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-
tion. This study, therefore, was performed to determine whether hypothermia or normothermia during resuscitation following trauma-hemorrhage produces any differential effects on cardiovascular and hepatocellular functions and on proinflammatory cytokine release.

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
pentobarbital sodium, approximately 15 mg/kg BW, cardiac output (CO) and hepatocellular function were measured.

To determine the alterations in body temperature during and following hemorrhage and resuscitation, additional rats (n = 5) were hemorrhaged and resuscitated with RL solution at ambient temperature. After fluid resuscitation, the rats were returned to a room with ambient temperature and body temperature was monitored up to 4 hours after the completion of resuscitation.

MEASUREMENT OF CO
Cardiac output was determined using an indocyanine green (ICG) dilution technique with a fiberoptic catheter and an in vivo hemoreflectometer, as previously described.20 Cardiac output was expressed as milliliters per minute per 100 g BW, and stroke volume (SV) (measured in microliters per beat per 100 g BW) was calculated as follows: SV = (CO/heart rate) × 1000. Total peripheral resistance (measured in millimeters of mercury per milliliter per 100 g BW) was calculated as follows: total peripheral resistance = MAP/CO.

MEASUREMENT OF HEPATOCELLULAR FUNCTION
Hepatocellular function (maximal velocity of ICG clearance [Vmax] and efficiency of ICG active transport [Km]) was also measured by the in vivo ICG clearance technique. Three separate doses (50 μL of 1, 2, and 5 mg/mL) of ICG were administered via the right jugular vein catheter. The arterial concentration of ICG was recorded each second for 5 minutes using the fiberoptic catheter and in vivo hemoreflectometer. The initial velocity of ICG clearance (Vmax) for each dose was calculated by performing a nonlinear regression of the ICG clearance curves using the constant e raised to a second-order polynomial function. The calculation of Vmax and Km was performed according to previous publications.12,13 In this active hepatocellular membrane transport system, Vmax represents the functional hepatocyte ICG receptors, whereas Km represents the efficiency of the active transport process.13

MEASUREMENT OF IN VIVO HEART PERFORMANCE

After the determination of CO and hepatocellular function, the fiberoptic catheter in the right carotid artery was replaced with PE-50 tubing. The catheter was carefully advanced into the left ventricle. The position of the catheter was confirmed using an in vivo heart performance analyzer (Micro-Med, Louisville, Ky) as described previously.14 Various left ventricular performance variables, such as the maximal rate of pressure increase and decrease, were determined using a heart performance analyzer.

MEASUREMENT OF PLASMA INTERLEUKIN 6 (IL-6) LEVEL
Blood samples were drawn from the carotid artery into a heparinized syringe at the end of the experiment. The plasma was separated by centrifugation at 12 000g for 15 minutes at 4°C and then frozen in aliquots and stored at −70°C until assayed. The level of IL-6 in the plasma was measured using an enzyme-linked immunosorbent assay kit specific for rat IL-6 (Biosource, Camarillo, Calif).

STATISTICAL ANALYSIS
All data are expressed as mean ± SE unless otherwise indicated. The data were analyzed with a 1-way analysis of variance followed by the Tukey test. Differences were considered significant at P < .05.

HEPATOCELLULAR FUNCTION

The Vmax values decreased by 80% in the normothermic and 68% in the hypothermic groups following trauma-hemorrhage and resuscitation (Figure 4, top). Although the Vmax of the rewarmed animals increased significantly compared with the Vmax of the normothermic and hypothermic groups, the value remained significantly lower than that of the sham-operated animals (Figure 4, top). The Km was also decreased by 72% in the normothermic and 58% in the hypothermic animals. However, the Km 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.
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 (Vmax and Km) were significantly depressed at 24 hours after trauma-hemorrhage and resuscitation in the normothermic and hypothermic groups. Although Vmax increased in the rewarmed group, it was not restored to normal; Km 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 Pavlin23 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 al1 suggests that patients who

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**Table 1. Effects of Body Temperature on Various Hemodynamic Variables at 24 Hours After the Completion of Hemorrhage and Resuscitation**

<table>
<thead>
<tr>
<th>Variable</th>
<th>SHAM (n = 7)</th>
<th>NOR (n = 6)</th>
<th>HYPO (n = 8)</th>
<th>REW (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP, mm Hg</td>
<td>119 ± 3</td>
<td>75 ± 5†</td>
<td>84 ± 1†</td>
<td>94 ± 3‡</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>380 ± 9</td>
<td>370 ± 18</td>
<td>370 ± 15</td>
<td>385 ± 12</td>
</tr>
<tr>
<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>
</tr>
<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>
</tr>
<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>
</tr>
</tbody>
</table>

*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 rewarmed the body to normothermia during resuscitation following trauma-hemorrhage indeed has any salutary effects on organ functions. The present study indicates that rewarmed 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 rewarmed the body to normothermia during resuscitation improved the depressed cardiovascular and hepatocellular functions, we propose that rewarmed 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 rewarmed 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 rewarmed on cardiovascular and hepatocellular functions may be a result of improved tissue perfusion. The beneficial effects of rewarmed 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, rewarmed 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 rewarmed following trauma and hemorrhagic shock.

It could be argued that the rapid rewarmed 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 rewarmed rate accomplished within various institutions was 1.08°C/h. However, newer techniques have attempted to achieve more efficient rewarmed. Continuous arteriovenous rewarmed methods have been reported to achieve the rapid rewarmed 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, rewarmed 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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