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Hemodynamic stability to surface warming and cooling during sustained and continuous simulated hemorrhage in humans

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Abstract

One in 10 deaths worldwide is caused by traumatic injury, and 30–40% of those trauma-related deaths are due to hemorrhage. Currently, warming a bleeding victim is the standard of care due to the adverse effects of combined hemorrhage and hypothermia on survival. We tested the hypothesis that heating is detrimental to the maintenance of arterial pressure and cerebral perfusion during hemorrhage, while cooling is beneficial to victims who are otherwise normothermic. Twenty-one men (31 ± 9 y) were examined under 2 separate protocols designed to produce central hypovolemia similar to hemorrhage. Following 15 min of supine rest, 10 min of 30 mmHg of lower body negative pressure (LBNP) was applied. On separate randomized days, subjects were then exposed to skin surface cooling (COOL), warming (WARM) or remained thermoneutral (NEUT), while LBNP continued. Subjects remained in these thermal conditions for either 40 min of 30 mmHg LBNP ($N = 9$), or underwent a continuous LBNP ramp until hemodynamic decompensation ($N = 12$). Arterial blood pressure during LBNP was dependent on the thermal perturbation as blood pressure was greater during COOL ($P > 0.001$) relative to NEUT and WARM for both protocols. Middle cerebral artery blood velocity decreased ($P < 0.001$) from baseline throughout sustained and continuous LBNP, but the magnitude of reduction did not differ between thermal conditions. Contrary to our hypothesis, WARM did not reduce cerebral blood velocity or LBNP tolerance relative to COOL and NEUT in normothermic individuals. While COOL increased blood pressure, cerebral perfusion and time to presyncope were not different relative to NEUT or WARM during sustained or continuous LBNP. Warming an otherwise normothermic hemorrhaging victim is not detrimental to hemodynamic stability, nor is this stability improved with cooling.

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DISCLAIMER

All experiments were performed at the Institute for Exercise and Environmental Medicine. All authors contributed to the conception and design of the experiment, as well as data collection. All authors contributed to the interpretation of the data and to revision of the manuscript for important intellectual content. All authors have approved the final version of the manuscript.

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Keywords

Lower body negative pressure; skin surface warming and cooling; mean arterial pressure; cerebral perfusion; compensatory reserve index

INTRODUCTION

One in 10 deaths worldwide is caused by traumatic injury, with 30–40% of trauma-related deaths due to hemorrhage (1). Hemorrhage from major trauma is the predominant mechanism of death on the battlefield and in potentially survivable casualties (2). Among trauma patients who do not die immediately, hemorrhage-induced hypotension (systolic blood pressure < 90 mmHg) often occurs (3) that can contribute to cerebral hypoperfusion (4, 5). Severe hypothermia (core body temperature < 35°C) can accompany traumatic injuries and is associated with increased mortality rates (6, 7). In fact, mortality rate approaches 100% in trauma patients who are severely hypothermic, while a similar degree of hypothermia in the absence of trauma has a mortality rate of only 23% (8). These detrimental effects of hypothermia accompanying trauma are likely the primary justification for “the practice in emergency medicine of warming patients with hemorrhage” (9, 10). However, the use of this practice in all trauma victims has been questioned (10), particularly if the patient is not hypothermic (e.g., normothermic) since heating has the potential to prolong clotting time and reduces arterial blood pressure (11, 12).

Whole body heating during simulated hemorrhage (e.g., lower body negative pressure, head up tilt test) greatly compromises blood pressure and cerebral perfusion (11, 13, 14, 15, 16), culminating in an early onset of symptoms (attenuated mental status) and/or hemodynamic decompensation (11, 16, 17, 18). Based on these studies, heating may not be conducive, and may even be detrimental, to a hemorrhaging victim. Thus, identification of more effective therapies that can prevent or attenuate hemorrhage induced hypotension and cerebral hypoperfusion, and/or prolong hemorrhagic tolerance is an important undertaking.

Cooling interventions have been proposed as a potential therapy to treat hemorrhagic injuries, particularly when the individual is hyperthermic (10, 19). When skin surface cooling is applied during simulated hemorrhage, mean arterial pressure increases while the decrease in cerebral blood flow velocity is attenuated, suggesting better control, or maintenance of blood pressure and cerebral perfusion (20, 21, 22, 23). The current study examined the effects of skin surface warming and cooling during sustained and continuous simulated hemorrhage in otherwise normothermic individuals. It was hypothesized that arterial blood pressure and cerebral perfusion would be compromised (e.g., lowered) during simulated hemorrhage while being heated, resulting in reduced tolerance. Alternatively, skin surface cooling during simulated hemorrhage would elevate blood pressure and cerebral perfusion, resulting in prolonged tolerance.

MATERIALS AND METHODS

Two separate experimental protocols were performed to examine the effects of warming and cooling during sustained (Protocol 1) and continuous (Protocol 2) simulated hemorrhage.

Subjects

Nine men volunteered to participate in Protocol 1, and 12 men volunteered to participate in Protocol 2; 6 men participated in both protocols. Descriptive characteristics (mean $\pm$ SD) for Protocol 1: age, 30 ± 8 y; height, 177 ± 11 cm; body mass, 79 ± 15 kg, and Protocol 2: age, 29 ± 8 y; height, 179 ± 10 cm; body mass, 82 ± 16 kg. Subjects were non-smokers, were free of any known cardiovascular, respiratory, neurological or metabolic diseases and were not taking any medications. For both experimental protocols, randomized trials were performed at the same time of day within subject and each trial was separated by an average of one week. Subjects were asked to refrain from strenuous physical activity for 24 h, as well as from caffeine and alcohol for 12 h prior to the experimental visits. The informed consent and all experimental procedures were approved by the following Institutional Review Boards for Human Subjects: U. S. Army Medical Research & Materiel Command Human Research Protection Office, University of Texas Southwestern Medical Center, and Texas Health Presbyterian Hospital of Dallas. Written informed consent was obtained from all subjects prior to their participation in the study.

Measurements

Measurements were identical for both protocols. Subjects were dressed in a two-piece, tube-lined suit (Med-Eng, Ottawa, ON, Canada) that covered the entire body, except for the head, hands, feet, and one arm. Core temperature was measured with a telemetric pill (HQ Inc. Palmetto, FL, USA) that was swallowed a minimum of 1 h prior to the onset of data collection. Mean skin temperature was measured as the weighted average of 6 thermocouples attached to the skin surface on the abdomen, (14%), calf (11%), chest (22%), lower back (19%), thigh (13%) and upper back (21%). Heart rate was obtained from an electrocardiogram (GE Healthcare, Milwaukee, WI, USA) that was interfaced with a cardiometer (CWE, Ardmore, PA, USA). Blood pressure measurements were obtained by automated auscultation of the brachial artery (Tango+; SunTech Medical, Morrisville, NC, USA). Continuous blood pressure measurements were obtained non-invasively using photoplethysmography (Finometer Pro, FMS, Amsterdam, Netherlands) with the hydrostatic height at the finger corrected with respect to the heart level. Cerebral blood velocity was evaluated via transcranial Doppler of the middle cerebral artery, which is capable of detecting changes in blood velocity with high (> 90%) sensitivity and specificity (24).

The physiological reserve to compensate for reductions in central blood volume was determined via continuous beat-by-beat recordings of arterial pressure waveforms from a non-invasive photoplethysmographic device with a finger pulse oximeter (Flashback Technologies, Boulder, CO). The compensatory reserve was subsequently quantified using a machine learning algorithm, resulting in a compensatory reserve index (CRI) output (25). CRI provides a normalized value on a scale of 1-0, where '1' reflects the maximal capacity of the sum total of physiological mechanisms to compensate for deficits in central blood volume, and '0' implies imminent cardiovascular instability and decompensation (26).

Experimental Procedures Common to Both Protocols

Upon arrival to the laboratory, participants ingested the telemetric temperature-sensing pill. Subjects then provided a urine sample to ensure proper hydration, and weighed themselves

nude prior to instrumentation for measurements of mean skin temperature, heart rate and blood pressure. After donning the tube-lined suit, subjects laid in the supine position with the lower half of their body in a lower body negative pressure (LBNP) box, sealed at the level of the iliac crest. Mean skin temperature was initially clamped at $\sim 33\text{--}34^{\circ}\text{C}$ by adjusting the temperature of the water circulating through the suit. Subjects were then instrumented for the measurement of cerebral perfusion.

Experimental Protocol 1—Procedures for this protocol are graphically illustrated in Figure 1A. Following a 15 min period of baseline measurements, 10 min of 30 mmHg LBNP was applied to simulate a mild hemorrhage that might occur upon stopping active bleeding (e.g., tourniquet applied), without causing arterial hypotension (e.g., reduction > 10 mmHg in mean arterial blood pressure) while subjects remained normothermic. This approach has previously been verified to simulate central hypovolemia accompanying actual hemorrhage (27, 28). With this level of LBNP continuing, participants were then exposed to 40 min of the following thermal perturbations (LBNP+thermal):

1. COOL: $15\text{--}17^{\circ}\text{C}$ water perfused through the tube-lined suit to decrease mean skin temperature from normothermia ($\sim 34^{\circ}\text{C}$) to as low as possible, without causing shiver ($\sim 30^{\circ}\text{C}$). Water bath temperature was slightly elevated if the participant began to shiver, or if a 0.5°C decrease in core temperature was observed.
2. WARM: $40\text{--}44^{\circ}\text{C}$ water perfused through the tube-lined suit to elevate mean skin temperature from $\sim 34^{\circ}\text{C}$ (normothermia) to $\sim 37^{\circ}\text{C}$, and caused no more than a 0.5°C increase in intestinal temperature. This thermal condition was used to simulate the current medical practice of warming patients with blankets. Water bath temperature was adjusted if the participant's intestinal temperature surpassed a 0.5°C increase.
3. NEUT: $33\text{--}34^{\circ}\text{C}$ water continued to perfuse the tube-lined suit to maintain a normothermic mean skin temperature ($\sim 34^{\circ}\text{C}$).

Experimental Protocol 2—Procedures for this protocol are depicted in Figure 1B. Following 15 min of baseline measurements, 10 min of 30 mmHg LBNP was applied, while subjects remained normothermic (LBNP only). With LBNP continuing, subjects were then exposed to 5 min of either COOL, WARM or NEUT, as described above. The pressure within the LBNP device was then progressively decreased at a rate of $5\text{ mmHg}\cdot\text{min}^{-1}$ (to replicate continuous hemorrhage) until hemodynamic decompensation. Criteria for determining presyncope included: self-reporting by the subject of feeling faint, sustained nausea; rapid and progressive decrease in blood pressure resulting in a sustained systolic blood pressure < 80 mmHg; and/or relative bradycardia accompanied by a narrowing of pulse pressure. The order of the thermal challenges for both Protocols 1 and 2 were randomized between experimental days, with a minimum of 24 h between each trial. Randomization was determined by using a random assignment technique where thermal conditions were coded with a number (i.e., 1 = COOL, 2 = WARM, 3 = NEUT), and randomly selected for each participant.

Data Analysis

Data were collected with data acquisition software (Biopac MP150, Santa Barbara, CA, USA) at a sampling frequency of 50 Hz and subsequently converted into 1 min averages for data analysis. For Protocol 1, data were analyzed at 5 time points: Baseline, LBNP only, 5 min into LBNP+thermal (early), 30 min into LBNP+thermal (middle), and 40 min into LBNP+thermal (later). For Protocol 2, data were analyzed at the following 8 time points: Baseline, LBNP only, LBNP+thermal, 20%, 40%, 60% and 80% of completed LBNP ramp, and at the time of decompensation.

Statistical Analysis

Mixed effect repeated measures models were used to conduct the analysis of the crossover design of Protocols 1 and 2. For Protocol 1, three conditions and five time points were evaluated for thermal and hemodynamic variables. For Protocol 2, three conditions and eight time points were evaluated for thermal and hemodynamic variables, and tolerance time. For all crossover end points, the analysis was performed on an intention-to-treat basis including all available measurements. The mixed models include the condition effect, time effect and condition $\times$ time interaction fixed effects, in addition to incorporating the study period of the crossover design as a fixed effect. The study participant was modeled as a random effect and covariance structure was selected on the basis of Akaike information criterion and Bayesian information criterion as well as model parsimony. Following a significant condition $\times$ time interaction, pairwise comparisons were made from the least square means differences derived from the mixed models at an adjusted alpha = 0.01. Kaplan-Meier analysis with a log rank test to compare the “survival” distributions was used to depict the number of remaining subjects in each thermal condition during the LBNP ramp portion of Protocol 2. The “survival” probability at each min, beginning at the start of the LBNP ramp, was calculated by dividing the number of subjects remaining by the population.

Statistical analyses were performed using SigmaPlot (Systat Software Inc., San Jose, CA, USA) and SAS Proc Mixed version 9.4 (SAS institute, Cary, NC). Results are reported as mean $\pm$ SD, and a two-sided p-value < 0.05 was considered as the statistical probability of concluding wrongly that the means of the 3 thermal conditions during the protocols were in fact due to true differences, and did not arise from random variability for the given sample size of this experiment.

RESULTS

Experimental Protocol 1

Post-hoc tests revealed that mean skin temperature was elevated throughout WARM, whereas it was decreased throughout COOL (Table 1). Core temperature was maintained throughout all trials and no interaction between LBNP time and thermal condition was observed ($P = 0.07$). A main effect of time for core temperature ($P < 0.0001$) was detected, with post-hoc tests revealing that core temperature increased 0.1–0.2°C throughout the protocol, regardless of thermal conditions.

As shown in Table 2, both heart rate and mean arterial pressure responses during sustained LBNP were dependent on the thermal perturbations applied ($P < 0.0001$). The increase in heart rate was greatest during WARM ($\text{Baseline} = 19 \text{ beats} \cdot \text{min}^{-1}$), while COOL had the smallest increase ($\text{Baseline} = 6 \text{ beats} \cdot \text{min}^{-1}$). Post-hoc tests revealed that mean arterial pressure during WARM was reduced ($\text{Baseline} = -7 \pm 1 \text{ mmHg}$) throughout LBNP ($P < 0.0001$); whereas COOL elevated mean arterial pressure ($\text{Baseline} = +4 \pm 1 \text{ mmHg}$; $P = 0.0001$). Blood pressure responses during LBNP were unchanged during NEUT ($P = 0.38$).

A main effect of time was detected for cerebral perfusion ($P = 0.004$) and CRI ($P < 0.0001$), revealing that cerebral blood velocity and compensatory reserve decreased from Baseline throughout sustained LBNP ($-4.9 \pm 0.1 \text{ cm} \cdot \text{sec}^{-1}$ and -0.4 ± 0.1 , respectively). These decreases were independent of thermal status, as no interaction between thermal condition and LBNP time was observed for cerebral perfusion ($P = 0.82$) or CRI output ($P = 0.12$; Table 2).

Experimental Protocol 2

By design, mean skin temperature during the continuous LBNP ramp was dependent on the thermal perturbation applied ($P < 0.0001$; Figure 2, top panel), such that it was elevated during WARM ($36.4 \pm 0.5^\circ\text{C}$), and lowered during COOL ($30.5 \pm 0.9^\circ\text{C}$). Core temperature was elevated throughout the LBNP ramp by $0.2\text{--}0.3^\circ\text{C}$ similarly for all three thermal conditions ($P = 0.01$; Figure 2, bottom panel).

Heart rate ($P = 0.0004$; Figure 3) and arterial blood pressure ($P < 0.0001$; Figure 4) responses were dependent on the thermal perturbation applied during the continuous LBNP ramp. The increase in heart rate from Baseline throughout the LBNP until Presyncope was greatest during WARM ($\text{Baseline} = 53 \text{ beats} \cdot \text{min}^{-1}$), while COOL had the smallest increase ($\text{Baseline} = 45 \text{ beats} \cdot \text{min}^{-1}$), followed by NEUT ($\text{Baseline} = 49 \text{ beats} \cdot \text{min}^{-1}$). Post-hoc tests revealed that mean arterial blood pressure was elevated ($+7 \pm 3 \text{ mmHg}$; $P < 0.0001$) during COOL across the LBNP ramp. During WARM, blood pressure at 60 and 80% of the ramp was reduced ($\text{Baseline} = -4 \pm 1 \text{ mmHg}$; $P < 0.0001$) relative to Baseline. For all thermal conditions, blood pressure at the time of decompensation was reduced from Baseline ($P < 0.0001$).

Cerebral blood velocity ($\text{Baseline} = 26 \pm 1 \text{ cm} \cdot \text{sec}^{-1}$) and CRI ($\text{Baseline} = 0.7 \pm 0.1$) decreased throughout the LBNP ramp protocol ($P < 0.0001$), which were independent of the thermal conditions (cerebral blood velocity: $P = 0.69$, Figure 5; CRI: $P = 0.63$, Figure 6). Tolerance to LBNP, as defined by time to cardiovascular decompensation ($12.7 \pm 3.4 \text{ min}$; $P = 0.14$), or the LBNP level achieved at decompensation ($87.8 \pm 11.2 \text{ mmHg}$; $P = 0.09$), were similar between thermal conditions. Kaplan-Meier and log rank tests confirmed that LBNP tolerance was similar between trials, as “survival” curves were not shifted by the applied thermal conditions ($P = 0.57$; Figure 7; average time to hemodynamic decompensation, COOL: $13.0 \pm 2.8 \text{ min}$, NEUT: $13.1 \pm 3.9 \text{ min}$, WARM: $11.9 \pm 3.5 \text{ min}$).

DISCUSSION

Specific physiological effects of skin surface warming and cooling during two distinct simulated hemorrhagic challenges (sustained and continuous ramp) were examined in the present set of experiments. Our findings revealed that contrary to our hypothesis, cerebral blood velocity was unaffected by these thermal perturbations, despite a reduction and increase in arterial blood pressure during warming and cooling, respectively. Additionally, the physiological reserve to compensate for reductions in central blood volume (CRI) and subsequent tolerance to simulated hemorrhage (Protocol 2 only) were unaffected by either thermal manipulation. Overall, these data suggest that external body warming within the temperature limits applied in the present experiment, of an otherwise normothermic hemorrhaging victim is no more detrimental to hemodynamic stability or the reserve to compensate for reduced circulating central blood volume than that of a normothermic individual.

Despite differences in arterial pressure during the thermal provocations (Table 2; Figure 4), cerebral blood velocity responses were similar throughout LBNP between thermal conditions (Table 2; Figure 5). A possible explanation for this observation is that cerebral autoregulation maintained constant cerebral blood flow despite subtle deficits in central blood volume and corresponding reductions in arterial blood pressure (4, 5, 27). However, given recent challenges to the existence of cerebral autoregulation (29, 30), another explanation for the apparent uncoupling of cerebral blood flow with changing arterial blood pressures is the possibility that the thermal provocations caused cerebral vascular resistance and intracranial pressure (ICP) changes proportionate to and in the same direction as arterial pressures (i.e., COOL increased ICP, WARM decreased ICP), resulting in a constant cerebral perfusion pressure. The latter possibility is consistent with similar patterns of response in CRI (Figure 6), suggesting that similar “taxing” of compensatory mechanisms were required to maintain similar cerebral perfusion. That said, perhaps cerebral blood velocity would have directionally followed mean arterial pressure if greater cardiovascular instability (e.g., greater reductions in arterial pressure) occurred during the thermal provocations.

In Protocol 1, it is clear that an applied level of sustained stimulated hemorrhage of less than ~500 mL (30 mmHg LBNP) did not substantially alter cerebral perfusion, regardless of the thermal perturbations applied. Continuously increasing the level of LBNP (performed in Protocol 2), to replicate continuous bleeding, elicited greater reductions in arterial blood pressure, which was reflected in the average rate of decrease in CRI, and subsequently cerebral blood flow (Figures 4–6). However, there was no effect of mean skin temperature on hemorrhagic tolerance. Perhaps the lack of effectiveness of the thermal provocations on cerebral perfusion and tolerance to LBNP is due to the moderate level of heating and cooling applied, as well as the relatively short duration (5 min) of the thermal provocation prior to the onset of simulated hemorrhage. That said, the objective of the selected thermal provocations was to simulate the level and duration of heating and cooling that may occur in the field when treating a hemorrhaging victim. While 5 min may seem unrealistic, the thermal application continued throughout the simulated hemorrhage, which would normally occur (i.e., continually applying treatment) until emergency personnel begins treatment and/or the individual is transported to a field center.

Previous investigations showing that whole-body heat stress profoundly compromises tolerance to simulated hemorrhage utilized a substantially greater hyperthermic stress that increased core and skin temperatures to a much greater extent (~39°C for both measurements; 11, 16, 17, 18), relative to that which occurred in the present protocols. During profound hyperthermic stress, the cutaneous sympathetic vasodilator system is activated, (as well as locally induced vasodilation) to appreciably increase skin blood flow. This response has the potential to compromise tolerance to simulated hemorrhage as blood is displaced to the periphery and central blood volume is reduced (31, 32). Another factor that can negatively influence hemorrhagic tolerance is dehydration; Lucas et al. (34) reported that fluid loss during heat stress impaired LBNP tolerance by 64%. Notably, the onset for cutaneous vasodilation and sweating occurs only after a core temperature threshold is surpassed, which may vary individually (31, 32). The level of heating applied in the present studies, and likely what is being delivered on the battlefield, did not elicit a substantial change in core or mean skin temperatures. Further, the small sustained increase in core temperature across all conditions may have been due to reductions in skin blood flow due to the hypotensive challenge. Thus, it is unlikely that substantial cutaneous vasodilation or sweating occurred, which may explain why the heating stimulus did not compromise tolerance to LBNP.

Skin surface cooling elicited similar blood pressure responses relative to what has been previously reported (20, 21, 22, 23). Although no change in tolerance to reduced central blood volume was observed during Protocol 2 with the cooling stimulus, other studies show that cooling improves LBNP tolerance and cerebral blood velocity (23) in normothermic subjects (21, 35). Differences between these studies and the present one is likely due to differences in methodology. Durand et al. applied skin cooling for 30 min prior to the onset of a step-wise LBNP protocol, while Kean et al. (35) utilized environmental cooling for 100 min prior to sustained sub-hypotensive LBNP. In Protocol 2, cooling was imposed for only 5 min before a hemorrhagic ramp challenge. Although the time of exposure may have been insufficient to cause appreciable changes in skin temperature, the cooling challenge continued throughout the hemorrhagic ramp, which may be more applicable to what may occur in the current battlefield and civilian pre-hospital settings.. However, with anticipated requirements for prolonged field care (e.g., as much as 72 h), skin cooling at levels that does not compromise normal coagulation function may prove to be an important adjunct intervention that can delay the onset of life-threatening circulatory shock.

Wilson et al. (23) demonstrated that if individuals are sufficiently hyperthermic, such as that achievable in the military setting (i.e., elevated environmental temperatures, physical exertion, body armor), skin surface cooling improves the maintenance of cerebral perfusion and presumably tolerance during simulated hemorrhage. Given that observation, it is likely that skin surface cooling is most effective if the individual is sufficiently hyperthermic prior to the hemorrhagic insult, relative to being normothermic like in the present studies. That is, we proposed that an applied thermal provocation when administered to a hyperthermic hemorrhaging individual will be beneficial (with cooling) or detrimental (with warming) to hemorrhagic tolerance, relative to if that individual is normothermic; conclusions consistent with prior observations (11, 16, 17, 18, 20, 21, 22, 23). Additional experiments will be required

to test this hypothesis and provide evidence to support direction of such a clinical practice guideline.

CONCLUSION

The present findings demonstrate that skin surface cooling is not beneficial, while skin surface warming is not detrimental to the maintenance of cerebral perfusion and hemorrhagic tolerance during simulated hemorrhage in normothermic individuals within the temperature limits applied in the present investigation. While we acknowledge the limitation that the LBNP model does not encompass the complete cascade resulting from hemorrhage (e.g., there is no activation of hemostasis mechanisms or altered metabolic state), LBNP does mimic the integrative cardiovascular responses similar to an actual hemorrhagic insult (i.e., central hypovolemia, reduced blood pressure, and increased heart rate; 27, 28). Thus, the obtained results are translatable to non-invasive treatment of bleeding trauma patients and combat casualties in the prehospital setting. Moreover, we recognize that the present findings do not address a variety of other conditions and factors (e.g., sex, age, health status, medications, menstrual cycle, pre- and post-menopausal status, etc.) that may influence the outcomes. Further research will be necessary to address the potential impact of such factors on the observed findings.

Information from these studies can assist in the modification of clinical practice guidelines and identification of treatment(s) that may be beneficial to the care of hemorrhaging victims who are young (to middle-aged) and relatively healthy— particularly those patients with relatively short transport times to higher levels of care (i.e., Role 3). While the present data do not support the hypothesis that acute (5 min) cooling is beneficial for a normothermic hemorrhaging victim, these data indicate that warming would not be harmful during this short time frame.

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A Protocol 1

B Protocol 2

Figure 1.

Experimental schematic for Protocol 1 (panel A) and Protocol 2 (panel B). Subjects were supine within the lower-body negative pressure (LBNP) device under thermoneutral conditions but without LBNP (15 min Baseline). Subjects were then exposed to 10 min of LBNP (30 mmHg) while remaining thermoneutral. For Protocol 1: With LBNP continuing, subjects remained thermoneutral, underwent warming, or skin surface cooling (each on a different day and randomized) for 40 min. For Protocol 2: With LBNP continuing subjects were exposed to 5 min of one of the thermal manipulations, LBNP then continuously increased at $5 \text{ mmHg} \cdot \text{min}^{-1}$ until presyncope while the applied thermal manipulation continued. Thermal and hemodynamic variables were continuously measured throughout both protocols.

Figure 2. Mean ($\pm$ SD) skin temperature (top panel) and core temperature (bottom panel) for Protocol 2 during Baseline, lower body negative pressure (LBNP only), LBNP with the thermal perturbation (Thermal), 20%, 40%, 60% and 80% of LBNP ramp, and Presyncope; squares- COOL, circles- NEUT, triangles- WARM; ^, greater than Baseline and LBNP only for the WARM condition; #, less than Baseline and LBNP only for the COOL condition; *, greater than Baseline and LBNP only for all thermal conditions.

Figure 3.

Mean ($\pm$ SD) heart rate for Protocol 2 during Baseline, lower body negative pressure (LBNP only), LBNP with the thermal perturbation (Thermal), 20%, 40%, 60% and 80% of LBNP ramp, and Presyncope; squares- COOL, circles- NEUT, triangles- WARM; *, greater than Baseline for all thermal conditions.

Figure 4.

Mean ($\pm$ SD) arterial pressure for Protocol 2 during Baseline, lower body negative pressure (LBNP only), LBNP with the thermal perturbation (Thermal), 20%, 40%, 60% and 80% of LBNP ramp, and Presyncope; squares- COOL, circles- NEUT, triangles- WARM; ^, greater than Baseline for the COOL condition; #, less than Baseline for the WARM condition; *, less than Baseline and LBNP ramp.

Figure 5.

Mean ($\pm$ SD) cerebral blood flow velocity for Protocol 2 during Baseline, lower body negative pressure (LBNP only), LBNP with the thermal perturbation (Thermal), 20%, 40%, 60% and 80% of LBNP ramp, and Presyncope; squares- COOL, circles- NEUT, triangles- WARM; *, less than Baseline for all thermal conditions.

Figure 6.

Mean ($\pm$ SD) compensatory reserve index Protocol 2 during Baseline, lower body negative pressure (LBNP only), LBNP with the thermal perturbation (Thermal), 20%, 40%, 60% and 80% of LBNP ramp, and Presyncope; squares- COOL, circles- NEUT, triangles- WARM; *, less than Baseline for all thermal conditions.

Figure 7. Proportion of subjects remaining during lower body negative pressure ramp for COOL (dotted line), NEUT (solid line), and WARM (dashed line).

Table 1

Thermal Variables

	Baseline	LBNP only	LBNP+thermal (early)	LBNP+thermal (middle)	LBNP+thermal (later)
Tsk (°C)	COOL	34.0 ± 0.7	33.8 ± 0.7	30.7 ± 0.9 [#]	29.6 ± 1.0 [#]
	NEUT	33.8 ± 0.4	33.5 ± 0.4	33.5 ± 0.5	33.5 ± 0.3
	WARM	34.0 ± 0.3	33.7 ± 0.4	36.1 ± 0.4 [^]	36.7 ± 0.5 [^]
Tcore (°C)	COOL	37.0 ± 0.3	36.9 ± 0.2	37.3 ± 0.6 [^]	37.3 ± 0.2 [^]
	NEUT	36.8 ± 0.3	36.9 ± 0.2	37.1 ± 0.4 [^]	37.1 ± 0.3 [^]
	WARM	36.8 ± 0.2	36.9 ± 0.2	37.0 ± 0.3 [^]	37.1 ± 0.3 [^]

Mean (± SD) mean skin temperature (Tsk) and core temperature (Tcore) for Protocol 1 during Baseline, lower body negative pressure (LBNP only), and following 5 (early), 30 (middle) and 40 (later) min of combined LBNP and thermal perturbation (LBNP+thermal);

[^], greater than Baseline and LBNP;

[#], less than Baseline and LBNP.

Table 2

Hemodynamic Variables

	Baseline	LBNP only	LBNP+thermal (early)	LBNP+thermal (middle)	LBNP+thermal (later)
HR (beats·min ⁻¹)	<i>COOL</i>	62 ± 10	59 ± 11 [^]	60 ± 13 [^]	60 ± 14 [^]
	<i>NEUT</i>	62 ± 11	62 ± 11 [^]	63 ± 11 [^]	66 ± 11 [^]
	<i>WARM</i>	61 ± 10	67 ± 11 [^]	72 ± 12 [^]	75 ± 12 [^]
MAP (mmHg)	<i>COOL</i>	88 ± 5	95 ± 5 [^]	95 ± 3 [^]	95 ± 55 [^]
	<i>NEUT</i>	88 ± 7	89 ± 7	89 ± 8	90 ± 9
	<i>WARM</i>	91 ± 7	87 ± 7 [#]	87 ± 8 [#]	86 ± 7 [#]
MCA Vmean (cm·sec ⁻¹)	<i>COOL</i>	54.4 ± 10.9	52.2 ± 12.2 [*]	51.6 ± 10.2 [*]	50.7 ± 10.7 [*]
	<i>NEUT</i>	52.2 ± 12.0	51.7 ± 9.6 [*]	50.9 ± 9.7 [*]	50.2 ± 10.5 [*]
	<i>WARM</i>	56.1 ± 14.2	52.4 ± 13.7 [*]	51.9 ± 13.1 [*]	47.2 ± 12.2 [*]
CRI	<i>COOL</i>	0.9 ± 0.1	0.6 ± 0.1 [*]	0.7 ± 0.1 [*]	0.6 ± 0.2 [*]
	<i>NEUT</i>	0.9 ± 0.1	0.6 ± 0.1 [*]	0.6 ± 0.2 [*]	0.5 ± 0.1 [*]
	<i>WARM</i>	0.9 ± 0.1	0.6 ± 0.1 [*]	0.6 ± 0.1 [*]	0.5 ± 0.1 [*]

Mean (± SD) heart rate (HR), blood pressure (MAP), cerebral blood velocity (MCA Vmean), and compensatory reserve index (CRI) for Protocol 1 during Baseline, lower body negative pressure (LBNP only), and following 5 (early), 30 (middle) and 40 (later) min of combined LBNP and thermal perturbation (LBNP+thermal);

[^], greater than Baseline and LBNP;

[#], less than Baseline and LBNP;

^{*}, less than Baseline.