microvessel (diameter > 20 μm) and small microvessel (diameter < 20 μm) was measured after ROSC. Cerebral oxygen extraction ratio, internal jugular venous–artery lactate difference, and CO_2 difference were also calculated.

Results Cerebral MFI dramatically reduced after ROSC, and MH further aggravated the decrease in MFI of small microvessel compared with NH ($p < 0.05$). Internal jugular venous-arterial lactate difference and CO_2 difference, and oxygen extraction ratio were all significantly increased after ROSC. MH significantly decreased the values compared with NH ($p < 0.05$).

Conclusions MH decreases cerebral small microvessel blood flow and cerebral metabolism after ROSC compared with NH. However, the total effect is that cerebral oxygen supply–demand relationship is improved during hypothermia.

Keywords Cardiac arrest · Mild hypothermia · Cerebral metabolism · Cerebral microcirculation · Lactate · Animal models

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Introduction

Sudden cardiac arrest (CA) is one of the leading causes of death in the world [1]. Although cardiopulmonary resuscitation (CPR) techniques continue to improve for decades, average survival rate of CA is still less than 10% [1–3]. Post-resuscitation cerebral dysfunction remains the most common causes of death. Therapeutic hypothermia can provide effective neuroprotection to adult CA patients after return of spontaneous circulation (ROSC) [4–7]. During mild hypothermia (MH), blood pressure remains stable or increases slightly and cardiac output (CO) decreases [8], and middle cerebral artery flow velocity reduces [9]. However,

the effect of MH on the microvascular blood flow, especially the cerebral microcirculation, is controversial.

Donadello et al. [10] reported that sublingual microvascular flow is impaired in post-CA patients and may be affected by body temperature. Xinrong et al. [11] found the proportion and density of sublingual small perfused vessels were significant decreased during MH and returned to baseline levels during the rewarming phase in an ovine model. But Omar et al. [12] found that there was no a statistically significant difference in sublingual microvascular flow between CA patients treated with hypothermia and those who did not. Although it is difficult to measure the microcirculation of brain in clinic, sublingual microcirculation may not accurately correlate with cerebral microcirculation [13]. The metabolic and cardiovascular function of pig is very similar to human. Therefore, pig is a suitable animal for the model of cardiopulmonary cerebral resuscitation [14]. To determine the effects of MH on cerebral microvascular perfusion, we established a porcine model of CA to examine the cerebral large and small microvessels blood flow with the aid of side-stream dark field (SDF) imaging.

Materials and Methods

This protocol was approved by the Animal Care and Use Committee of Capital Medical University, China. All animals received humane care in compliance with the principles of laboratory animal use and care formulated by the Administration Office of Laboratory Animals.

Animal Preparation

Twenty-four domestic male pigs (2–3 months, 30 ± 2 kg) were used in this study. Animals were fasted overnight except for free access to water. Anesthesia was induced by intramuscular injection of midazolam (0.5 mg/kg) followed by ear vein injection of propofol (1 mg/kg) and was maintained with continuous intravenous infusion of pentobarbital (8 mg/kg/h). Analgesia and muscle relaxant drug were maintained with a continuous infusion of fentanyl (5–10 μg/kg/h) and pancuronium (0.5 mg/kg/h). All animals were continuously given normal saline (50 mL/h). A cuffed 6.5-mm endotracheal tube was advanced into the trachea, and animals were mechanically ventilated with a volume-controlled ventilator (Evita4, Drager Medical, Lubeck, Germany) using a tidal volume of 10 mL/kg, a respiratory frequency of 12/min with room air. End-tidal carbon dioxide (CO2) partial pressure was measured by an inline infrared capnography (CO$_2$SMO Plus monitor; Respironics Inc, Murrysville, PA, USA). The respiratory frequency was adjusted to maintain the end-tidal PCO2 between 35 and 40 mmHg before inducing CA and after ROSC. Room temperature was adjusted at 26 °C. A 5-F arterial catheter (Pulsiocath PV2015L20; Pulsion Medical Systems, Munich, Germany) was inserted into the descending aorta through the femoral artery. Another catheter was inserted into the left external jugular vein to place an electrode catheter and induce ventricular fibrillation (VF) by a programmed electrical stimulation instrument (GY-600A; Kaifeng Huanan Instrument Company, Henan, China). A temperature sensor was connected to the distal port of a standard central venous catheter in the external jugular location. The arterial and central venous catheters were connected to an integrated bedside monitor (PiCCO; Pulsion Medical Systems, Munich, Germany) for continuous hemodynamic monitoring including aortic pressure and CO. A catheter was retrograde inserted into the right internal jugular vein for collection of vein blood for blood gas analyses. Arterial blood samples were drawn from the 5-F arterial catheter for blood gas analysis. A cooling catheter was inserted via the femoral vein and connected to an intravascular cooling instrument (Cool Gard XP; Alsius, Los Angeles, CA). A vesical catheter with a thermometric detector was intubated into the bladder for core temperature and urine output monitoring.

Experimental Protocol

Thirty minutes after operation, baseline values were obtained. Four animals were randomized into sham operation (SO) group, in which the same surgical procedure was performed, but without inducing CPR, and hypothermia treatment.

VF was induced in 20 pigs by a programmed electrical stimulation instrument, mode S1S2 (300/200 ms), 40 v, 8:1 proportion, and -10 ms step length [15]. VF was verified by electrocardiogram and blood pressure. After successful inducing of VF, mechanical ventilation was discontinued and electrode catheter was extracted. After 8 min of untreated VF, CPR was performed. Manual chest compressions were immediately initiated at a rate of 100 times/min. Compression-to-ventilation ratio was 30:2, and ventilation was performed by bag respirator with room air. Defibrillation was attempted after 2 min CPR. Defibrillation shock was administered at 120 J (Smart Biphasic) for the first attempt. If ROSC was not achieved, another 2 min CPR was performed. All subsequent defibrillation attempts used 150 J. Mechanical ventilation began at the beginning of the first defibrillation attempt with 100% oxygen and was continued until 30 min after ROSC, after which 40% oxygen was used. ROSC was defined as maintenance of a systolic blood pressure of at least 50 mmHg for at least 10 consecutive minutes. Animals of no ROSC after four times of defibrillation were announced dead. After ROSC, the

animals were placed in a lateral position. A mid-sagittal incision (10 cm length) was made over the frontal and parietal portions of the scalp. Parietal cranial window (diameter = 15 mm) was opened by drilling. Then dura mater was incised to observe the cerebral microcirculation [16]. When there was no observation, the brain surface was kept moist by covering a saline cotton ball.

Four pigs failed to ROSC. Sixteen animals were randomized into MH group ($n = 8$) and non-hypothermia group (NH, $n = 8$) after ROSC. One hour after ROSC, rapid cooling was initiated using the intravascular cooling instrument in the MH group. The core temperature was reduced to 33 °C for 12 h and then passively rewarmed (0.5 °C/h) to 37 °C. The dose of normal saline was adjusted to maintain the balance of body fluid during hypothermia treatment. After the completion of rewarming period (at about ROSC 24 h), animals were euthanized with an intravenous injection of 100 mg/kg pentobarbital. In the NH group, animals received the same treatment except for cooling and rewarming. The experimental procedure is shown in Fig. 1.

Microcirculatory Imaging

Cerebral microcirculation imagings were visualized by an SDF imaging video microscope (MicroScan; MicroVision Medical Inc, Amsterdam, The Netherlands) with a 5 × optical probe [17]. The SDF image shows a region of interest of approximately $1000 \times 750 \ \mu m^2$. Individual videos of 10 s were analyzed off-line using a score previously described by Spronk et al. [18]. The image was divided into four quadrants, and the predominant type of blood flow (0 represents no flow, 1 represents markedly reduced flow, 2 represents reduced flow, and 3 represents normal flow) was assessed in the large microvessel (diameter > 20 μm) and small microvessel (diameter < 20 μm) of each quadrant. The microvascular flow index (MFI) score represented the average value of four quadrants for the predominant type of blood flow.

Measurements

Core temperature, CO, and mean arterial pressure (MAP) were continuously measured and recorded. Microcirculatory images were obtained at 1, 4, 8, 12, 16, and 24-h after ROSC. Following the guidelines [19], we determined MFI both for large and small microvessels. Arterial and internal jugular vein blood samples for blood gas and lactate levels analyses (GEM Premier 3000 blood gas analyzer, Instrumentation Laboratory, USA) were drawn at baseline, 1, 4, 8, 12, 16, and 24-h after ROSC. Arterial oxygen content (CaO_2) and internal jugular venous oxygen content ($CijvO_2$) were calculated by the formula: $CaO_2 = [Hb \times 1.34 \times (SaO_2/100)] + (PaO_2 \times 0.0031)$ and $CijvO_2 = [Hb \times 1.34 \times (SijvO_2/100)] + (PijvO_2 \times 0.0031)$. Cerebral oxygen extraction ratio (ERO_2) was calculated by the formula: $ERO_2 = (CaO_2 - CijvO_2)/CaO_2 \times 100$. Internal jugular venous–artery lactate difference (ijv-a LAC) and CO_2 difference (ijv-a CO_2) were also calculated and used to, respectively, represent cerebral anaerobic metabolism and aerobic metabolism [20, 21].

Statistical Analysis

Data with normal distribution are reported as mean ± standard deviations and those with non-normal distribution as median (25th and 75th percentiles). Discrete variables, such as 24 h survival, were compared with Fisher exact test. Continuous variables were compared by repeated measures and multivariate analysis of variance or using one-way analysis of variance. Shocks and duration of CPR before ROSC, which were skewed distribution, were compared by Mann–Whitney Test. A value of $p < 0.05$ was regarded as being statistically significant. All analyses were conducted using the SPSS 19.0 software (SPSS Inc, Chicago, IL) and GraphPad PRISM version 5 (GraphPad Software Inc, San Diego, CA).

Fig. 1 Experimental procedure. *CPR* cardiopulmonary resuscitation, *ROSC* return of spontaneous circulation, *VF* ventricular fibrillation
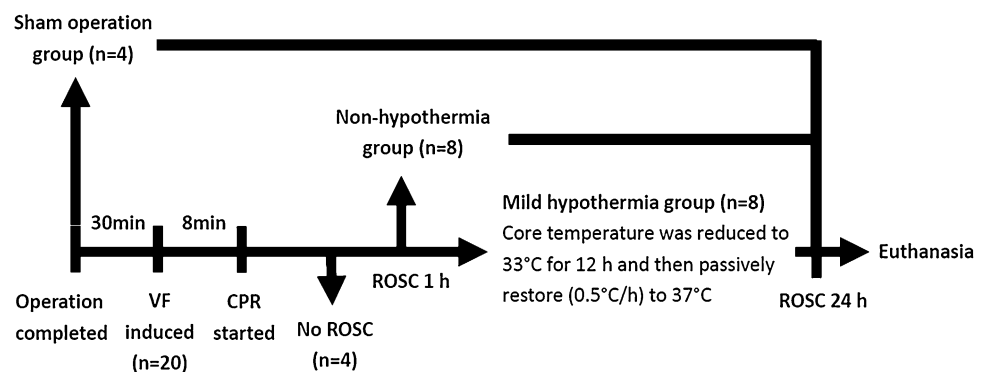
Results

All animals survived for more than 24 h in the MH and SO group, but one animal died at 20 h after ROSC in the NH group. There was no significant difference in the rate of 24 h survival in the MH and NH groups (8/8 vs. 7/8, $P > 0.05$). There were no significant differences in shocks and duration (s) of CPR before ROSC between the MH and NH groups [1.5 (1.3, 2.0) vs. 2.0 (1.4, 2.1) and 197 (170,254) vs. 256 (178, 272), all $p > 0.05$].

Compared with the SO group, the core temperature decreased to the target temperature (33 °C) within 3 h after the start of rapid cooling and maintained at this temperature for 12 h, and then gradually rewarmed to 37 °C in the MH group. However, the core temperature gradually increased to 39.3 ± 0.4 °C after ROSC in the NH group. There were significant differences in core temperature at 4, 8, 12, 16, and 24-h after ROSC between the MH and NH groups (p all < 0.05; Supplemental digital content—Figure 1).

From Fig. 2, the MAP values were higher after ROSC in the MH and SO group than the values in the NH group, but there were statistical significances only at 16 h after ROSC (p both < 0.05). Compared with the NH group, the CO values were higher after rewarming (ROSC 24 h) in the MH group ($p < 0.05$). However, the CO values were lower at 8 h after ROSC in the MH group when compared with the SO group ($p < 0.05$).

Examples of the images of cerebral microcirculation at 4 h after ROSC are shown in Fig. 3. In both MH and NH groups, cerebral large and small microvessels blood flow were all dramatically reduced after ROSC compared with the SO group. The small microvessel blood flow was lower in the MH group compared with the NH group.

As shown in Fig. 4, the MFI values of both large and small microvessels after ROSC in the MH and NH groups were all lower than the values in the SO group. During the cooling stage such as 4, 8, 12, and 16-h after ROSC, the MFI values of small microvessel in the MH group were lower than the values in the NH group, but there were no significant differences in large microvessel. After rewarming, just as 24 h after ROSC, the MFI values of both large and small microvessels were significantly increased in the MH group when compared with the NH group.

Animals demonstrated significant increases in the cerebral ERO_2 and ijv-a LAC value after ROSC in the MH and NH groups when compared with the SO group. But compared with the NH group, ERO_2 were significantly reduced at any time point during hypothermia treatment, and ijv-a LAC values were significantly reduced during cooling and maintenance stage in the MH group. Ijv-a CO_2 was also significantly increased at ROSC 1 h in the MH and NH groups compared with the SO group. However, compared with the NH group, ijv-a CO_2 values were reduced at ROSC 4, 8, and 16-h in the MH group (Fig. 5).

Discussion

The present study demonstrated that cerebral large microvessel (diameter > 20 μm) and small microvessel (diameter < 20 μm) blood flows were all dramatically reduced after ROSC, and MH may further aggravate the decrease in small microvessel blood flows compared with NH. But this reduction can be significantly improved after rewarming. Cerebral aerobic metabolism (ijv-a CO_2) and anaerobic metabolism (ijv-a LAC) were all dramatically increased after ROSC, and MH can significantly decreased the cerebral metabolism compared with NH. The cerebral ERO_2 in the MH group was also reduced significantly compared with the NH group. Therefore, the cerebral oxygen supply–demand relationship was improved although the microcirculation perfusion was reduced during hypothermia.
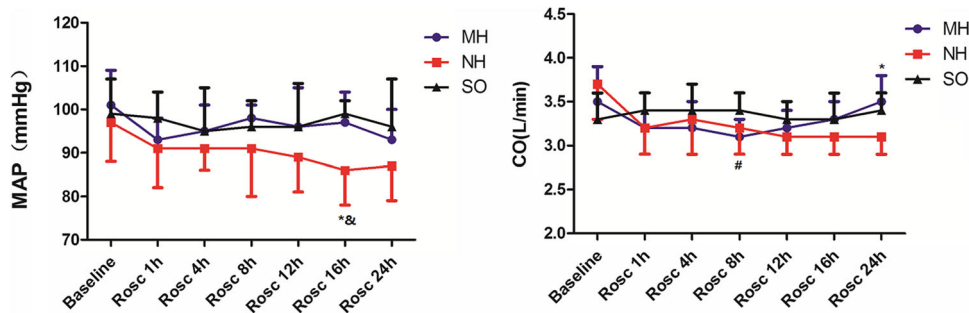

Fig. 2 Changes of mean arterial pressure and cardiac output. There were no significant differences in MAP values between the MH group and the NH group, except at ROSC 16 h ($n = 8$ per group). And the CO values were significantly improved after rewarming (ROSC 24 h) in the MH group ($n = 8$) than the NH group ($n = 7$). CO cardiac output, MAP mean arterial pressure, MH mild hypothermia group, NH non-hypothermia group, ROSC return of spontaneous circulation, SO sham operation group. Data are presented as means ± standard deviations. $^*p < 0.05$ MH versus NH, $^\#p < 0.05$ MH versus SO, $^\&p < 0.05$ NH versus SO
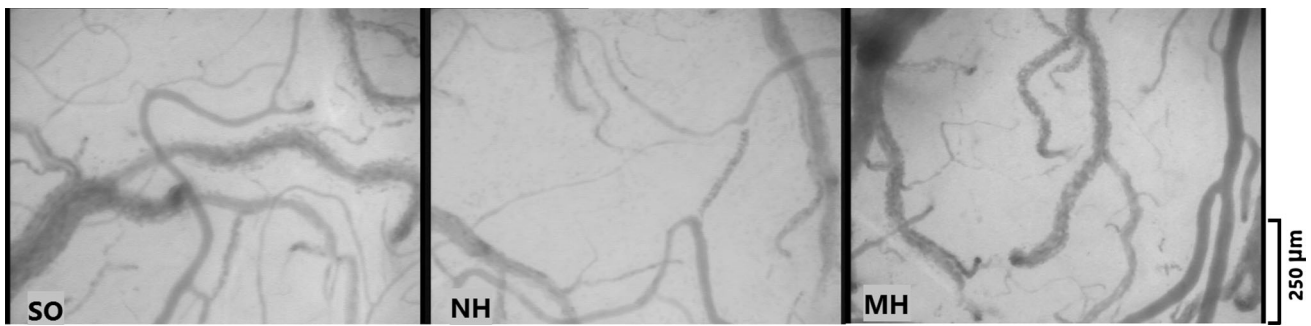
Fig. 3 Stills of video clips of the cerebral microcirculation at 4 h after ROSC. Compared with the SO group, cerebral large microvessels (diameter > 20 μm) and small microvessels (diameter < 20 μm) blood flow significantly reduced at 4 h after ROSC in the MH and NH groups, and some small microvessels occlusion resulted in no flow. Compared with the NH group, there were more severe reduction of blood flow and occlusion of the small microvessels after rapid cooling (ROSC 4 h) in the MH group. *MH* mild hypothermia group, *NH* non-hypothermia group, *SO* sham operation group
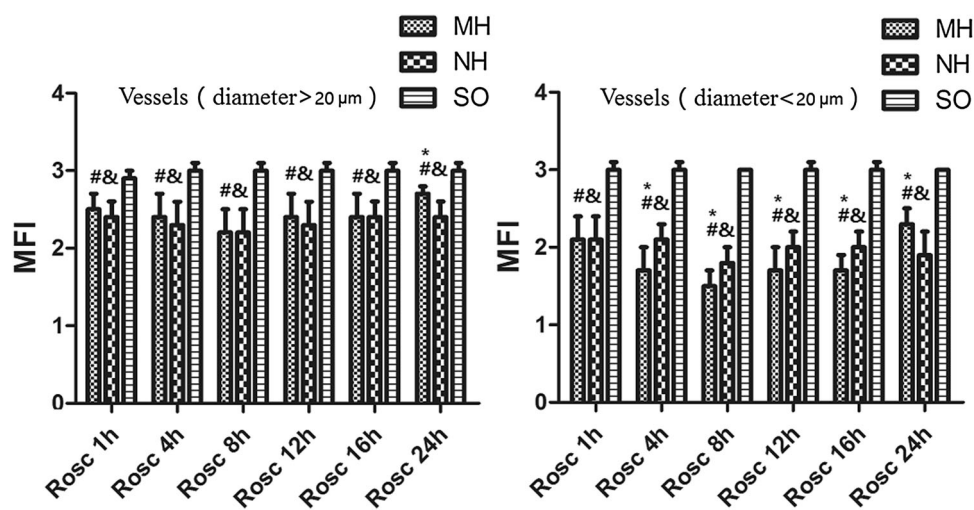

Fig. 4 Changes of microvascular flow index. Compared with non-hypothermia, mild hypothermia reduced the MFI values of the cerebral small microvessels (diameter < 20 μm) during rapid cooling and maintenance stage (ROSC 4, 8, 12, and 16 h, $n = 8$ per group), and improved the values after rewarming (ROSC 24 h, $n = 8$ in the MH group, $n = 7$ in the NH group). *MFI* microvascular flow index, *MH* mild hypothermia group, *NH* non-hypothermia group, *ROSC* return of spontaneous circulation, *SO* sham operation group. Data are presented as means ± standard deviations. $^*p < 0.05$ MH versus NH, $^\#p < 0.05$ MH versus SO, $^\&p < 0.05$ NH versus SO
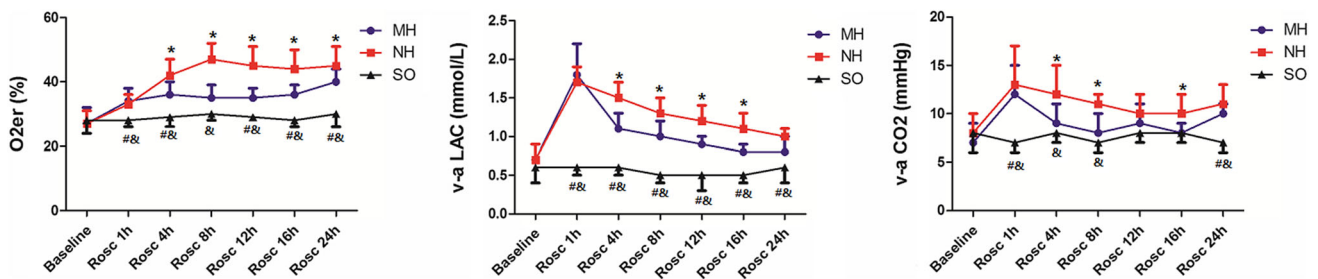

Fig. 5 Changes of cerebral oxygen extraction ratio, anaerobic and aerobic metabolism. Compared with the NH group, ERO_2 and ijv-a LAC were significantly reduced during rapid cooling and maintenance stage (ROSC 4, 8, 12, and 16 h) in the MH group ($n = 8$ per group). ERO_2 oxygen extraction ratio, *ijv-a CO_2* internal jugular venous–artery carbon dioxide difference, *ijv-a LAC* internal jugular venous–artery lactate difference, *MH* mild hypothermia group, *NH* non-hypothermia group, *ROSC* return of spontaneous circulation, *SO* sham operation group. Data are presented as means ± standard deviations. $^*p < 0.05$ MH versus NH, $^\#p < 0.05$ MH versus SO, $^\&p < 0.05$ NH versus SO

Microcirculation is the ultimate determinant to deliver oxygen and vital substrates and remove CO_2, and determine the ultimate severity of cerebral ischemic injury after resuscitation from CA [22]. Some clinical studies have shown that sublingual microvascular flow is impaired in post-CA patients [10, 12]. The results of our [23, 24] and Qian et al's [25] animal experiments also found intestinal microcirculatory dysfunction was presented after resuscitation from CA. In the present study, we demonstrated that cerebral microvascular flow was also dramatically reduced after ROSC, and MH further aggravate the decrease in small microvessel blood flows compared with NH. This effect is similar to an observation in a healthy ovine model without inducing CA, in which MH was associated with decreased sublingual microvascular flow compared to normothermia [11]. A clinical experiment also found there was a significant decrease in sublingual microvascular flow index during MH [26]. The reason for the decrease in microvascular flow may be that hypothermia induces increase in plasma norepinephrine levels and activation of the sympathetic nerve system [27]. However, in the other two experiments, there was an opposite conclusion that MH by surface cooling improves the cerebral cortex microcirculatory blood supply after resuscitation [28, 29]. In one of the studies, core temperature was reduced after ROSC with a combination of ice packs, an electrical fan and a cooling blanket in a rat model of CA [28]. In another study, hypothermia was performed by putting ice bags around the body in a rabbit model [29]. The reasons for the different conclusion are not clear and may be related to different species or cooling methods. Further experiments are needed to determine whether surface cooling can increase the contraction of skin capillary bed so as to lead a shift of blood to core compartment of the body such as brain compared with intravascular cooling.

The magnitude of the microvascular perfusion is commonly evaluated by means of the MFI [30]. MFI in large microvessel and small microvessel was highly correlated [24, 31]. But in the present study, MH only significantly reduced the small microvessel blood flow compared with NH group. This may be explained by that the vasoconstriction effect of hypothermia on small microvessel is more sensitive than large microvessel. The reduction of the small microvessel blood flow can be significantly improved after rewarming in the present study, which is similar to the result of another clinical experiment [10].

In our study, the ijv-a CO_2 and ijv-a LAC values were all dramatically increased after ROSC, which represents an increase in cerebral aerobic and anaerobic metabolism [20, 21]. But the values were significant reduced during cooling in the MH group compared with the NH group. These results are consistent with the conclusion that cerebral metabolism decreases by 6–10% for each 1 °C reduction in body temperature during cooling [27]. In the present study, the cerebral ERO_2 in the MH group was significantly reduced compared with the NH group, which is similar to the result of Gong et al's study [28]. Our previous study found one possible explanation for this reduction was that mild hypothermia inhibited cerebral cortex mitochondrial respiration, thus leading to a reduction in oxygen utilization [32]. Therefore, although MH reduces both the blood supply and metabolism, the total effect is that supply of oxygen is greater than demand. Polderman et al. [8] also found hypothermia-induced decrease in metabolic rate usually equals or exceeds the decrease in blood supply, so that the balance between supply and demand remains constant or improves.

There were some limitations to the design of this study. The assessment of the exact cerebral blood flow velocity such as Doppler method was not determined in this study. The data of brain injury by serum or histological markers were not measured in the present study; however, the molecular mechanism by which MH following resuscitation improves neurological function had been explored in our previous study [33]. In order to observe the cerebral microcirculation, parietal cranial window was opened and dura mater was incised so that intracranial pressure might have been altered. Use of the semiquantitative score described by Spronk et al. [18] is not an objective measurement.

In conclusion, our experiments demonstrate that mild hypothermia reduces cerebral small microvessel (diameter < 20 μm) blood flow, but also significantly reduces cerebral aerobic and anaerobic metabolism after resuscitation. Therefore, the cerebral ERO_2 is significantly reduced during hypothermia. In other words, the cerebral oxygen supply–demand relationship is improved although the microcirculation perfusion is reduced during hypothermia. This may reflect the changes of cerebral microcirculation perfusion and metabolism in CA patients during mild hypothermia and provide an additional mechanism of cerebral protection during hypothermia.

Authors' Contributions CL designed and conducted the study protocol, took part in the animal experiment, coordinated the study, and reviewed the final manuscript; JW helped design the study protocol, took part in the animal experiment, analyzed experimental data and prepared the figures, and drafted the manuscript; WY and J-BL took part in the animal experiment, analysis of experimental data, and

interpretation of the results. YZ, JL and ZL took part in the animal experiment, helped draft and review the manuscript.

Compliance with Ethical Standards

Conflict of interest The authors report no conflicts of interest.

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