Active and passive heat stress similarly compromise tolerance to a simulated hemorrhagic challenge.

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Abstract

Passive heat stress increases core and skin temperatures and reduces tolerance to simulated hemorrhage (lower body negative pressure; LBNP). We tested whether exercise induced heat stress reduces LBNP tolerance to a greater extent relative to passive heat stress, when skin and core temperatures are similar. Eight participants (6 males, 32±7 yrs, 176±8 cm, 77.0±9.8 kg) underwent LBNP to pre-syncope on three separate and randomized occasions: 1) passive heat stress, 2) exercise in a hot environment (40°C) where skin temperature was moderate (36°C, Active 36), and 3) exercise in a hot environment (40°C) where skin temperature was matched relative to that achieved during passive heat stress (~38°C, Active 38). LBNP tolerance was quantified using the cumulative stress index (CSI). Prior to LBNP, increases in core temperature from baseline were not different between trials (1.18±0.20°C; P>0.05). Also prior to LBNP, mean skin temperature was similar between passive heat stress (38.2±0.5°C) and Active 38 (38.2±0.8°C; P = 0.90) trials, while it was reduced in the Active 36 trial (36.6±0.5°C; P≤0.05 compared to passive heat stress and Active 38). LBNP tolerance was not different between passive heat stress and Active 38 trials (383±223 and 322±178 CSI, respectively; P=0.12) but both were similarly reduced relative to Active 36 (516±147 CSI, both P≤0.05). LBNP tolerance is not different between heat stresses induced either passively or by exercise in a hot environment when skin temperatures are similarly elevated. However LBNP tolerance is influenced by the magnitude of the elevation in skin temperature following exercise induced heat stress.
Introduction

Passive heat stress increases core and skin temperatures, and is accompanied with profound reductions in tolerance to central hypovolemia (e.g., lower body negative pressure -LBNP), that simulates a hemorrhagic state (2, 26, 29, 31, 48, 51). This is due, in part, to a large displacement of blood to the cutaneous circulation and associated reductions in systemic vascular resistance (42) and central blood volume (12, 13), coupled with inadequate cutaneous vasoconstriction during the hypotensive challenge (11, 38). Such tolerance is likewise reduced following short-term exercise in a thermoneutral environment that is not accompanied by profound increases in skin and core temperatures (6). This response may be due to post-exercise reductions in baroreflex sensitivity (40, 49), lowered arterial blood pressure (9, 16, 27, 39) and an impaired transduction of sympathetic outflow into vasoconstriction (20) coupled with elevations in vascular conductance in the previously active limb (34).

Blood pressure and vascular alterations following exercise may be exacerbated if the exercise is performed under hot environmental conditions owing to heightened skin and core temperatures, as well as elevated limb muscle and skin vascular conductances (34, 36, 41, 44, 50). Such a response may reduce tolerance to a simulated hemorrhagic challenge to a greater extent relative to a passive heat stress, when increases in core and skin temperatures are similar. To that end, the first objective of this project was to test the hypothesis that tolerance to a simulated hemorrhagic challenge (via LBNP) is lower following exercise in a hot environment relative to a similar thermal provocation induced by passive heat stress.

Skin temperatures following passive heat stress can markedly affect tolerance to a subsequent hypotensive challenge, with cooler skin improving this tolerance (52). It remains unknown whether skin temperature following an exercise heat stress likewise affects tolerance to such
a challenge. To this end, the second objective of this study was to test the hypothesis that
tolerance to a simulated hemorrhagic challenge following exercise in a hot environment is
influenced by skin temperature. The obtained information has direct implications for the
understanding of blood pressure control in a soldier who may be heat stressed passively (e.g.,
turret gunner, sniper, etc.) or actively (e.g., foot patrol) and experiences a subsequent
hemorrhagic injury.
Methods

Subjects

Eight subjects (six males) participated in this study. Subject characteristics were; age $32 \pm 7$ years; height, $176 \pm 8$ cm; weight $77.0 \pm 9.8$ kg; peak oxygen uptake (VO$_2$ peak) $43.6 \pm 8$ ml/kg/min; and peak power output $262 \pm 33$ watts (mean $\pm$ SD). Women were tested in the follicular phase of the menstrual cycle or the placebo phase if they were taking birth control pills. Subjects were not taking medications (aside from birth control pills), were non-smokers, were free of any known cardiovascular, metabolic, or neurological diseases and refrained from alcohol, caffeine, and exercise for 24 h before the study. Subjects were informed of the purpose, procedures and risks of the study before providing their informed written consent. The protocol and consent were approved by the Institutional Review Boards at the University of Texas Southwestern Medical Center at Dallas and Texas Health Presbyterian Hospital Dallas.

Instrumentation and Experimental Protocol

In preparation for experimental days, subjects completed a graded exercise test on a cycle ergometer (Lode, Groningen, Netherlands) in thermoneutral conditions. Power output was recorded from the cycle ergometer while oxygen uptake, including peak, was measured using standard indirect calorimetry procedures (Parvo Medics' TrueOne® 2400, Utah, USA).

On experimental days, $\sim$2 hours prior to the onset of data collection, subjects swallowed an ingestible telemetry pill for the measurement of core temperature from intestinal temperature (HQ, Palmetto, Florida). Subjects voided their bladder before nude body mass was recorded. Adequate hydration was confirmed via urine specific gravity ($<1.028$) which was measured using a digital refractometer. Height was measured using a stadiometer.
Mean skin temperature was measured from the weighted average temperature across six sites (Taylor et al., 1989) using thermocouples fixed to the skin with porous adhesive tape. Arterial blood pressure was continuously measured non-invasively using photoplethysmography (Finometer Pro, FMS, Amsterdam, Netherlands), which was used to calculate mean arterial pressure. Heart rate was obtained from an electrocardiogram (ECG, Agilent, Munich, Germany) that was interfaced with a cardiotachometer (1000 Hz sampling rate, CWE, Ardmore, PA, USA). Following instrumentation, subjects rested in the supine position for 30 minutes to allow for the stabilization of fluid shifts. Baseline data were subsequently obtained.

Subjects were then exposed to three randomized and counterbalanced trials separated by at least 3 days. During one trial, each subject donned a water-perfused tube lined suit (Med-Eng, Ottawa, Canada) that covered their entire body except for the head, hands and feet. The suit permitted the control of whole-body skin and internal temperatures by adjusting the temperature of the water perfusing the suit. Subjects were exposed to whole-body heating by perfusing 48-50°C water through the suit to elevate core temperature by ~1.2°C (Passive). During the other two trials, subjects exercised on an upright cycle ergometer at 50% of their predetermined peak power output in an environmental chamber set to 40°C and 30% relative humidity until core temperature increased by ~1.2°C. After achieving the desired increase in core temperature, the subject rapidly donned the aforementioned water perfused suit. The temperature of the water perfusing the suit was adjusted such that mean skin temperature was clamped at ~36.5°C to match skin temperature at the end of exercise (i.e., Active 36) or clamped at ~38.0°C to match skin temperature during the passive heat stress trial (i.e., Active 38). These two trials (Active 36 and Active 38) were designed to address the influence of skin temperature upon LBNP tolerance following exercise induced heat stress. Given the influence of heightened skin temperatures in compromising cutaneous vasoconstriction to
LBNP (11, 38), clamping skin temperature in the Active 38 trial was an important control measure to ensure appropriate comparison with the passive heat stress trial.

Participants were encouraged to ingest 7 ml/kg body mass of warm water (37.1 ± 1.2°C) in all trials during the thermal provocation prior to LBNP. The volume of water ingested during the passive heat stress trial (403 ± 238 mL) was slightly less than the volume ingested in both Active 36 and Active 38 trials (551 ± 264 and 575 ± 256mL respectively, both P ≤ 0.05) while fluid ingestion was not different between Active 36 and Active 38 trials (P > 0.05).

In all trials, following the desired increase in core and mean skin temperatures, subjects underwent a supine LBNP tolerance test to the onset of pre-syncope. LBNP began at 20 mmHg for 3 min, followed by increasing negative pressure by 10 mmHg in 3 min stages until pre-syncope. The termination of LBNP was based upon subject self-reporting of feeling faint and/or nauseous, a rapid and progressive decrease in blood pressure resulting in sustained systolic blood pressure being ≤80 mmHg, and/or a relative and pronounced bradycardia. Throughout LBNP, arterial blood pressures were also measured at the brachial artery by auscultation (Tango, Suntech Medical Instruments, Raleigh, NC, USA). Tolerance to LBNP was quantified using the cumulative stress index (CSI) (33), calculated by summing the time at each level of LBNP multiplied by that level (i.e., 20 mmHg * 3 min + 30 mmHg * 3 min + 40 mmHg * 3 min, etc.) until pre-syncope. Nude body mass was obtained prior to any provocation and following the LBNP tolerance test.

**Data Analysis**

Temperature and hemodynamic data were collected via a data-acquisition system (Biopac System, Santa Barbara, CA). Data were averaged across 60 seconds at baseline and after the desired increase in core and mean skin temperatures prior to LBNP. During LBNP, data were averaged over a 30 second period immediately preceding 20%, 40%, 60% and 80% of the
maximal CSI, and also during the 15 seconds immediately preceding the termination of LBNP (i.e. pre-syncope). Data were statistically analyzed using a two-way analysis of variance with repeated measures, with main factors of thermal condition (levels: Passive, Active 36, Active 38) and time (levels: baseline, pre-LBNP, 20%, 40%, 60%, 80% max CSI, and pre-syncope). For CSI, data were analyzed via one way repeated measures ANOVA across the three perturbations. Post-hoc analyses were performed using paired t-tests with a bonferroni correction when a significant main effect or interaction was identified. Data are reported as mean ± SD.
Results

Cardiovascular and temperature variables were not different at baseline between trials (Table 1). Mean skin temperature was elevated from baseline due to both passive and active heat stress perturbations prior to LBNP (all $P \leq 0.05$ within trials relative to baseline, Fig. 1). Prior to LBNP, mean skin temperatures were not different between passive heat stress and Active 38 trials, but both were higher relative to the Active 36 trial (both $P \leq 0.05$). Core temperature increased in all trials ($P \leq 0.05$), with this measure not being different between trials immediately prior to LBNP. Relative to baseline, heart rate increased and blood pressure decreased at pre-LBNP in all trials (all $P \leq 0.05$), but both the absolute and the change in these measures to the heating stimuli were not different between trials (Fig. 2).

The duration of passive heat stress (39 ± 9 min) prior to achieving a 1.2 °C increase in core temperature was shorter than the exercise duration in both Active 36 and Active 38 trials (48 ± 11 and 47 ± 12 min, respectively, both $P \leq 0.05$ relative to passive heat stress), while exercise time was not different between Active 36 and Active 38 trials ($P > 0.05$). The magnitude of the reduction in body mass was not different between trials (Passive: 1.1 ± 0.3, Active 36: 1.4 ± 0.7 and Active 38: 1.4 ± 0.5 kg, respectively, $P > 0.05$).

Regardless of the trial, mean skin temperature did not change during LBNP (Fig. 1). However, during this period core temperature increased ~0.3°C in the passive and Active 38 trials ($P \leq 0.05$) but did not change in the Active 36 trial (Table 1). During LBNP heart rate increased relative to baseline ($P \leq 0.05$), but then declined from 80% CSI to pre-syncope in all trials ($P \leq 0.05$, Fig. 2). Arterial blood pressure declined in all trials during LBNP through pre-syncope ($P \leq 0.05$), with the magnitude of this reduction not being different between trials. Despite differing modes of heating, LBNP tolerance was not different between passive heat stress (340 ± 204 CSI units) and Active 38 (346 ± 167 CSI units, $P = 0.119$) trials, while
LBNP tolerance during the Active 36 trial (513 ± 188 CSI units) was greater relative to both passive and Active 38 trials (P ≤ 0.05, Fig. 3). The lower LBNP tolerance in the Active 38 trial relative to the Active 36 trial was evident in seven out of eight subjects; with difference in tolerance of 201 ± 95 CSI units. In the one subject where LBNP tolerance was not reduced in the Active 38 relative to the Active 36 trial, LBNP tolerance was 313 and 241 CSI units respectively.
Discussion

Given that both passive heat stress (2, 26, 29, 31, 48, 51) and exercise in a thermoneutral environment (6) impair tolerance to a hypotensive challenge, we hypothesized that the combination of exercise in the heat would further reduce LBNP tolerance, relative to passive heat stress alone, when controlling for internal and mean skin temperatures. Counter to that hypothesis, LBNP tolerance was not different between these two perturbations when mean skin temperatures were clamped at similar levels. A secondary objective tested the hypothesis that mean skin temperature influences LBNP tolerance following exercise in a hot environment. Consistent with that hypothesis, LBNP tolerance following exercise in the heat was influenced by the magnitude of the elevation in mean skin temperature.

During a simulated hemorrhagic challenge, such as LBNP, central blood volume is reduced and the drive for neurally-mediated vasoconstriction increases (5, 18, 43, 45). Given that skin and muscle vascular conductance increase in hyperthermic humans (22, 30, 35, 37, 42), the ability to vasoconstrict appropriately in these vascular beds is important for blood pressure control during a subsequent hypotensive challenge. Vascular control is impaired following exercise in thermoneutral conditions (i.e., in the absence of appreciable increases in core and/or skin temperatures) (19, 34), evidenced by a reduction in baroreflex sensitivity (40, 49) and mean arterial pressure (34), a reduced transduction of sympathetic outflow into vascular resistance, and lower sympathetic outflow for any given blood pressure (20). Consistent with these responses, orthostatic tolerance is impaired following a short term bout of exercise in a thermoneutral environment (6). Passive heat stress places a significant burden on the cardiovascular system, which in part is due to pronounced increases in systemic vascular conductance (42) and reductions in central blood volume (13). Vascular control is impaired following passive heat stress through a decreased vasoconstrictor responsiveness to reductions in central blood volume (11). Given the influences of passive heat stress and
exercise in altering vascular control via unique mechanisms, we expected an additive effect resulting in lower tolerance to LBNP following exercise in a hot environment, relative to passive heat stress, when controlling for the elevation in core and skin temperatures. However, counter to that hypothesis, LBNP tolerance was not different between passive heat stress and active 38 trials (Fig. 3).

The lack of difference in LBNP tolerance between these two trials may be explained by two possibilities. First, it is possible that increases in muscle vascular conductance associated with dynamic exercise decreased to levels similar to passive heat stress (22, 30, 37) during the period between the cessation of exercise and the onset of LBNP (14.7 ± 3.4 min). However, femoral vascular conductance remains elevated for up to 90 min following cycling exercise in a warm environment (34). It is therefore unlikely that exercise induced elevations in leg vascular conductance had completely returned to baseline values prior to the onset of LBNP. Second, a more likely explanation is that similar increases in cutaneous vascular conductance, owing to similar increases in mean skin temperature (1, 4, 25), between the passive heat stress and Active 38 trials contributed to comparable LBNP tolerances. This argument is strengthened by findings that such elevations in mean skin temperature and cutaneous vascular conductance are associated with an inadequate cutaneous vasoconstrictor response (38), which contributes to reduced tolerance to LBNP (11). Therefore, the present results suggest that LBNP tolerance is more closely related to the elevation in mean skin temperature rather than the methodology of increasing core temperature (e.g., passive vs. exercise-induced), and that vascular responses post-exercise do not have an additive effect in contributing to compromised tolerance to central hypovolemia. Thus, exercise itself does not further compromise tolerance to a simulated hemorrhagic challenge relative to passive heat stress, when elevations in mean skin temperature are similar between conditions.
LBNP tolerance was attenuated in the Active 38 trial relative to the Active 36 trial. The most likely explanation for this observation is the difference in mean skin temperature between these trials, which affected tolerance perhaps via two unique mechanisms. First, the extent of cutaneous vasodilation under the water perfused suit, and thus presumably the reduction in central blood volume (13) before LBNP, would be greater in the Active 38 trial relative to the Active 36 trial. Consistent with this hypothesis, decreasing mean skin temperature by actively cooling the skin of otherwise hyperthermic individuals increases central blood volume and greatly improves tolerance to an orthostatic stress (14, 52). Second, elevated skin temperatures attenuate cutaneous vasoconstrictor responses to a hypotensive challenge (38), perhaps through nitric oxide mechanisms (15, 24, 46, 47, 53). The extent of cutaneous vasoconstriction at pre-syncope via LBNP is greatly attenuated in skin heated to 38°C relative to skin heated to 35°C (38). Therefore, differences in LBNP tolerance between Active 38 and Active 36 may be due, in part, to both: A) local temperature-induced differences in the magnitude of cutaneous vasodilation prior to LBNP and B) differences in the extent of cutaneous vasoconstriction under the water perfused suit during LBNP between trials. Those mechanisms aside, throughout LBNP core temperature slightly increased in the Active 38 trial (~Δ0.3°C) but was unchanged in the Active 36 trial. One may propose that such differences in core temperature could have contributed to the observed differences in LBNP tolerance. However, the magnitude of increase in core temperature during heat stress, between ~Δ0.9 – 1.8°C, is not associated with differences in LBNP tolerance (17). It is therefore unlikely that a relatively small difference in core temperature during LBNP in the Active 38 trial contributed to reduced LBNP tolerance relative to the Active 36 trial; rather such tolerance differences were likely attributed to differences in skin temperature.

Limitations and considerations to the interpretation of the findings
The present study did not include a normothermic LBNP challenge. Such a challenge was not necessary to address the proposed hypotheses, and thus inclusion of a normothermic LBNP challenge would expose subjects to an unnecessary procedure and therefore some level of risk. That said, using a similar LBNP ramp, as well as CSI criteria to evaluate LBNP tolerance, we consistently observe CSI mean values in the ~900-1100 mmHg×min range in normothermic subjects (7, 28, 29, 32), which is well above what was observed in any of the three trials in the present experiment.

In Active 36 and 38 trials, after obtaining the appropriate increase in core temperature, participants donned the water perfused suit for the control of skin temperature and were transferred into position for LBNP. The duration of this process varied between ~ 8 - 15 minutes. Despite this time delay, exercise induced alterations in baroreflex sensitivity (40, 49), blood pressure (16, 21), sympathetic nerve activity (20) and limb blood flow (34) are evident for at least 60 minutes after the cessation exercise. It is therefore unlikely that the influence of exercise induced neural and cardiovascular alterations upon LBNP tolerance diminished due to this period between the cessation of exercise and the onset of LBNP.

The duration of the heat stress perturbation was not different between Active 36 and 38 trials but was lower in the passive heat stress trial. Methodologically, it may have been more appropriate to clamp the heat stress duration between trials, though this would be very challenging given a variety of factors that influence the rate of heating during passive heat stress (e.g., size of the individual, water temperature and perfusion rate of the suit, etc), resulting in multiple passive heat stress trials to achieve a desired temperature within a specified duration. Nevertheless, there is currently no evidence to suggest that the duration of heat stress \textit{per se} is a significant contributor to LBNP tolerance. However, it is recognized that longer heating periods may lead to more pronounced dehydration, which could influence
LBNP tolerance yet in the present protocol the reduction in body mass (i.e., fluid loss) was similar between trials.

In both Active trials subjects exercised at an intensity equal to 50% of their peak power output. This workload was selected for two reasons: 1) it is a similar intensity to that commonly occurring during routine military foot/reconnaissance patrols (3, 23), and 2) it is a workload that can be maintained for sufficient period of time in relatively non-trained subjects to achieve the desired increases in core temperature. While it may be insightful to identify the combined influence of heat stress and exercise at substantially higher (or even maximal) intensities on LBNP tolerance, the subjects may not have been able to tolerate the workload for a sufficient duration to achieve the required increases in core temperature. That said, the responses observed in the present observation should not be extrapolated to what may occur following high intensity exercise in hot environmental conditions.

**Perspectives and significance**

These data have implications for individuals who become hyperthermic through either passive heat stress or exercise, and who are at risk for a hemorrhagic injury, such as firefighters and soldiers. For example, military personnel are often deployed in warm environments where they are exposed to both passive (i.e., snipers, turret gunners, etc.) and active heat stresses (i.e., foot patrols) while wearing body armor. Buller *et al* reported comparable increases in both skin and core temperatures during military procedures in Iraq relative to the present observations (8). The present data indicate that the implications of a hemorrhagic injury are similarly dire between actively and passively heat stressed individuals, when skin temperatures are equally elevated. Furthermore, given that LBNP tolerance was prolonged following active heat stress when mean skin temperature was ~2°C lower, reducing skin temperature of hyperthermic and hemorrhaging individuals could prove
beneficial towards survival. This small reduction in skin temperature may be achieved without cooling the skin with ice or related modalities. Therefore, identification of a light weight non-ice dependent cooling modality to decrease skin temperature ~2°C may be beneficial in the treatment of a hemorrhaging hyperthermic soldier in the pre-hospital setting. Finally, it is noteworthy that soldiers are currently warmed following a hemorrhagic injury (10). Based upon the present findings, this action may actually be harmful for the soldier who is not hypothermic, as recently proposed (10).

**Conclusions**

The present results show that tolerance to a simulated hemorrhagic challenge resulting in central hypovolemia and accompanying hypotension is not different between actively and passively heat stressed individuals, when internal and mean skin temperatures are controlled for. Second, during active heat stress resulting in comparable increases in internal temperatures, relatively small differences in mean skin temperature can appreciably affect tolerance to a hypotensive challenge. These data suggest that exercise itself does not further decrease tolerance to a simulated hemorrhagic challenge when compared to passive heat stress, which may have important implications towards the treatment of a hyperthermic individual who has experienced a hemorrhagic injury.
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References


Figure 1: Core and skin temperatures prior to and during LBNP to pre-syncope in all conditions.

Mean skin and core body temperatures increased with all methods of heat stress prior to LBNP. However, by design, mean skin temperatures were higher following passive heat stress and Active 38 trials when compared to Active 36 (both \( P \leq 0.05 \)), and remained higher throughout LBNP to pre-syncope. At pre-syncope, mean skin temperature was unchanged (\( P > 0.05 \)) while core temperature was slightly elevated in the passive heat stress and Active 38 trials. Data are mean ± SD at baseline, immediately prior to LBNP (pre-LBNP), throughout LBNP at 20, 40, 60 and 80% of maximal CSI and at pre-syncope.* Different from baseline in all trials (\( P \leq 0.05 \)). # Different from pre-LBNP in passive heat stress and Active 38 trials only (\( P \leq 0.05 \)). λ Different from Active 36 (\( P \leq 0.05 \)).

Figure 2: Heart rate and blood pressure responses prior to and during LBNP to pre-syncope in all conditions.

When expressed relative to a percent of maximal CSI, heart rate and mean arterial pressure were not different between trials at any point. In all trials, blood pressure and heart rate decreased at pre-syncope relative to 80% CSI. Data are mean ± SD at baseline, immediately prior to LBNP (pre-LBNP), throughout LBNP at 20, 40, 60 and 80% of maximal CSI and at pre-syncope. * Different from baseline in all trials (\( P \leq 0.05 \)). § Different from 80% CSI in all trials (\( P \leq 0.05 \)).

Figure 3: Cumulative stress index in all trials
Tolerance to simulated hemorrhage (expressed as cumulative stress index; CSI) was similarly reduced in passive heat stress and Active 38 trials relative to Active 36 (P ≤ 0.05). Data are mean ± SD. * Different from Active 36 (P ≤ 0.05).
Table 1: Thermal and hemodynamic measures during baseline, pre-LBNP, 80% CSI, and at pre-syncope for all three trials.

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<tr>
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<th>Passive Heat Stress</th>
<th>Active 36</th>
<th>Active 38</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>Pre-LBNP</td>
<td>80% CSI</td>
</tr>
<tr>
<td>Tcore (°C)</td>
<td>36.8 ±0.4</td>
<td>38.0 ±0.4 *</td>
<td>38.3 ±0.5 * #</td>
</tr>
<tr>
<td>Tsk (°C)</td>
<td>32.9 ±0.7</td>
<td>38.2 ±0.6 *</td>
<td>37.9 ±0.6 *</td>
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<tr>
<td>MAP (mmHg)</td>
<td>82 ±8</td>
<td>79 ±13 *</td>
<td>71 ±16 *</td>
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<tr>
<td>HR (bpm)</td>
<td>53 ±8</td>
<td>99 ±12 *</td>
<td>140 ±15 *</td>
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Tcore, body core temperature; Tsk, mean skin temperature; MAP, mean arterial pressure; HR, heart rate. Values are means ± SD for 84 participants. * Different from baseline within trial (P ≤ 0.05). # Different from Pre-LBNP within trial (P ≤ 0.05). § Different from passive heat stress and active 38 trials (P ≤ 0.05). § Different from 80% CSI within trial (P ≤ 0.05).
Cumulative Stress Index (mmHg * min)

- Active 36
- Active 38
- Passive

* denotes statistical significance.