Original Article

Effects of environmental hypothermia on hemodynamics and oxygen dynamics in a conscious swine model of hemorrhagic shock

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BACKGROUND: Hypothermia is associated with poor outcome in trauma patients; however, hemorrhagic shock (HS) model with anesthetized swine was different from that of clinical reality. To identify the effects of environmental hypothermia on HS, we investigated hemodynamics and oxygen dynamics in an unanesthetized swine model of HS under simulating hypothermia environment.

METHODS: Totally 16 Bama pigs were randomly divided into ambient temperature group (group A) and low temperature group (group B), 8 pigs in each group. Venous blood (30 mL/kg) was continuously withdrawn for more than 15 minutes in conscious swine to establish a hemorrhagic shock model. Pulmonary arterial temperature (Tp), heart rate (HR), mean arterial pressure (MAP), pulmonary arterial pressure (PAP), pulmonary arterial wedge pressure (PAWP), central venous pressure (CVP), cardiac output (CO), hemoglobin (Hb), saturation of mixed venous blood (SvO₂) and blood gas analysis were recorded at the baseline and different hemorrhagic shock time (HST). The whole body oxygen delivery indices, DO₂I and VO₂I, and the O₂ extraction ratio (O₂ER) were calculated.

RESULTS: Core body temperature in group A decreased slightly after the hemorrhagic shock model was established, and environmental hypothermia decreased in core body temperature. The mortality rate was significantly higher in group B (50%) than in group A (0%). DO₂I and VO₂I decreased significantly after hemorrhage. No difference was found in hemodynamics, DO₂I and VO₂I between group A and group B, but the difference in pH, lactic acid and O₂ER was significant between the two groups.

CONCLUSION: Environmental hypothermia aggravated the disorder of oxygen metabolism after hemorrhagic shock, which was associated with poor prognosis.

KEY WORDS: Hemorrhagic shock; Environmental hypothermia; Hemodynamics; Oxygen dynamics

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INTRODUCTION

During hemorrhagic shock (HS), patients are easy to suffer from hypothermia because of environmental exposure, clothing removal or administration of resuscitation fluids. Clinical retrospective analysis has suggested that hypothermia is associated with poor outcome in trauma patients.^[1-3] This supports

the recommendations that hypothermia should be avoided in trauma patients.^[4,5] The US Emergency War Surgery guidelines require early recognition, aggressive prevention, and treatment of hypothermia (including heat lamps, warmed fluids, forced air heating, and warm water immersion).^[6] In contrast with clinical data, studies in experimental models have consistently showed

that mild hypothermia induced by surface cooling or intravenous infusion of ice-cold fluids improves survival during and after HS.^[7-9] In a previous study, we found that HS model with anesthetized swine was different from that of clinical reality. This might explain the contradiction between experimental studies and clinical scenario. To identify the effects of environmental hypothermia on HS, we investigated hemodynamics and oxygen dynamics in an unanesthetized swine model of HS under simulating hypothermia environment.

METHODS

Animal preparation

We used 16 juvenile Bama pigs (Shichuang Piglet Cultivation Center, Heilongjiang Province), weighing 17-25 kg, for this study. The pigs were housed in controlled environment with free access to food and water. They were fasted overnight with free access to water, and premedicated with intramuscular injection of ketamine 20 mg/kg and atropine 0.5 mg. General anesthesia was induced by administration of 1.5%-2% isoflurane via a cone mask and endotracheal intubation was not necessary. After subcutaneous local infiltration of 0.25% bupivacaine, a sterile cutdown on the right side of the neck was performed. A 9F introducer catheter sheath was inserted 20 cm into the external jugular vein. A Swan-Ganz thermal dilution catheter (Edwards Lifesciences, Irvine, CA) was inserted via the right external jugular vein into the pulmonary artery to measure the mixed venous oxygen saturation (SvO₂), pulmonary arterial pressure (PAP), cardiac output (CO) and pulmonary artery temperature (Tp) continuously. After a sterile cutdown was performed in the right groin, a venous catheter (Edwards Lifesciences, Irvine, CA) was inserted into the right femoral artery and right femoral vein for continuous monitoring of the mean arterial pressure (MAP), collecting blood samples and withdrawing blood. Additional bupivacaine was infused into the incision before closing, and the catheters were taped to the neck and back. Electrocardiogram monitoring pads were also placed over each shoulder and hind limb. The animals were then placed in a special cage and allowed to awaken from anesthesia. Each animal was placed in a 90 cm × 30 cm × 70 cm iron cage and the venous catheters were connected to fluid-filled pressure-sensitive elements (Biosensors International PET. Ltd, Singapore) for monitoring pressure. The dimensions of the cage allowed the animal to stand or lie down with minimal disturbance

of the catheters.^[10] These preparative processes were completed within 50 minutes. After a 1-hour recovery period, the animals were observed for additional 2 hours for baseline values before hemorrhage. We prolonged observation periods properly if pigs displayed obvious restlessness. The Institutional Animal Care and Use Committee and the Research Animal Resources of the hospital approved the protocols of the study.

Baseline measurements

After the above preparations, the animals reached a steady state. The heart rate (HR), arterial pressure, MAP, PAP, pulmonary arterial wedge pressure (PAWP), central venous pressure (CVP), CO and SvO₂ were recorded at the baseline (Datex-Ohmeda S/5, Deyan, Finland) (Edwards Lifesciences, Vigilance, CA). Arterial blood gases and arterial hemoglobin levels were measured at the baseline (Bayer Rapidlab 865, Germany).

Induction of hemorrhagic shock

Volume-controlled hemorrhage was initiated by withdrawal of 40% blood volume (30 mL/kg, based on 7% blood volume) at a constant rate over 15 minutes via the right femoral vein catheter using a roller pump.^[11] The start of the hemorrhage was designated as the hemorrhagic shock time 0 (HST 0 min). Without any resuscitative fluid administration, all animals were observed until death (defined as no pulses and a state of apnea) or until HST 240 minutes maximum.

Experimental protocol

The experiment was performed in awake pigs. The pigs were divided into two groups: ambient temperature group (group A, *n*=8) and low temperature group (group B, *n*=8). Pigs in group A were left at room temperature (22 °C) and were continuously observed after models had been established. For animals in group B, they were put into under -10 °C circumstance after models had been established. We used ice cabinet (SD/SC-376BP, Xingxing, Zhejiang), which was set to -10 °C to simulate low temperature environment.

Measurements

Tp, HR, MAP, PAP, PAWP, CVP, CO, Hb, SvO₂ and arterial blood gases were recorded/measured at the baseline, at HST 15 minutes, every 15 minutes until HST 60 minutes, and every 30 minutes after HST 60 minutes. Cardiac index (CI) was calculated by dividing them by the body surface area estimated from the body

weight.

The whole body oxygen delivery indices, DO_2I , VO_2I and O_2 the extraction ratio (O_2ER) were calculated by the following formulas:

$$\text{O}_2\text{ER} (\%) = \text{VO}_2 / \text{DO}_2 = (\text{CaO}_2 - \text{CvO}_2) / \text{CaO}_2 \times 100\%;$$

$$\text{DO}_2\text{I} (\text{mL/min per meter squared}) = \text{CaO}_2 \times \text{CI} \times 10;$$

$$\text{VO}_2\text{I} (\text{mL/min per meter squared}) = (\text{CaO}_2 - \text{CvO}_2) \times 10 \times \text{CI}$$

Statistical analysis

Data are expressed as the mean $\pm$ SD. Survival analysis was determined by using the Kaplan-Meier method. Analysis of variance (for repeated measures) was used with the unpaired *t* test for comparisons between the two groups at equivalent time points and with the paired *t* test for comparisons between values at the baseline and subsequent time points in each group. For all analyses, we used SPSS version 11 and levels of *P* value <0.05 were considered statistically significant.

RESULTS

Core temperature

As shown in Figure 1, T_p in group A was significantly decreased from the mean baseline value of 39.0°C (range, $38.3\text{--}40.0^\circ\text{C}$) to approximately 37.9°C (range, $37.0\text{--}38.9^\circ\text{C}$) at HST 150 minutes and to 37.5°C ($36.1\text{--}38.6$) at HST 210 minutes ($P<0.05$), meanwhile, T_p in group B was decreased from the mean baseline value of 39.4°C (range, $38.8\text{--}40.5^\circ\text{C}$) to 37.5°C (range, $36.7\text{--}39.1^\circ\text{C}$) at HST 90 minutes ($P<0.05$). Hemorrhage resulted in a significant reduction of core body temperature in both groups,

but the differences between the groups at specific time points, from HST 120 minutes ($38.2\pm 0.9^\circ\text{C}$, $36.8\pm 0.7^\circ\text{C}$, $P<0.05$) to HST 240 minutes after shock, were statistically significant. None of the pigs in group A shivered at any time during observation, but all the animals in group B shivered severely after they had been put into low temperature environment.

Blood gases

As shown in Table 1, blood PCO_2 levels dropped significantly in both groups after hemorrhage and then resumed normal. There were no significant differences between the two groups in arterial PO_2 or PCO_2 ($P>0.05$) at any time point. The arterial pH after bleeding increased from the mean baseline value of 7.49 ± 0.04 to 7.60 ± 0.06 at HST 15 minutes in group A ($P<0.05$), and from baseline value of 7.48 ± 0.05 to 7.60 ± 0.11 at HST 15 minutes in group B ($P<0.05$). Subsequently, they both decreased gradually. Blood pH levels in group A did not drop after reaching normal

Figure 1. Effect of environmental temperature on core temperature during HS. Compared with group A from HST 120 minutes, $P<0.05$

Table 1. Effect of environmental temperature on PO_2 , PCO_2 , HR, DO_2I and VO_2I during HS (mean $\pm$ SD)

Variables	BL	HST 30min	HST 1h	HST 2h	HST 3h	HST 4h
PO_2 (mmHg)						
Group A	102 $\pm$ 15	97 $\pm$ 12	96 $\pm$ 18	95 $\pm$ 17	99 $\pm$ 21	95 $\pm$ 14
Group B	99 $\pm$ 8	100 $\pm$ 11	94 $\pm$ 19	92 $\pm$ 13	98 $\pm$ 13	93 $\pm$ 16
PCO_2 (mmHg)						
Group A	38 $\pm$ 4.1	24 $\pm$ 4.3	29 $\pm$ 4.2	34 $\pm$ 2.9	35 $\pm$ 3.8	34 $\pm$ 4.2
Group B	39 $\pm$ 4.7	28 $\pm$ 7.1	32 $\pm$ 6.1	34 $\pm$ 7.7	34 $\pm$ 7.2	36 $\pm$ 3.7
HR (beats/min)						
Group A	99 $\pm$ 23	166 $\pm$ 15	160 $\pm$ 26	146 $\pm$ 31	125 $\pm$ 33	130 $\pm$ 26
Group B	103 $\pm$ 19	174 $\pm$ 39	161 $\pm$ 34	155 $\pm$ 17	146 $\pm$ 27	155 $\pm$ 15
DO_2I (mL/min $\cdot$ m ²)						
Group A	834 $\pm$ 65	221 $\pm$ 64	284 $\pm$ 85	283 $\pm$ 66	306 $\pm$ 75	288 $\pm$ 77
Group B	783 $\pm$ 74	197 $\pm$ 54	217 $\pm$ 95	236 $\pm$ 69	242 $\pm$ 52	206 $\pm$ 51
VO_2I (mL/min $\cdot$ m ²)						
Group A	347 $\pm$ 76	160 $\pm$ 37	185 $\pm$ 39	176 $\pm$ 36	170 $\pm$ 44	167 $\pm$ 56
Group B	299 $\pm$ 71	146 $\pm$ 32	137 $\pm$ 27	172 $\pm$ 51	186 $\pm$ 33	152 $\pm$ 36

Compared with group B, * $P<0.05$

levels, but pH levels in group B decreased continuously to the nadir at HST 90 minutes and then increased gradually. pH levels remained to be significantly lower in group B than in group A from HST 120 minutes (7.49 ± 0.05 vs. 7.37 ± 0.09 , $P < 0.05$) (Figure 2). Lactate levels after hemorrhage increased from 2.47 ± 0.2 mmol/L and 2.08 ± 0.7 mmol/L to 6.86 ± 1.2 mmol/L and 8.72 ± 3.2 mmol/L in groups A and B at HST 15 minutes respectively. Lactate levels in group A reached culmination at HST 60 minutes and then decreased gradually, but lactate levels in group B remained high during the observation phase. The differences in lactate levels between the two groups, from HST 90 minutes (7.16 ± 3.1 mmol/L vs. 12.83 ± 4.2 mmol/L, $P < 0.05$), were statistically significant (Figure 3).

Hemodynamics

The heart rate significantly increased from the mean baseline value of 99 ± 20 beats/min (range, 70-134) to 193 ± 19 beats/min (range, 158-214) at HST 15 minutes in group A ($P < 0.01$), and from baseline 103 ± 19 beats/min (range, 82-115) to 182 ± 30 beats/min (range, 134-211) at HST 15 minutes in group B ($P < 0.01$), but no significant difference between the two groups was found at any time point during observation periods ($P > 0.05$)

(Table 1). MAP decreased from the mean baseline levels of 128 ± 10 mmHg (range, 118-142) to 49 ± 14 mmHg (range, 31-72) after the volume-controlled hemorrhage in group A ($P < 0.01$), and from mean baseline 124 ± 14 mmHg (range, 112-141) to 47 ± 8 mmHg (range, 41-63) in group B ($P < 0.01$). Although the differences in MAP between the two groups, at any time points, were not statistically significant ($P > 0.05$) (Figure 4), MAP levels were much higher in survivors of group B than in those of group A from HST 45 minutes (69 ± 19 mmHg vs. 98 ± 14 mmHg) ($P < 0.05$). MPAP showed a similar tendency with MAP (data unpublished).

Oxygen dynamics

DO_2I decreased from the mean baseline value of 834 ± 65 mL/min per square meter to 213 ± 40 mL/min per square meter at HST 15 minutes in group A ($P < 0.01$), and from 783 ± 74 mL/min per square meter to 198 ± 47 mL/min per square meter in group B ($P < 0.01$). Then, DO_2I remained significantly lower in both groups and no statistical significances were found between them ($P > 0.05$) (Table 1). VO_2I decreased from the baseline value of 347 ± 66 mL/min per square meter to 171 ± 49 mL/min per square meter at HST 15 minutes in group A ($P < 0.01$), and from 299 ± 64 mL/min per

Figure 2. Effect of environmental temperature on pH during HS

Figure 3. Effect of environmental temperature on lactate during HS

Figure 4. Effect of environmental temperature on MAP during HS

Figure 5. Effect of environmental temperature on O_2ER during HS

square meter to 165 ± 38 mL/min per square meter in group B. VO_2I levels remained low in both groups and no statistical significance was found at any time point ($P > 0.05$) (Table 1). Overall, DO_2I and VO_2I were not changed significantly by cooling. O_2ER increased rapidly after models had been established in both groups. Subsequently, it declined gradually in group A, but remained high in group B. From HST 150 minutes, the differences in O_2ER between the two groups were statistically significant ($P < 0.05$) (Figure 5).

Survival

All eight pigs in group A survived beyond HST 240 minutes, whereas four pigs died at HST 65 minutes, HST 185 minutes, HST 210 minutes and HST 240 minutes respectively in group B. Life table analysis revealed that surface cooling significantly shortened the survival time compared with no cooling ($P < 0.05$) (Log rank, $P = 0.025$).

DISCUSSION

Animal models of HS have often been used to investigate the mechanisms, pathophysiologic alteration, and therapeutic intervention of HS. Because swine models of HS have similar cardiovascular and hemodynamic responses to HS as humans, they are often used to investigate the effects of HS on hemodynamics and prognosis.^[12-14] At present, anesthetized swine models of hemorrhagic shock were used in many studies. However, HS and anesthesia can not only interfere with the cardiovascular system and body temperature regulation, but also interact each other.^[15,16] It can be inferred that experimental conclusions obtained from anesthetized models are not credible.

To eliminate anesthesia interference and make HS model accordance with clinical reality, we referred to Zink and Rhee's design^[10,17] and developed an unanesthetized swine model of HS. Generally, pigs needed 30-45 minutes to recover from anesthesia after stop inhalation of isoflurane. After 50-150 minutes environmental adaptation periods, pigs' physiological indexes including hemodynamics, oxygen dynamics, blood gas analysis and pulmonary artery temperature retrieved to physiological state. The model not only ensured feasibility, but also preserved shivering and sympathetic responses which mimicked the clinical condition.

The finding that environmental hypothermia

worsened survivals from HS corroborates clinical notions, which consistently demonstrated that environmental hypothermia is associated with deteriorated outcome. No significant differences were found in HR and MAP, but the differences in core temperature, PH, lactate and O_2ER were significant, which emphasized the importance of oxygen metabolic disturbance to prognosis. 40% blood volume loss during HS decreased DO_2I and VO_2I to 3/4 and 1/2 respectively and increased O_2ER by 80% through compensation mechanism. Energy production reduction and lactate accumulation caused by oxygen deficiency had more influence on group B than group A in PH and core temperature. It is inferable that environmental hypothermia inevitably causes surface temperature reduction. Although changes in the surface temperature contribute only about 20% to the cold response,^[18-20] we found animals in group B shivering all the time. Even if O_2ER had increased to a high level, oxygen equilibrium could not be maintained because shiver increased oxygen demand greatly. Core temperature decreased because of reduction of energy production, heat conduction and heat emission, and this aggravated shivering.^[21-23] This regenerative feedback vicious cycle exaggerated internal environment disorder. Its consequence must be acidosis exacerbation, circulation responsibility degeneration, and progressive exhaustion. High lactate, low PH, high O_2ER , hypothermia and circulatory collapse in group B provided evidences that environmental hypothermia was "the second hit" after HS. Although some researchers have argued that it is difficult to directly translate the results obtained from animal studies into clinical setting, one advantage of using animal studies is the ability to obtain information under well-defined conditions that mimic specific clinical scenarios.

Contrary to Wu and George's reports, we didn't arrive at the conclusions that surface cooling could improve survival during HS.^[7,8] Obviously, it was the unanesthetized model of HS that made experimental results contrary to those of George's. If pigs' normal physiological reaction was blocked under low temperature circumstance, results derived from these animals were not reliable. Our model preserved sympathetic responses which make it consistent with clinical condition, and thus results would be more reliable. Actually, hypothermia after anesthesia is a protective inducible hypothermia, which is far away from spontaneous hypothermia.^[24-26] Hypothermia occurred in group B met with spontaneous hypothermia

features: hypothermia, acidosis and coagulopathy caused by the exhaustion of ATP stores during anaerobic metabolism.^[27-30] To prevent hypothermia, we should avoid low temperature stimulation during HS resuscitation.

Compared with the anesthetized model of HS, unanesthetized model's reaction to hemorrhage was more severe in hemodynamics and oxygen dynamics. Similarly, anesthesia suppression free made changes in core temperature more characteristic. Although our model was simple, it was valuable in establishing a more complicated shock, trauma and resuscitation model.

We investigated the effects of environmental hypothermia on hemodynamics and oxygen metabolism in an unanesthetized swine model of HS. The results revealed that environmental hypothermia had more influence on oxygen dynamics than hemodynamics, and hypothermia was associated with poor outcome. Our study was helpful in re-analyzing findings of previous experimental studies and useful in establishing more practical study platform.

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Ethical approval: The study was approved by the Animal Ethical Committee of the General Hospital of Shenyang Military Command, Shenyang, China.

Conflicts of interest: The authors declare that there is no conflict of interest.

Contributors: Zhang C wrote the paper. All authors read and approved the final version of the manuscript.

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