ORIGINAL PAPERS

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Pre-Hospital Induced Hypothermia Improves Outcomes in a Pig Model of Traumatic Hemorrhagic Shock*

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation;
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Abstract

Background. Extensive preclinical evidence suggests that induced hypothermia can protect tissues from ischemia-reperfusion injury, reduce organ damage, and improve survival in the advanced stages of shock.

Objectives. We assessed the effects of induced hypothermia on the hemodynamic parameters and coagulation capacity during hemorrhagic shock (HS) and fluid resuscitation, in a pig model of HS with multiple intestinal perforations.

Material and Methods. Pigs (n = 16) were randomized into 2 groups: a hypothermia (HT) group (n = 8, 34°C) and a normothermia (NT) group (n = 8, 38°C). Hypothermia to 34°C was induced with a cold blanket at the pre-hospital stage. Traumatic HS shock was induced using multiple intestinal perforations. Pulse indicator continuous cardiac output (PiCCO) was used to monitor hemodynamic changes. Coagulation capacity was measured using thromboelastography (TEG) at baseline as well as during resuscitation periods. Survival was documented for 72 h post-trauma.

Results. Mortality in the hypothermic HS group was low, but there were no significant differences in mortality between the groups (mortality = 2/8 HT vs. 5/8 NT, p = 0.137). During hypothermia, the heart rate, extravascular lung water index (EVLWI), oxygen uptake index (VO2), and oxygen delivery index (DO2) in the HT group were significantly lower than those in the NT group. There were no significant differences between the 2 groups in the other hemodynamic indices or prothrombin time. Analyses of thromboelastometry at 34°C during hypothermia showed significant differences for reaction time (R) and alpha angle, but not for maximal amplitude (MA).

Conclusions. Rewarming reversed the coagulation changes induced by hypothermia. Induced mild hypothermia (34°C) in the pre-hospital stage affects hemodynamic parameters and the coagulation system but does not worsen outcomes in a pig HS model. The hypothermia-induced coagulation changes were reversed during rewarming without evidence of harmful effects. Our results suggest that pre-hospital induced hypothermia can be performed carefully following major trauma (**Adv Clin Exp Med 2015, 24, 4, 571–578**).

Key words: hemorrhage, mild hypothermia, shock, coagulation, thromboelastograph.

Trauma is the leading cause of death in young individuals aged 1–34 years, and it is estimated that 66–80% of these deaths are from traumatic hemorrhagic shock (HS) [2]. Following severe trauma, many patients suffer from hypothermia secondary to exposure (environmental as well as cavitary), wet clothes, winter conditions, intravenous fluid administration, and a decreased ability to maintain normothermia due to intoxication, shock, blood loss, and sedation/anesthesia [3, 4]. Spontaneous

hypothermia secondary to HS that occurs following injuries is linked with increased mortality [5, 6] and indicates depleted energy stores and disrupted cellular homeostasis [7]. It, along with coagulopathy and acidosis, comprise a "lethal triad" that results in deleterious outcomes in trauma patients.

Especially noteworthy is that induced hypothermia and spontaneous hypothermia secondary to HS are 2 different physiological states that produce correspondingly disparate outcomes. In comparison with the negative impact of spontaneous hypothermia, numerous studies have indicated that the controlled induction of hypothermia is a potent strategy for attenuating the deleterious effects of ischemia and reperfusion after HS [8, 9]. Induced hypothermia has been reported to blunt the inflammatory and immune responses, reduce activation of cell death pathways, and decrease the metabolic and oxygen demands in tissues [10–12]. The primary difference between induced hypothermia and spontaneous hypothermia is that induced hypothermia is controlled and based on the use of sedation to prevent shivering and neuromuscular blockade during cooling, while spontaneous hypothermia is uncontrolled and involves shivering.

However, the combined effect of HS and pre-hospital hypothermia on hemodynamic indices and the coagulation process has received little attention. It remains unclear whether hemodynamic and coagulation disorders occur when the core temperature remains > 34°C (i.e. mild hypothermia) in HS. The aim of this study was to examine the effects of pre-hospital induced hypothermia (34°C) on hemodynamic and coagulopathy parameters during HS and fluid resuscitation.

Material and Methods

The experimental protocol was approved by the Institutional Animal Care and Use Committee of Jingling Hospital in Nanjing, Jiangsu, China. The study was performed in line with the National Institutes of Health Guidelines on the use of experimental animals. The timeline for the experimental procedure is described in Fig. 1.

Experimental Protocol

Animal Preparation (Phase I)

Sixteen female experimental pigs, with an average weight of 27.5 kg (range: 25.5–31.3 kg) were used in the study following a 1-week adaptation period. The pigs were fasted for 24 h and not allowed access to water for 8 h before surgery. Anesthesia was induced with ketamine (20 mg/kg), atropine (0.1 mg/kg), and diazepam (8 mg/kg) intramuscularly and then maintained with an intravenous injection of 150 $mg·kg^{-1}·min^{-1}$ propofol and 8 $mg·kg^{-1}·h^{-1}$ diazepam. The pigs were intubated and then ventilated on volume control mode with room air at a tidal volume setting of 10 mL/kg, respiratory rate of 18 breaths/min, and positive end expiratory pressure of 3 mm Hg. Pulse indicator

Phase I preparation	Phase II injury by gunshot	Phase III controlled shock	Phase IV pre-hospital resuscitation and hypothermia	Phase V In-hospital resuscitation	Phase VI survival
(20-30 min)	(15 min)	(60 min)	(240 min)	(120 min)	(72 h)

exsanguination

to simulate the delay in the arrival of hospital personnel

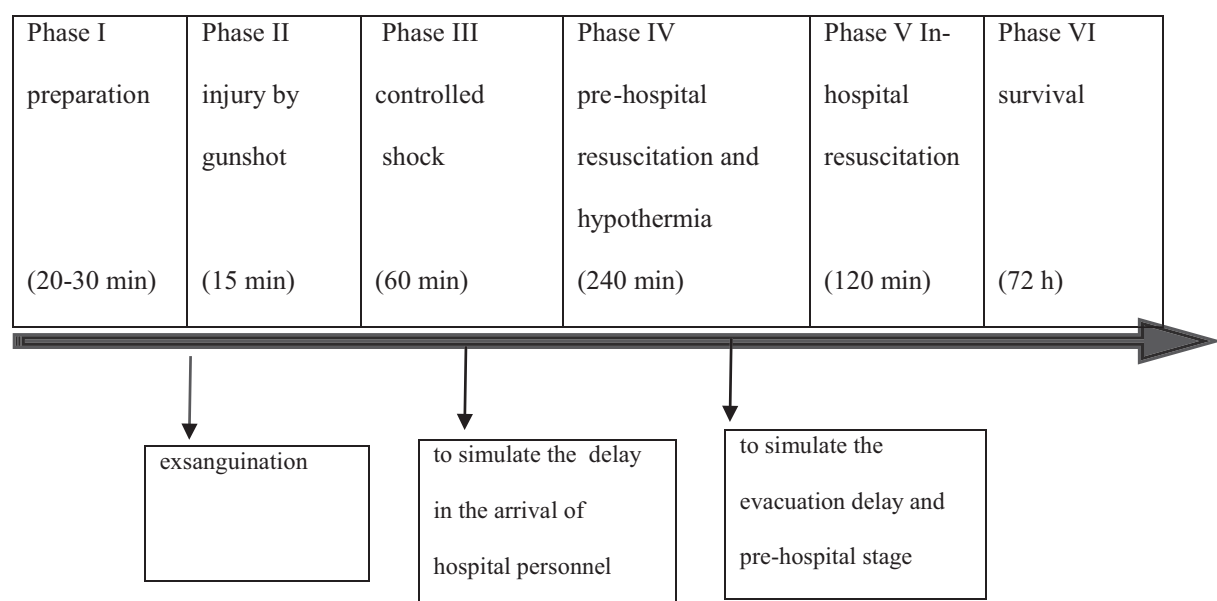to simulate the evacuation delay and pre-hospital stage

Fig. 1. Timeline followed during the experimental procedure to determine the combined effects of mild hypothermia (34°C) on hemodynamic and coagulopathy parameters during hemorrhagic shock and fluid resuscitation in a porcine model (n = 16)

continuous cardiac output (PiCCO) was also used to monitor hemodynamic changes; a 5-Fr PiCCO catheter (FT-Pulsion-cath; Pulsion Medizintechnik, Munich, Germany) was placed in the femoral artery to observe the pulmonary arterial temperature and hemodynamic parameters. Catheters were aseptically inserted into the internal jugular vein and femoral artery for intravenous access, sample collection, and blood pressure monitoring. Then, a urinary catheter was placed in the bladder. After instrumentation and a 20-min equilibration period, baseline measurements were obtained.

Traumatic Shock Model

An HS porcine model with multiple intestinal perforations was used to mimic traumatic HS and is a standard model that has been used in other studies [13, 14]; this model was also successfully used in our previous studies [15, 16]. This model is very similar to the traumatic shock porcine model involving a gunshot and resulting in superior mesenteric artery injuries that we have also used in other previous studies [17, 18].

The first step (Phase II) included a power-actuated gunshot. Anesthetized pigs were laid in a right lateral decubitus position and then shot in the abdomen 1 time with a power-actuated gun (bullet diameter 7.62 mm, firing rate 250–260 m/s) to create a severe abdominal trauma. The bullet was positioned 10 cm from the medioventral line and 20 cm above the symphysis pubis. The shooting scope was 40 cm. This process results in a penetrating injury in only the small intestinal segments and mesentery, resulting in little abdominal bleeding (< 180 mL). Following the gunshot and until randomization, all animals were covered with warming blankets and surgical drapes in order to maintain normothermia.

The second step involved controlled shock (Phase III) using exsanguination immediately following the shooting. The animals were randomized into a hypothermia (HT) group (n = 8) or a normothermia (NT) group (n = 8) immediately before induction of the hemorrhage. A standardized, controlled hemorrhage was performed by withdrawing 40% of each animal's calculated blood volume over a period of 3 to 5 min through the left common carotid artery until a mean arterial pressure (MAP) of 40 mm Hg was obtained. To mimic the delay in the arrival of hospital personnel, the MAP was maintained at the same level for 1 h by intravenously infusing lactated Ringer solution (10 mL/kg).

Pre-Hospital (Hypothermia) Phase

Resuscitation was simulated during the pre-hospital phase (Phase IV), starting 1 h after the induction of shock and lasting for 4 h, based on the fact that an evacuation delay on the battleground was one of the major factors resulting in "critically injured patients with active bleeding" [19] that required surgery for damage control. In addition, Arnaud et al. [20, 21] previously imitated a pre-hospital period of 4 h in HS models.

Ringer's acetate was infused at a volume of 3 times the bled volume and a rate of 39 mL·kg^{-1}·h^{-1} for a period of 60 min. A maintenance dose of 10 mL·kg^{-1}·h^{-1} was infused during the remainder of the experiment. Hypothermia was induced using ice packs as soon as the 40% bleed started. Active cooling in the HT group was performed until a core temperature of 34°C was reached as indicated by the thermodilution catheter. The animals were maintained at their core temperature of 34°C for 4 h.

In-Hospital Resuscitation and Monitoring

Following the 4 h of induced hypothermia, rewarming to a core temperature of 38°C was performed in the HT group during the in-hospital phase (Phase V). The shed blood, together with Ringer's solution, was retransfused over a period of 60 min. At the same time, damage control surgery was performed to resect the injured small bowel, and the resected ends were ligated to stop the flow of blood. The abdomen was temporarily closed with towel clips. Euthanasia was performed with KCl under deep anesthesia 72 h after the induction of trauma.

Measurement of Hemodynamic and Coagulopathy Parameters

Hemodynamic Parameters

The core temperature, measured using pulmonary arterial temperature and rectal temperature; MAP; heart rate (HR); cardiac index (CI); global end-diastolic volume (GEDV); extravascular lung water (EVLW); left ventricular contractile index (dPmx); and mixed venous oxygen saturation (SvO2) were recorded using PiCCO before shock induction and at different time points following the HS.

Blood Samples

Prothrombin time (PT) was analyzed using an Automated Blood Coagulation Analyzer (CA-6000; Sysmex, Kakogawa, Japan). The blood samples were analyzed using thromboelastography (TEG) system analysis (Thromboelastograph 5000; Haemoscope Corp., Niles, IL, USA) for reaction time (R), clotting rate (alpha angle [α]), and clot strength (maximal amplitude [MA]). Thromboelastometry measurements were performed at 38°C and 34°C during hypothermia. Hemoglobin (Hb), central venous hemoglobin oxygen saturation (ScvO2), and serum lactate were measured using arterial blood-gas analysis (ABL510; Radiometer, Copenhagen, Denmark). The whole body oxygen uptake index (VO2) and oxygen delivery index (DO2) were calculated.

Statistical Analysis

The data is presented as mean ± SEM, as appropriate. Statistical analyses were performed using SPSS v. 19.0 (IBM Corp; Armonk, NY, USA). For comparison of different observations within and between the groups, the data was first analyzed by repeated measures analysis of variance, and differences were then calculated by *post hoc* testing. The Kaplan-Meier method was used to compare the survival between the 2 groups. Survival rates were compared with a Fisher's exact test. P < 0.05 was considered statistically significant. The figures were generated using GraphPad Prism 5.0c for Mac (GraphPad Software; La Jolla, CA, USA).

Results

Survival

Three animals died of their injuries prior to randomization and were excluded from the analysis. This resulted in a sample size of 16. Five pigs in the NT group died during the experiment, and 2 pigs in the HT group died (p = 0.137). The Kaplan-Meier survival curve is provided in Fig. 2.

Hemodynamic Parameters

Representative data is provided in Fig. 3. At 3 h and 4 h during the hypothermia stage, EVLWI and HR significantly decreased in the HT group (both p < 0.01). During the last 1 h following hypothermia, dPmx decreased more in the HT group than in the NT group (p < 0.01). At 4 h, cooling induced a further decrease in VO2 and DO2 in the HT animals (p < 0.005 and p < 0.001, respectively).
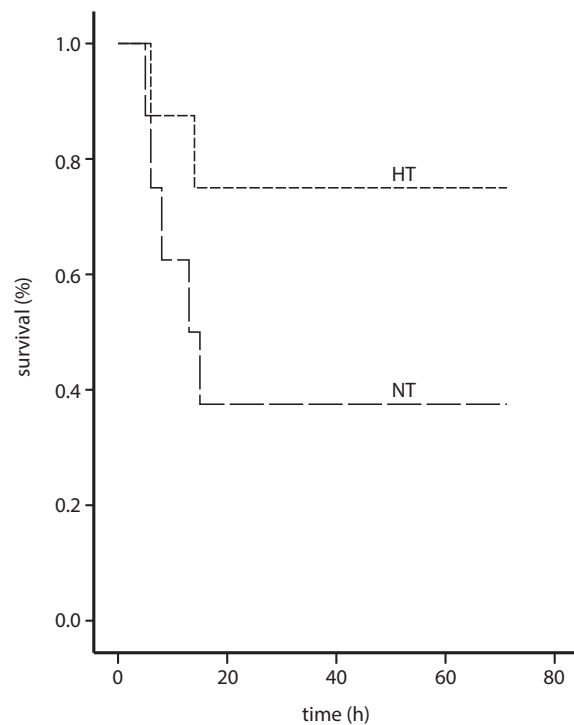

Fig. 2. The Kaplan-Meier survival curve indicating the 72-h mortality of the hypothermia group (HT, n = 8) and normothermia group (NT, n = 8) of pigs following the induction of hemorrhagic shock and fluid resuscitation. The difference in survival between the 2 groups was not statistically significant, as indicated by a Fisher's exact test (p = 0.137)

No significant differences were detected in MAP, GEDV, or CI between the NT and HT groups in successive measurements. Arterial lactate was 2.3 ± 0.3 mmol/L and 2.0 ± 0.4 mmol/L in the HT and NT groups, respectively, at the end of the hypothermia stage (p = 0.48).

Coagulation Parameters

During hypothermia, there was no difference in PT between the groups. At 3 h during the hypothermia stage, thromboelastometry analyses indicated significant differences in R and α, but not in MA. These coagulation changes occurred when the animals had a core temperature of 34°C and also following recovery during rewarming (Fig. 4).

Discussion

The present study analyzed the effect of prehospital induced hypothermia on hemodynamic and coagulation parameters in a pig model of multiple trauma. Lower heart rates were observed in the HT group than in the NT group, resulting in a prolonged diastolic period. This may have
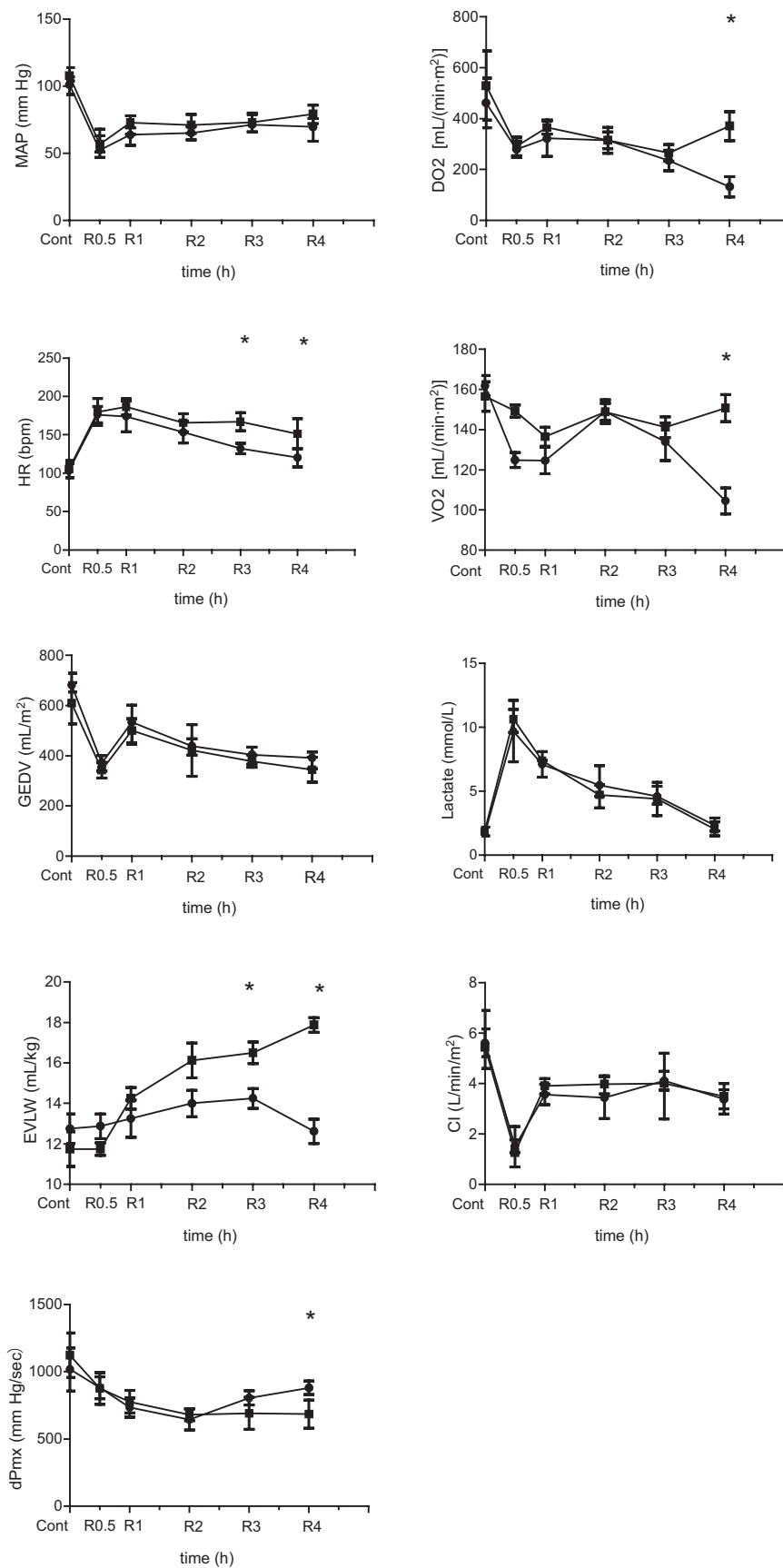
Fig. 3. Changes in the hemodynamic parameters at different time points following the induction of hemorrhagic shock in 2 groups of pigs (mean ± SEM). Cont, baseline or control values $R_{0.5}$, R_1, R_2, R_3, and R_4 represent 0.5, 1, 2, 3, and 4 h after resuscitation, ● hypothermic (HT) group; ■ normothermic (NT) group; * statistically significant difference ($p < 0.05$) between the HT and NT groups

improved coronary pyrfusion and decreased oxygen requirements during HS and resuscitation, resulting in better preservation of cardiac function. In addition, total body VO2 and DO2 were lower in hypothermic HS than in normothermia. We suggest that this decrease in cardiac oxygen metabolism and the reduction in systematic oxygen requirements protect the cardiac system. At the same
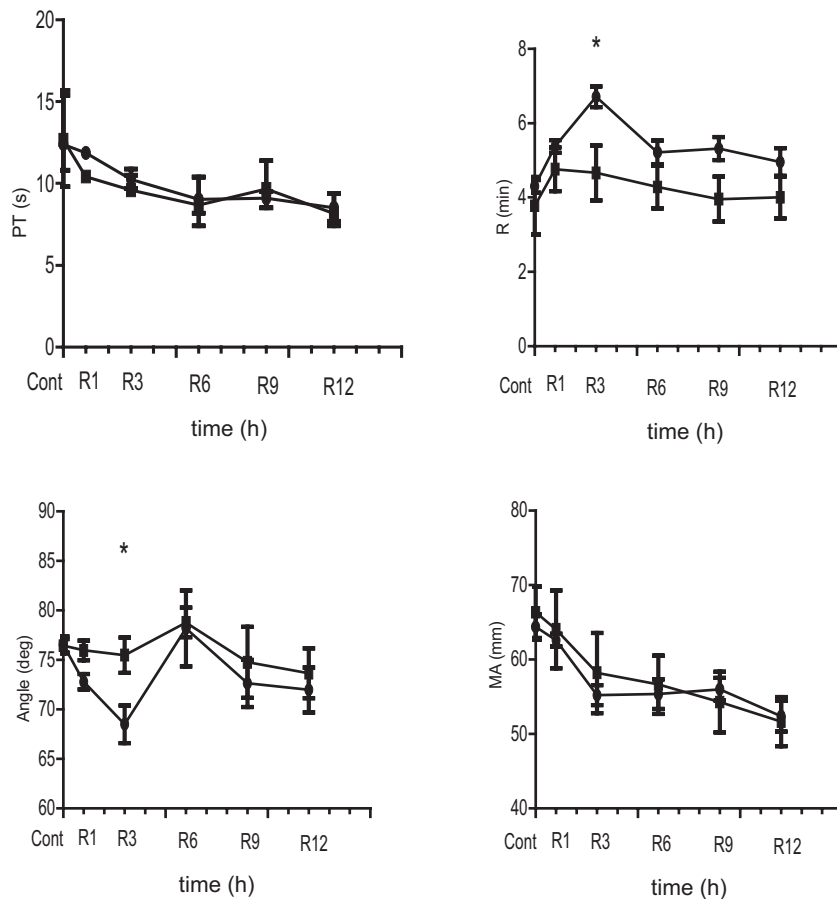
Fig. 4. Changes in thromboelastography (TEG) measurements (mean ± SEM) in pigs at different time points following the induction of hypothermia and hemorrhage with subsequent resuscitation. Cont, baseline or control values R_1, R_3, R_6, R_9, and R_{12} represent 1, 3, 6, 9, and 12 h after resuscitation, ●— hypothermic (HT) group; ■— normothermic (NT) group; * statistically significant difference ($p < 0.05$) between the HT and NT groups

time, the enhanced dPmx in the HT group would enable blood flow to vital organs, such as the brain, heart, and kidneys.

In the course of HS, the loss of colloidal solution will inevitably lead to a decline in intravascular colloid osmotic pressure, making it easy to transfer effective blood volume to the lung tissue space, which is prone to pulmonary edema. The EVLW, as a measure of lung water content, seems to be a good predictor of mortality in critical patients [22]. The positive effects of mild hypothermia on lung injuries are well established [23–26], and this may have been reflected in the HT group in this study by the decreased EVLW at the 240-min measurement. Induced mild hypothermia is involved in numerous protective mechanisms that may mitigate acute lung injury, including the reduction in mitochondrial dysfunction and metabolic demand, the reduction in free radical production, the inhibition of various pro-inflammatory reactions, and a decrease in cell and vascular permeability [27]. Therefore, the occurrence of these protective qualities with mild hypothermia without significant adverse events may be an advantage over drug therapies, which target a single injury pathway and are largely ineffective [28]. In this way, mild hypothermia may be an effective treatment for an acute lung injury.

Hemorrhagic coagulopathy is a notable complication after traumatic injury, affecting the development and therapy of traumatic HS. Hypothermia, with a core temperature < 34°C, has a significant effect on coagulation [29, 30], whereas hypothermia, with a core temperature > 34°C, has little or no effect [31, 32].

Our study revealed a significant impact on R and α in the HT group, when compared with the NT group. At the same time, the MA, which reflects the clot quality and strength, was not affected by hypothermia, and this is similar to findings reported in other studies [31]. Prolonged R, together with a smaller α, indicate a decrease in the activity of coagulation factors and platelet function, resulting in a decrease in the speed of clot formation, fibrin building, and cross-linking.

Spontaneous hypothermia is very different from induced hypothermia; induced hypothermia during HS improves outcomes without impairing coagulation function [33]. Furthermore, large-scale studies conducted for stroke, traumatic brain injury, and cardiac arrest have not detected a significant increase in bleeding risks associated with induced hypothermia [34]. In addition, a small retrospective clinical case series of 5 trauma patients conducted by Tuma et al. [35] reported no bleeding complications following management

with induced hypothermia of 32°C to 34°C for 24 h following cardiac arrest. This is noteworthy given the negative reputation for hypothermia among those treating multi-traumatized patients. This contradiction may be explained by the interplay between hypothermia and acidosis. The effects of artificially induced (deep) hypothermia on coagulation are remarkable and difficult to reverse, particularly if accompanied by acidosis. However, most patients receiving protective therapy with induced mild hypothermia will not suffer from severe acidosis. Therefore, the effects of induced mild hypothermia on coagulation will be minimal.

Our study had a few limitations that should be mentioned. First, we induced uncontrolled HS using intestinal injuries created by a gunshot to mimic the clinical condition of severely traumatized patients. This procedure does not result in a perfect simulation of multiple injuries. Second, the physical response to pain may have an impact on hemodynamic parameters and coagulation capacity, and this was not taken into account in this study. Finally, analyses of the cause of death in the pigs were not performed, because gross necropsy was determined without pathologic analysis.

In our model, pre-hospital induced hypothermia affected the coagulation system and hemodynamic parameters but did not aggravate trauma-induced outcomes. Based on these results, we suggest that, following stabilization, pre-hospital induced mild hypothermia can be safely performed after major trauma. However, the lack of a clear notable difference between spontaneous hypothermia and induced mild hypothermia could be a primary limiting factor in the potential incorporation of mild hypothermia into trauma care. Before induced hypothermia can be confidently performed in a clinical setting, future research is required to provide guidelines on how to distinguish between spontaneous hypothermia and induced hypothermia.

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