Restoration of Body Temperature to Normothermia During Resuscitation Following Trauma-Hemorrhage Improves the Depressed Cardiovascular and Hepatocellular Functions

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**Hypothesis:** Rewarming the body to 37°C during resuscitation following trauma-hemorrhage has salutary effects on cardiovascular and hepatocellular functions.

**Design, Interventions, and Main Outcome Measures:** Male rats underwent laparotomy (trauma induced) and were then bled to and maintained at a mean arterial pressure of 40 mm Hg until 40% of the maximum shed blood volume was returned in the form of Ringer lactate solution. Rats were exposed to ambient temperature and allowed to become hypothermic during hemorrhage. The animals were then resuscitated with 4 times the volume of shed blood with Ringer lactate solution for 60 minutes. In 1 group, the body temperature was rewarmed to 37°C during resuscitation. In another group, the body temperature was maintained at hypothermia (32°C) for 4 hours after resuscitation. In an additional group, the body temperature was kept at 37°C during hemorrhage and resuscitation. At 4 hours after resuscitation, the rats were returned to a room with ambient temperature. Various in vivo heart performance variables (maximal rate of pressure increase and decrease), cardiac output, hepatocellular function, and plasma IL-6 level were determined at 24 hours after resuscitation.

**Results:** Either maintenance of normothermia during hemorrhage or prolonged hypothermia following resuscitation had deleterious effects on cardiovascular variables and hepatocellular function and up-regulated plasma IL-6 levels. In contrast, rewarming the body to 37°C during resuscitation improved cardiac contractility, cardiac output, and hepatocellular function and reduced plasma IL-6 level.

**Conclusion:** Since rewarming the body temperature to normothermia during resuscitation improved depressed cardiovascular and hepatocellular functions, this should be considered as a useful adjunct to fluid resuscitation after trauma-hemorrhage.


Despite major advances in the management of trauma, traumatic injury remains one of the leading causes of death during the first 3 decades of life. Moreover, effective treatment of critically injured patients with hypovolemic shock continues to be a formidable challenge in trauma management. Hypothermia is a well-recognized consequence of severe injury and frequently occurs during fluid resuscitation of persons who have experienced trauma. Retrospective studies have shown that posttraumatic hypothermia is an accurate predictor of mortality. However, it is not clear from those retrospective studies whether hypothermia per se affects mortality, because other factors that affect body temperature, such as alcohol or illicit drug use or the number of blood transfusions, were not described in those studies. A recent randomized and prospective study showed that hypothermia increases the fluid required and the short-term mortality after major trauma compared with rapid rewarming after trauma. However, the precise mechanism by which hypothermia increased mortality still remains unknown. Several experimental studies have shown that hypothermia has protective effects during ischemia or organ preservation. Moderate hypothermia has also been reported to increase survival rates during hemorrhage. Although the effects of hypothermia in trauma remain controversial, there is no information available that clearly indicates whether rewarming from hypothermia following trauma-hemorrhage and resuscitation has any deleterious or beneficial effects on organ func-

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MATERIALS AND METHODS

EXPERIMENTAL MODEL OF TRAUMA-HEMORRHAGE AND RESUSCITATION

A previously described nonheparinized model of trauma-hemorrhage in the rat was used in this study with some modification. Briefly, male Sprague-Dawley rats with a mean ± SD weight of 291 ± 19 g (Charles River Labs, Wilmington, Mass) underwent overnight fasting before the experiment but were allowed water ad libitum. The animals were then anesthetized with methoxyflurane, and a 5-cm ventral midline laparotomy was performed to induce tissue trauma before the onset of hemorrhage. The abdominal incision was then closed in layers, and both femoral arteries and the left femoral vein were cannulated with PE-50 tubing. The mean arterial pressure (MAP) and heart rate were monitored. The animals were rapidly bled to an MAP of 40 mm Hg within 10 minutes. The MAP of 40 mm Hg was maintained by further withdrawing blood until the animal could no longer maintain that pressure unless Ringer lactate (RL) solution was infused. This time was defined as maximum, and the MAP of 40 mm Hg was maintained until 40% of the shed blood volume was returned in the form of RL solution. At that time (<90 minutes from the initiation of hemorrhage), the rats were resuscitated with 4 times (≈45 mL per rat) the volume of maximal bleedout for 60 minutes with RL solution. Sham-operated animals underwent the same surgical procedure but were neither bled nor resuscitated. The experiments described herein were performed in adherence to guidelines for the use of experimental animals from the National Institutes of Health, Bethesda, Md, and the project was approved by the Institutional Animal Care and Use Committee of Rhode Island Hospital, Providence.

RESULTS

ALTERATIONS IN BODY TEMPERATURE

As shown in Figure 1, body temperature decreased rapidly from a baseline of approximately 36.5°C to below 30°C at the end of hemorrhage and remained relatively constant during the course of fluid resuscitation. Although the body temperature increased gradually after resuscitation, it remained lower than 35°C even at 4 hours after the completion of fluid resuscitation.

ALTERATIONS IN HEMORRHAGE-ASSOCIATED VARIABLES AND MORTALITY

The mean time to reach maximum bleedout was 56 ± 3 minutes in normothermic, 54 ± 2 minutes in hypothermic, and 56 ± 1 minute in rewarmed animals. Similarly, the maximal bleedout volume in hemorrhaged animals was not significantly different (9.2 ± 0.2 mL in normothermic, 9.8 ± 0.2 mL in hypothermic, and 9.9 ± 0.3 mL in rewarmed animals). The total hemorrhage time was 83 ± 3 minutes in normothermic, 87 ± 1 minute in hypothermic, and 87 ± 3 minutes in rewarmed rats. Three rats died in the hypothermic (total, 11 rats) and rewarmed (total, 10 rats) groups, while 6 rats died in the normothermic group (total, 12 rats) within 24 hours after hemorrhage and resuscitation.

ALTERATIONS IN HEMODYNAMIC VARIABLES

The results in Figure 2, top, indicate that CO decreased significantly in the normothermic and hypothermic groups of animals at 24 hours after resuscitation. Rewarming during resuscitation, however, improved CO to levels not significantly different from sham-operated animals. Stroke volume also decreased significantly following hemorrhage and resuscitation in normothermic and hypothermic animals compared with sham-operated animals (Figure 2, bottom). Rewarming the body to normothermia during fluid resuscitation increased SV to a level not significantly different from sham-operated...
thermic and hypothermic rats was significantly decreased following trauma-hemorrhage (Figure 3, top). However, rewarmed rats had an increased maximal rate of pressure increase after trauma-hemorrhage and resuscitation, with no statistical difference from sham-operated animals. The maximum rate of pressure decrease in the normothermic and hypothermic groups was also significantly decreased. The values of the maximal rate of pressure decrease in the rewarmed group, however, increased significantly and they were not different from those of sham-operated animals (Figure 3, bottom).

HEPATOCELLULAR FUNCTION

The V<sub>max</sub> values decreased by 80% in the normothermic and 68% in the hypothermic groups following trauma-hemorrhage and resuscitation (Figure 4, top). Although the V<sub>max</sub> of the rewarmed animals increased significantly compared with the V<sub>max</sub> of the normothermic and hypothermic groups, the value remained significantly lower than that of the sham-operated animals (Figure 4, top). The K<sub>m</sub> was also decreased by 72% in the normothermic and 58% in the hypothermic animals. However, the K<sub>m</sub> in rewarmed animals was improved to a level that was not statistically different from that in sham-
The alterations in body temperature during and after hemorrhage and resuscitation without additional body temperature control. Animals were exposed to ambient temperature and then hemorrhaged. Rats were resuscitated with room temperature Ringer lactate solution. Data are expressed as mean ± SE. BH indicates before hemorrhage; EH, end of hemorrhage; R30, 30 minutes from the onset of resuscitation; and ER, end of resuscitation.

The plasma IL-6 level was 23.6 ± 6.0 pg/mL in sham-operated animals at 24 hours after the completion of hemorrhage and resuscitation (Figure 4, bottom).

**PLASMA IL-6 LEVEL**

The plasma IL-6 level was 23.6 ± 6.0 pg/mL in sham-operated animals, and it increased to 178.8 ± 48.4 pg/mL (P = .004) and 109.6 ± 26.0 pg/mL (P < .05, analysis of variance) at 24 hours after hemorrhage and resuscitation in normothermic and hypothermic rats, respectively. In the rewarmed rats, however, the plasma level of IL-6 was 69.5 ± 10.5 pg/mL, which was not significantly different from the level in the sham-operated animals at 24 hours after the completion of hemorrhage and resuscitation.

**COMMENT**

Previous experimental studies dealing with ischemia demonstrated that reduction of body temperature may have protective effects. The beneficial effects of hypothermia during hemorrhagic shock have also been seen in hemorrhage models.7-8,15,16 However, other studies2-4 have indicated that hypothermia in persons who have experienced trauma is associated with an increased mortality rate. Patients with severe injury are prone to remain hypothermic following resuscitation because of administration of room temperature fluids, blood transfusion, or anesthetic agents. Because of these findings, it has been recommended that hypothermic patients who have experienced trauma should be rewarmed.17,18 Although the discrepancy between experimentally induced hypothermia (which appears to be beneficial) and clinical hypothermia (which is deleterious) is not known, it is important to distinguish between the situation in which hypothermia has occurred only during hemorrhage and the one in which hypothermia persists following resuscitation. In contrast to ischemia and reperfusion or less severe hemorrhage, the body temperature of a person undergoing severe hemorrhagic shock declines spontaneously due to decreased heat production, alterations in the thermoregulatory mechanism, or both. Several studies19,20 have indicated that shivering is absent in severely hypotensive animals and humans. Because of inadequate blood flow to the thermoregulatory hypothalamus, the set point would be altered to a low temperature level for initiating physiological thermogenesis. In our hemorrhage model, body temperature decreased rapidly during hemorrhage and none of the rats shivered. Moreover, if rearming was not provided, rats remained hypothermic for several hours following fluid resuscitation. Thus, hypothermia may function as a protective response during hemorrhage by diminishing the metabolic demand. In this regard, Jurkovich et al21 demonstrated that hypothermia decreased intestinal capillary permeability leak associated with ischemia reperfusion injury. The work by Cornejo et al22 showed that mild hypothermia was also protective during reperfusion after ischemia in the rabbit ear. Although hypothermia appears beneficial for organ ischemia,5,21,22 it remains unknown whether raising the body temperature to normothermia during resuscitation, or maintenance of prolonged hypothermia following hemorrhagic shock, has any deleterious or beneficial effects on cardiovascular and hepatocellular function.

The data presented in this study indicate that left ventricular performance, CO, and SV were significantly depressed at 24 hours after trauma-hemorrhage and resuscitation in normothermic and hypothermic groups. These findings agree with the work of other investigators15,16 who have demonstrated that, compared with hypothermia, normothermia during hemorrhage de-
presses organ function. In addition, our findings demonstrate that maintenance of prolonged hypothermia following trauma-hemorrhage and resuscitation also depresses cardiac contractility and CO after trauma-hemorrhage. Rewarming the body to normothermia during crystalloid resuscitation, however, restored the maximal rate of pressure increase and significantly improved the maximal rate of pressure decrease at 24 hours following trauma-hemorrhage. Improved cardiac contractility was reflected by the restored cardiac index and SV in those rats that were rewarmed during resuscitation. Our results indicate that hepatocellular functions \( V_{\text{max}} \) and \( K_m \) were significantly depressed at 24 hours after trauma-hemorrhage and resuscitation in the normothermic and hypothermic groups. Although \( V_{\text{max}} \) increased in the rewarmed group, it was not restored to normal; \( K_m \) values increased significantly in the rewarmed group compared with those in the normothermic and hypothermic groups and were not different from values in the sham-operated animals.

The study of Morray and Pavlin suggests that rewarming the body following transient vs prolonged hypothermia created a differential response in oxygen delivery and oxygen consumption. In addition, a clinical study by Gentilello et al demonstrated that patients who

<table>
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<th>Variable</th>
<th>SHAM (n = 7)</th>
<th>NOR (n = 6)</th>
<th>HYPO (n = 8)</th>
<th>REW (n = 7)</th>
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<tr>
<td>MAP, mm Hg</td>
<td>119 ± 3</td>
<td>75 ± 5†</td>
<td>84 ± 1†</td>
<td>94 ± 3†‡</td>
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<td>HR, beats/min</td>
<td>380 ± 9</td>
<td>370 ± 18</td>
<td>370 ± 15</td>
<td>385 ± 12</td>
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<td>TPR, mm Hg · mL⁻¹ · min⁻¹ · 100 g BW</td>
<td>3.11 ± 0.08</td>
<td>2.41 ± 0.13†</td>
<td>2.71 ± 0.09†</td>
<td>2.64 ± 0.11†</td>
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<tr>
<td>PCV</td>
<td>0.45 ± 0.002</td>
<td>0.21 ± 0.008†</td>
<td>0.21 ± 0.008†</td>
<td>0.21 ± 0.004†</td>
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<tr>
<td>BT, °C</td>
<td>37.4 ± 0.2</td>
<td>38.0 ± 0.6</td>
<td>37.7 ± 0.2</td>
<td>38.2 ± 0.3</td>
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* Data are given as the mean ± SE and compared by 1-way analysis of variance and the Tukey test. SHAM indicates sham-operated animals; NOR, animals kept at 37°C during hemorrhage and resuscitation; HYPO, animals maintained at hypothermia (32°C) for 4 hours after resuscitation; REW, animals rewarmed to 37°C during resuscitation; MAP, mean arterial pressure; HR, heart rate; TPR, total peripheral resistance; BW, body weight; PCV, packed cell volume; and BT, body temperature.

†P < .001 vs SHAM.
‡P < .001 vs NOR.
Despite advances in the treatment of persons who have experienced trauma, many of those patients subsequently die of sepsis, septic shock, and the ensuing multiple organ failure in surgical intensive care units. Hypothermia is a well-recognized consequence of major injury, and although persons who have experienced trauma are usually rewarmed during fluid resuscitation, it remains controversial whether rewarming the body to normothermia during resuscitation following trauma-hemorrhage indeed has any salutary effects on organ functions. The present study indicates that rewarming the body temperature to 37°C during crystalloid resuscitation significantly improves cardiac contractility, CO, and hepatocellular function and reduces the plasma level of IL-6. In contrast, prolonged hypothermia following resuscitation produced deleterious effects on those variables. Since rewarming the body to normothermia during resuscitation improved the depressed cardiovascular and hepatocellular functions, we propose that restoring the body temperature to normothermia during resuscitation should be carried out to optimize the effects of fluid resuscitation on organ functions following trauma and hemorrhagic shock.

had experienced trauma and who remained hypothermic had a higher oxygen consumption than those who were rapidly rewarmed. Prolonged hypothermia results in oxygen debt as oxygen consumption increases out of proportion to oxygen delivery. In contrast, transient hypothermia does not increase oxygen debt. Nevertheless, hypothermia is thought to be associated with a decrease in oxygen delivery and a proportional decrease in oxygen consumption. Hypothermia is also known to be a powerful short-term stimulator of the sympathetic nervous system and can result in lactic acidosis. The short-term effects of hypothermia result in decreased metabolic demands that may be advantageous in the ischemic state. Nevertheless, prolonged hypothermia may produce deleterious sympathetic discharge with severe acidosis and lactate production, which impairs tissue perfusion. It may also result in increased peripheral vascular resistance and limit CO. Thus, it is possible that oxygen debt may be more predominant in patients with prolonged hypothermia and thereby explain the deleterious effects of hypothermia following resuscitation.

Although the precise mechanisms responsible for the beneficial effects of rewarming following trauma-hemorrhage and resuscitation remain unknown, a recent study has shown that hepatic perfusion is significantly improved at 4 hours after trauma-hemorrhage if body temperature is rewarmed to normothermia during resuscitation. Rewarming may increase vasodilation of peripheral vascular beds and, therefore, improve tissue perfusion. Consequently, the improvement in microvascular blood flow would be expected to ameliorate hypoxemia encountered following hemorrhage. Thus, it is possible that the beneficial effects of rewarming on cardiovascular and hepatocellular functions may be a result of improved tissue perfusion. The beneficial effects of rewarming on organ function may also be related to the reduction in proinflammatory cytokine release. In this study, we have shown that circulating levels of IL-6 were significantly increased in normothermic animals. Although plasma levels of IL-6 in hypothermic animals were lower than those in normothermic animals at 24 hours after the completion of fluid resuscitation, such a decrease was not significantly different. However, rewarming during resuscitation decreased circulating levels of IL-6 compared with prolonged hypothermia following resuscitation. This IL-6 decrease may also contribute to better hepatic perfusion and thus to improvement in hepatocellular function. A study examining the relation between inflammatory cytokines and perfusion has shown that the down-regulation of the synthesis of inflammatory cytokines is associated with improvement in hepatic blood flow and hepatocellular function after trauma-hemorrhage. However, it remains to be determined whether up-regulated IL-6 can directly or indirectly produce any deleterious effects on hepatocellular function. Further studies are required to evaluate this possibility and to determine the precise mechanism of the salutary effects of rewarming following trauma and hemorrhagic shock.

It could be argued that the rapid rewarming rate used in this study may not be applicable or appropriate to the clinical situation. The study by Danzl et al indicated that the average rewarming rate accomplished within various institutions was 1.08°C/h. However, newer techniques have attempted to achieve more efficient rewarming. Continuous arteriovenous rewarming methods have been reported to achieve the rapid rewarming rate of 4.5°C/h in the clinical setting.

In summary, our results indicate that maintenance of normothermia or prolonged hypothermia following trauma-hemorrhage and resuscitation does not protect cardiovascular and hepatic functions and decreases IL-6 levels. Rewarming the body to normothermia during resuscitation, however, significantly improves cardiac contractility, CO, and hepatocellular function. Thus, restoring the body temperature to normothermia during resuscitation should be carried out to optimize the effects of fluid resuscitation on cardiovascular and hepatocellular functions following trauma and hemorrhagic shock.

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REFERENCES

3. Luna GK, Maier RV, Pavlin EG, Anardi D, Copass MK, Oreskovich MR. Incidence