Effects of Mild Hypothermia on Cardiac and Neurological Function in Piglets Under Pathological and Physiological Stress Conditions

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To investigate the different effects of mild hypothermia on pathological and physiological stress conditions in piglets, 30 pigs were randomized into four groups: cardiac arrest and mild hypothermia (CA-MH group), cardiac arrest and normothermia (CA-NH group), non-CA-MH (NCA-MH group), and a sham operation. The same hypothermia intervention was implemented in both CA-MH and NCA-MH groups. The CA-NH group did not undergo therapeutic hypothermia after resuscitation. The hemodynamic parameters were recorded. Cerebral metabolism variables and neurotransmitters in the extracellular fluid were collected through microdialysis tubes. The serum of venous blood was used to detect levels of inflammatory factors. The cerebral function was evaluated. At 24 and 72 hours after resuscitation, the cerebral performance category and neurological deficit score in the CA-NH group had higher values. Heart rate and cardiac output (CO) in the CA-MH group during cooling were lower than that of the CA-NH group, but CO was higher after rewarming. Glucose was higher during cooling, and extracellular lactate and lactate/pyruvate ratio in the CA-MH group were lower than that of the CA-NH group. Noradrenaline and 5-hydroxytryptamine in the CA-MH and NCA-MH groups were lower than that of the CA-NH group and sham group during cooling, respectively. Inflammatory factor levels, including interleukin (IL)-1β, IL-2, IL-4, IL-6, IL-8, and tumor necrosis factor-α, in the CA-MH group were lower than that of the CA-NH group at cooling for 12 hours. These values in the NCA-MH group were higher than that of the sham group. Under a light and an electron microscope, the worse pathological results of heart and brain were observed in the two cardiac arrest groups. Mild hypothermia can provide limited organ protection in the specific pathological condition caused by ischemia–reperfusion, but it may produce a negative effect in a normal physiological state.

Keywords: mild hypothermia, post-resuscitation cooling, animal studies

Introduction

For hypoxic–ischemic encephalopathy caused by cardiac arrest, mild hypothermia is the only effective treatment recommended by the American Heart Association (Neumar et al., 2015). A large number of experimental data have shown that mild hypothermia can reduce death and long-term disability of resuscitated patients (Bernard and Buist, 2003; Polderman, 2004; Nolan et al., 2005). Actually, the main role of mild hypothermia therapy is to alleviate a series of secondary responses caused by ischemia–reperfusion injury after cardiopulmonary resuscitation (CPR). This effect is beneficial in specific pathological conditions, but may cause some harmful effects on organs under physiological stress. A reduction in core temperature by a few degrees can alter the physiology of almost every system and organ (Wood and Thoresen, 2015).

This study aimed to determine the different effects of mild hypothermia on pathological and physiological stress conditions. In the present study, we implemented the same intervention of hypothermia in piglets with cardiac arrest and without cardiac arrest to determine changes in cardiac and neural functions and the immune system.

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Materials and Methods

Animal care

Thirty male, Beijing Landrace pigs were used for this experiment. The pigs were 11 ± 2 months old, weighed 31 ± 3.1 kg, and were provided by a registered laboratory animal center in Beijing, China. This study was carried out in strict accordance with the guidelines for animal care and use that were established by the Capital Medical University Animal Care and Use Committee. The study experimental protocol was approved by the Committee on the Ethics of Animal Experiments of Capital Medical University (Permit Number 2010-D-013). The pig experiments were in compliance with the Guiding Principles for the Care and Use of Animals expressed in the Declaration of Helsinki (World Medical Association, 2013).

Anesthesia and perioperative management

The pigs were preoperatively fasted overnight with free access to water before surgery. They were secured in the supine position on the operation table after receiving 2 mg/kg propofol anesthesia via an ear vein injection. An initial dose of 30 mg/(kg·h) pentobarbital sodium was administered, followed by continuous intravenous maintenance anesthesia using 8 mg/(kg·h) pentobarbital sodium. The pigs received tracheotomy, tracheal intubation, and ventilatory support (Drager-Evata IV; Dreger, Germany) with room air, a ventilation frequency of 12–20 breaths/min, and a fraction of inspiration O2 of 0.21. The tidal volume and ventilation rate were adjusted to maintain normocapnia (end-tidal CO2 partial pressure of 35–45 mmHg), which was monitored with an infrared capnometer (Model NPB-75; Nellcor Puritan Bennett, Inc., Pleasanton, CA).

All hemodynamic parameters were monitored with a patient monitoring system (M1165; Hewlett-Packard, Palo Alto, CA). 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, heart rate (HR), cardiac output (CO), extravascular lung water (EVLW), and mean arterial blood pressure (MAP). Reference arterial blood samples were drawn from a catheter for blood gas analysis. A catheter was retrogradely inserted into the right internal jugular vein for venous blood collection.

A cooling catheter was inserted for intravascular cooling via the right femoral vein. A vesical catheter with a thermometric detector was intubated into the bladder after fistulation to simultaneously measure core body temperature and keep the bladder empty. Sinus rhythm was measured by electrocardiography after ensuring that the pigs were stable. All operations were performed using aseptic surgical techniques. The room temperature was maintained at 25–26°C.

Treatment groups

Thirty male pigs were randomized into four groups as follows: cardiac arrest and mild hypothermia (CA-MH group; n = 8), cardiac arrest and normothermia (CA-NH group; n = 8), non-CA-MH (NCA-MH group; n = 8), and a sham operation (sham group; n = 6).

Experimental protocol

CPR procedure. In the CA-MH and CA-NH groups, a medical programmable stimulator (GY-600 A; Kaifeng South China Instrument Co., HeNan, China) and esophageal stethoscope output (S1/S2; 300/200 ms) were used to trigger ventricular fibrillation (VF) with continuous electrical stimulation consisting of 10-ms steps (8:1; Zhang and Li, 2013). The diagnostic criteria for VF included a rapid decrease in arterial blood pressure and electrocardiography waveforms characteristic of VF.

Once VF occurred, mechanical ventilation was discontinued. After 8 minutes of untreated VF, a compression-to-ventilation ratio of 30:2 CPR with manual external chest compression was performed. The quality of CPR, rate of compressions, and defibrillation shocks were maintained using a Heart-Start MRx Monitor/Defibrillator (M3535 A; Philips Medical Systems, Best, Holland). This equipment helped to maintain chest compression rates at 100–120 beats/min and compression depth at 50–60 mm with complete release (Wu et al., 2009). The piglets in the two cardiac arrest groups received the same quality of CPR.

During CPR, 100% oxygen was delivered with the same baseline ventilator settings, and no adrenaline was administered. After 2 minutes of CPR, a single 150-J biphasic electrical shock was attempted with a Smart Biphasic defibrillator (Philips Medical Systems, Andover, MA). If VF persisted, CPR was then resumed for 2 minutes, and 200 J was used for the second and all subsequent defibrillation attempts. Resuscitation procedures were terminated if the pig had no return of spontaneous circulation (ROSC) after 15 minutes of CPR.

ROSC was defined as 10 consecutive minutes of maintenance of systolic blood pressure at 50 mmHg. The piglet was considered dead if spontaneous circulation was not restored after 15 minutes of CPR (Wang et al., 2010). After ROSC, mechanical ventilation was resumed using the same settings as before induction of VF. In the NCA-MH and sham groups, the piglets did not have VF induced.

Mild hypothermia procedure. At 1 hour after ROSC, piglets in the CA-MH group received intravascular cooling (target temperature of 33°C, maintained for 12 hours) and then were passively restored to 37°C (0.5°C/h) using an intravascular cooling instrument (Cool Gard XP; Alsius, Los Angeles, CA; Fig. 1). At 1 hour after ROSC, the CA-NH group did not undergo therapeutic hypothermia.

The NCA-MH group had the same hypothermia protocol implemented after stability, but without inducing VF and CPR. The sham group did not undergo hypothermia.

During induction and maintenance of mild hypothermia, the piglets received pancuronium bromide (0.1 mg/kg, intravenously) to prevent shivering and muscle movement. Two groups without hypothermia received the equivalent drug during the same phase in the experiment. Administration was repeated if required. After the rewarming procedure was complete, intravascular catheters were removed, incisions were sutured, and the piglets were returned to their cages.

Sample collection

After establishment of vascular catheters, a small hole (1 mm diameter) was drilled into the skull. The hole was...
located in the right hemisphere and allowed access to the superficial cerebral cortex. A microdialysis catheter (CMA70; Microdialysis AB, Sweden) was implanted. The CMA70 catheter was perfused with Ringer’s solution in situ for 15 minutes before baseline measurements were obtained, and a constant flow was maintained (3 μL/min) using a microdialysis pump (CMA106; Microdialysis AB).

We recorded hemodynamic parameters and collected cerebral microdialysis samples at four time points as follows: baseline, 1 hour after ROSC (or starting to cool), cooling at 6 hours (reaching a target temperature of 33°C), cooling at 16 hours (maintaining at 33°C for 12 hours or starting to rewarm), and after rewarming. Hemodynamic parameters included HR, MAP, CO, and EVLW. Dialysate samples were measured to determine the concentrations of glucose, lactate, and pyruvate, as well as of noradrenaline (NA) and 5-hydroxytryptamine (5-HT).

Venous blood was collected at the same time point. Serum was used to detect pro-inflammatory factor and anti-inflammatory factor levels by using an enzyme-linked immunosorbent assay, including interleukin (IL)-1β, IL-2, IL-4, IL-6, IL-8, and tumor necrosis factor (TNF)-α.

Cerebral performance category and neurological deficit score

Cerebral function was evaluated using the cerebral performance category (CPC) and neurological deficit score (NDS; Wenzel et al., 2000) at baseline, and 24 and 72 hours after ROSC.

Myocardial and brain tissue sampling

The pigs were euthanized with propofol (3 mg/kg, intravenously) followed by 10 mL potassium chloride (10 mol/L, intravenously) 48 hours after rewarming. The myocardium of the anterior left ventricular wall and the right posterior frontal lobes was dissected. Myocardial tissue was fixed with 10% paraformaldehyde, and conventional hematoxylin–eosin staining was used for pathology. Cerebral cortex tissue was immediately collected on ice for morphological examination. A portion of tissue was fixed in 4% buffered formalin for hematoxylin–eosin staining and preserved to observe pathological changes under a light microscope. Another portion of cortex tissue was preserved to observe changes in ultrastructure under a transmission electron microscope.

Statistical analysis

All analyses were conducted using SPSS 19.0 software (SPSS, Chicago, IL). Data for continuous variables are expressed as mean±SD. Student’s t-test was used for comparisons between every two groups. Differences at different time points were assessed by repeated-measures analysis of variance and the Bonferroni correction for post hoc comparisons between multiple experimental groups. Additionally, continuous variables were fixed to a normal distribution, and equal variances were analyzed using the Kolmogorov–Smirnov test and homogeneity of variance test. Discrete variables were compared by Fisher’s exact test. A p value <0.05 was defined as statistically significant.

Results

Comparison of neurological outcomes among the four groups

No significant differences were found in the number of shocks or duration of CPR before ROSC between the CA-MH and CA-NH groups (Table 1). At 24 and 72 hours after ROSC, the CPC scale and NDS in the CA-NH group had higher values than that of the CA-MH group (24 hours: pCPC = 0.026, pNDS = 0.044; 72 hours: pCPC = 0.013, pNDS = 0.003), with no differences between the NCA-MH and sham groups.

Hemodynamic parameters

HR and CO in the CA-MH group during cooling were significantly lower than those in the CA-NH group (HR: p < 0.001; CO: p0h < 0.001, p16h = 0.014), but CO was much higher after rewarming in the CA-MH group (p = 0.030; Fig. 2A–D). During cooling, HR and CO in the NCA-MH group were significantly lower than those of the sham group (p < 0.001), but there was no difference between the groups.
after rewarming \((p=0.503)\). No significant differences were found in MAP and EVLW between the CA-MH and CA-NH groups during the experimental protocol. There were also no differences in MAP and EVLW between the NCA-MH and sham groups.

**Cerebral metabolic variables and neurotransmitters in the extracellular fluid**

Glucose levels in the CA-MH group were significantly higher during cooling \((p<0.001)\), and extracellular lactate levels and lactate/pyruvate \((L/P)\) ratio were significantly lower compared to those in the CA-NH group (lactate: \(p_{6h}=0.018, p_{16h}=0.002; L/P\) ratio: \(p_{6h}=0.005, p_{16h}<0.001\); Fig. 3A–E). Glucose levels in the NCA-MH group under hypothermia were higher than those of the sham group \((p<0.001)\). However, there were no significant differences in lactate levels and \(L/P\) ratio between the two groups at each time point.

NA and 5-HT in the CA-MH group were significantly lower than those of the CA-NH group during cooling (NA: \(p_{6h}=0.009, p_{16h}=0.002; 5-HT: p_{6h}=0.018, p_{16h}=0.016\)). Furthermore, NA and 5-HT values in the NCA-MH group under hypothermia were also lower than those of the sham group (NA: \(p_{6h}=0.002, p_{16h}=0.001; 5-HT: p_{6h}=0.001, p_{16h}<0.001\)).

**Serum inflammatory factor levels**

In the CA-MH and CA-NH groups, all inflammatory factors continued to rise after ROSC (Fig. 4A–F). However, during cooling, especially at 12 hours, inflammatory factor levels in the CA-MH group were lower than those of the CA-NH group (IL-1\(\beta\): \(p<0.001\); IL-2: \(p=0.011\); IL-4: \(p=0.001\); IL-6: \(p=0.009\); IL-8: \(p<0.001\); TNF-\(x\): \(p<0.001\)). Compared to the sham group, some inflammatory factors in the NCA-MH group showed higher values with cooling at 6 hours, such as IL-4 \((p=0.004)\), IL-6 \((p=0.007)\), and IL-8 \((p=0.002)\). With cooling after 12 hours, all of the measured inflammatory factors in the NCA-MH group were higher than those of the sham group (IL-1\(\beta\): \(p=0.002\); IL-2: \(p=0.025\); IL-4: \(p<0.001\); IL-6: \(p<0.001\); IL-8: \(p<0.001\); TNF-\(x\): \(p=0.001\)).

**Myocardium and cerebral histology**

Disordered arrangement of myocardial cells and enlarged or ruptured myocardial fibers were observed in the CA-MH and CA-NH groups (Fig. 5A–L). These findings were different than those in the NCA and sham groups, which showed a regular arrangement of myocardial fibers without edema and necrosis.

Most of the neurons in the CA-NH group showed diffuse loss of Nissl substance. Some neuronal nuclei had disappeared, which resulted in homogeneous, eosinophilic cell silhouettes, and shrinkage of the perikaryon under light microscopy. Under transmission electron microscopy, a destroyed structure of the blood–brain barrier and swollen mitochondria were observed in the CA-NH group. In contrast, the CA-MH group only showed slight edema in brain cells and a clearer structure of the blood–brain barrier. In contrast to the other two groups, the NCA-MH and sham groups did not show obvious pathological changes.

**Discussion**

The present study showed that mild hypothermia resulted in a series of beneficial effects on functions of the brain and immune system after ROSC. However, under physiological stress, mild hypothermia had an adverse effect, including inducing a reversible reduction in CO, impeding brain carbohydrate use, interfering with neurotransmitter secretion, and disrupting immune function.

With regard to hemodynamic indices, although HR and CO were significantly decreased under hypothermia after ROSC, CO in the CA-MH group ultimately exceeded that of the CA-NH group after rewarming. This finding suggests that mild hypothermia has a protective effect on the myocardium after resuscitation, which may be attributed to a reduction in oxygen consumption (Thoresen, 2008). Moreover, even under the cooling process, there was no increase in pulmonary water because of a decrease in CO. Unfortunately, this protective

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**Table 1. Comparison of Neurological Outcomes Among Four Groups**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>CA-MH group ((n=8))</th>
<th>CA-NH group ((n=8))</th>
<th>NCA-MH group ((n=8))</th>
<th>Sham group ((n=6))</th>
<th>(p) (CA-MH vs. CA-NH)</th>
<th>(p) (NCA-MH vs. sham)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shocks before ROSC</td>
<td>2.00±0.54</td>
<td>1.88±0.64</td>
<td>NA</td>
<td>NA</td>
<td>0.678</td>
<td>NA</td>
</tr>
<tr>
<td>Duration of CPR before ROSC (seconds)</td>
<td>287.38±63.11</td>
<td>279.76±66.30</td>
<td>NA</td>
<td>NA</td>
<td>0.817</td>
<td>NA</td>
</tr>
<tr>
<td>24-hour survival</td>
<td>8</td>
<td>6</td>
<td>8</td>
<td>6</td>
<td>0.467</td>
<td>NA</td>
</tr>
<tr>
<td>72-hour survival</td>
<td>8</td>
<td>6</td>
<td>8</td>
<td>6</td>
<td>0.467</td>
<td>NA</td>
</tr>
<tr>
<td>CPC at baseline</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>CPC at 24 hours</td>
<td>3.13±0.64</td>
<td>4.00±0.76</td>
<td>1.25±0.46</td>
<td>1</td>
<td>0.026</td>
<td>0.215</td>
</tr>
<tr>
<td>CPC at 72 hours</td>
<td>2.63±0.92</td>
<td>3.88±0.83</td>
<td>1.25±0.46</td>
<td>1</td>
<td>0.013</td>
<td>0.215</td>
</tr>
<tr>
<td>NDS at baseline</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>NDS at 24 hours</td>
<td>262.50±65.90</td>
<td>330.55±55.03</td>
<td>5.61±9.04</td>
<td>0</td>
<td>0.044</td>
<td>0.157</td>
</tr>
<tr>
<td>NDS at 72 hours</td>
<td>186.88±102.85</td>
<td>343.125±49.92</td>
<td>5.00±9.64</td>
<td>0</td>
<td>0.003</td>
<td>0.232</td>
</tr>
</tbody>
</table>

All indexes were compared by the independent-samples \(t\)-test. Discrete variables were compared by Fisher’s exact test. The values are means±SD, or number (\(n\)). NDS is expressed as median (interquartile range).

CA-MH, cardiac arrest and mild hypothermia; CA-NH, cardiac arrest and normothermia; CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; NA, noradrenaline; NCA-MH, non-CA-MH; NDS, neurologic deficit score; ROSC, return of spontaneous circulation.
FIG. 2. Hemodynamic parameters in four groups. HR (A), CO (B), EVLW (C), MAP (D). CA-MH vs. CA-NH: $\Delta p < 0.05$, $\Delta\Delta p < 0.001$; NCA-MH vs. sham: **$p < 0.001$. CO, cardiac output; EVLW, extravascular lung water; HR, heart rate; MAP, mean aortic pressure. Color images are available online.
effect was insufficient to counteract myocardial injury-induced ischemia during resuscitation. In our study, myocardial pathology showed a disorder of myocardial fibrous structures, and rupture and edema of myocardial fibers in the two cardiac arrest groups.

Under physiological stress conditions, mild hypothermia had the same effect on HR and CO, which could be eliminated after rewarming and did not cause pathological changes in cardiac myocytes. Additionally, hypothermia had no obvious effect on MAP. This finding could be due to an...
increase in total peripheral resistance that compensated for a decline in CO (Thoresen and Whitelaw, 2000; Cavallaro et al., 2013). However, whether this finding is detrimental to perfusion of other organs, such as the gastrointestinal system and the kidney, needs to be determined.

The protective effect of mild hypothermia on neurological function after resuscitation is initiated by a variety of mechanisms (Aoki et al., 1993; Ehrlich et al., 2002; Erecsinska et al., 2003). In the present study, extracellular glucose levels under hypothermia were higher compared to...
normothermia after ROSC. This finding indicates that hypothermia can reduce energy consumption of brain tissue and be beneficial for relieving energy exhaustion after resuscitation. Moreover, a lower lactate level and L/P ratio in the CA-MH group after ROSC indicated that hypothermia reduced oxygen demand of brain tissue, decreased accumulation of glycolytic waste, and alleviated secondary brain injury. However, under physiological stress conditions, the same effect caused by hypothermia may hinder carbohydrate use in brain cells. This could occur regardless of our finding that hypothermia did not affect lactate levels and the L/P ratio by simultaneously reducing brain oxygen demand and oxygen consumption (Eicher et al., 2005; Zhou et al., 2010).

NA and 5-HT represent two different types of monoamine neurotransmitters. Ischemia–reperfusion injury caused by resuscitation irritates overflow of monoamine neurotransmitters in brain tissue (Kondoh et al., 1994; Gerevich et al., 2001; Hachimi-Idrissi et al., 2004). The release of NA into the synaptic cleft and brain tissue can stimulate cerebral vasospasm and aggravate secondary injury (Frank et al., 2003). The accumulation of 5-HT can trigger overexcitation of neurons and accelerate metabolism and ATP exhaustion. Furthermore, 5-HT can mediate vasoconstriction and platelet aggregation by 5-HT2 receptors in vascular smooth muscle and platelet membranes. This then leads to the disturbance of microcirculation and increases permeability of the blood–brain barrier and exacerbates cerebral edema (Joseph et al., 1992).

In our study, NA and 5-HT levels during cooling were lower compared to normothermia. This finding suggests that hypothermia can suppress post-ischemic overflow of neurotransmitters, which may trigger excitotoxic pathways, damaging cells (Vizi, 1998). Under physiological stress conditions, inhibition of normal release of neurotransmitters may cause neurological dysfunction, such as cognitive impairment (González–Burgos and Feria-Velasco, 2008; Sarubbo et al., 2015). Unfortunately, assessing neurological

FIG. 5. Myocardium and cerebral histology. The myocardium of the anterior left ventricular wall from CA-MH group (A), CA-NH group (B), NCA-MH group (C), and sham group (D). Original magnification, ×400. The disordered arrangement of myocardial cells and enlarged or ruptured myocardial fibers are observed in the CA-MH group (black arrow), which is different than the NCA-MH group and the sham group that maintained a regular arrangement of myocardial fibers without edema and necrosis. The comparisons of the right posterior frontal lobe from CA-MH group (E), CA-NH group (F), NCA-MH group (G), and sham group (H). Original magnification, ×400. Scale bar indicates 200 μm. Most of the neurons in the two cardiac arrest groups exhibited a diffuse loss of Nissl substance, some neuronal nucleus had disappeared, leaving homogeneous, eosinophilic cell silhouettes, and shrinkage of the perikaryon (black arrow) under light microscopy. Moreover, the NCA-MH and sham groups did not exhibit similar features. Under transmission electron microscopy, the structure of blood–brain barrier and mitochondria of CA-MH group (I), CA-NH group (J), NCA-MH group (K), and sham group (L) were as demonstrated in Figure 5. Original magnification, ×3000. Scale bar indicates 2.6 μm. The structure of the blood–brain barrier (BBB) was destroyed and interrupted partially (black arrow); and the mitochondria were swollen. Reversely, the structure of the BBB was integrated in the NCA-MH and sham groups, without severe pathological changes. Color images are available online.
function of animals under hypothermia is not possible because the anesthetic cannot be stopped.

In our study, brain tissue edema and necrosis was observed in the CA-MH group, and the blood–brain barrier structure was also damaged, as shown by the CPC and NDS at 24 and 72 hours after resuscitation. However, neurological function of the piglets under hypothermia therapy after ROSC was still better than that in the CA-NH group. This finding indicates that mild hypothermia can alleviate secondary injury caused by ischemia–reperfusion and improve neurological outcome. There was no distinct difference in neurological functional assessment and cerebral histology between the NCA-MH group and the sham group. This finding suggests that under physiological stress conditions, mild hypothermia only has a functional effect on brain tissue, not an organic effect.

In the two cardiac arrest groups, serum inflammatory factor levels gradually increased within 24 hours after ROSC. This finding is consistent with the fact that ischemia–reperfusion injury usually induces systemic inflammatory response syndrome (Kimura et al., 2002). Compared to the CA-NH group, lower inflammatory factor levels in the CA-MH group suggested that mild hypothermia could relieve this pathological state finitely. Interestingly, in our study, mild hypothermia such as a “cold stress” also stimulated the release of inflammatory factors under physiological stress conditions, regardless of pro-inflammatory or anti-inflammatory factors. This effect may promote an inflammatory response, inhibit immune function, and then increase the probability of infection.

The current study has some limitations. First, our study aimed to determine the different effects of hypothermia under pathological and physiological stress conditions. However, in clinical practice, mild hypothermia has not been widely applied in areas other than ischemic injury. Therefore, mild hypothermia has limited practical significance. Second, when microdialysis catheters were implanted into the brain, some damage occurred in local brain tissue. However, this damage only slightly affected our results and was equal in each group.

Finally, induction anesthesia consisted of propofol, and pentobarbital was used for maintenance anesthesia. Use of anesthetic hinders assessment of neurological function under hypothermia. However, these anesthetics may provide some neuroprotection, but no significant difference was observed in the amount of anesthetics used among the three groups. Furthermore, the use of anesthetics impeded the observation of complications, such as seizures, which may lead to significant changes in cerebral metabolism.

Conclusion

The present study shows that mild hypothermia can provide limited organ protection in the specific pathological condition caused by ischemia–reperfusion. However, mild hypothermia may produce a negative effect in the normal physiological state.

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Author Disclosure Statement

No competing financial interests exist.

References


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