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Normothermic central hypovolemia tolerance reflects hyperthermic tolerance

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Abstract

Purpose—To test the hypothesis that those who are highly tolerant to lower body negative pressure (LBNP) while normothermic are also highly tolerant to this challenge while hyperthermic.

Methods—Sixty pairs of normothermic and hyperthermic LBNP tests to pre-syncope were evaluated. LBNP tolerance was quantified via the cumulative stress index (CSI), which is calculated as the sum of the product of the LBNP level and the duration of each level until test termination (i.e., 20 mmHg × 3 min + 30 mmHg × 3 min, etc.). CSI was compared between normothermic and hyperthermic trials. Internal and skin temperatures, heart rate, and arterial pressure were measured throughout.

Results—Hyperthermia reduced ($P < 0.001$) CSI from 997 ± 437 to 303 ± 213 mmHg min. There was a positive correlation between normothermic and hyperthermic LBNP tolerance ($R^2 = 0.38$; $P < 0.001$). As a secondary analysis, the 20 trials with the highest LBNP tolerance while normothermic were identified (indicated as the HIGH group; CSI $1,467 \pm 356$ mmHg min), as were the 20 trials with the lowest normothermic tolerance (indicated as the LOW group; CSI 565 ± 166 mmHg min; $P < 0.001$ between groups). While hyperthermia unanimously reduced CSI in both HIGH and LOW groups, in this hyperthermic condition CSI was ~threefold higher in the HIGH group (474 ± 226 mmHg min) relative to the LOW group (160 ± 115 mmHg min; $P < 0.001$).

Conclusions—LBNP tolerance while hyperthermic is related to normothermic tolerance and, associated with this finding, those who have a high LBNP tolerance while normothermic remain relatively tolerant when hyperthermic.

Keywords

Lower body negative pressure; Heat stress; Simulated hemorrhage; Syncope

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Conflict of interest

There are no known conflicts of interest.

Introduction

The ability to tolerate central hypovolemia, induced by lower body negative pressure (LBNP), greatly varies between individuals [7–9, 16, 17, 21, 25]. Greater tolerance to LBNP is associated with a number of factors, including an augmented vasoactive hormone response [9, 16], higher increases in vascular resistance [7, 9, 26], greater increases in heart rate [7, 8, 26], enhanced protection of central blood volume and cerebral perfusion [21], and augmented oscillations in arterial pressure and cerebral perfusion [25].

Hyperthermia (i.e., increases in internal and skin temperatures) universally decreases LBNP tolerance [19, 28]. The mechanisms by which this occurs are numerous and likely involve insufficient increases in peripheral resistance during LBNP [12, 15, 24], hyperthermia-induced reductions in the central blood volume [13, 14] and accompanying decreases in ventricular filling pressures [14, 29], altered arterial baroreflex control of blood pressure [11], and reductions in cerebral perfusion [4, 23, 28]. Notably, substantial inter-individual differences in LBNP tolerance likewise persist while hyperthermic [3, 12, 19, 20].

The mechanisms mediating variations in normothermic LBNP tolerance appear comparable to those mediating such variations while hyperthermic (e.g., altered vascular resistance, protection of central blood volume). Thus, the mechanisms underlying inter-individual variability in normothermic LBNP tolerance may explain such variations in tolerance while hyperthermic. If so, we would expect that those observed to be highly tolerant to LBNP while normothermic would also exhibit a high tolerance to this challenge while hyperthermic. In accordance, the primary objective of this study was to test the hypothesis that hyperthermic LBNP tolerance is related to normothermic LBNP tolerance, and by extension that those observed to have high normothermic LBNP tolerance will also be relatively tolerant during hyperthermic LBNP.

Methods

Subjects and study design

Data were retrospectively queried to identify subjects who had undergone progressive LBNP challenges to pre-syncope while both normothermic and hyperthermic. Only those in which the normothermic and hyperthermic trials were carried out in identical experimental conditions were selected, thereby allowing for a repeated measures experimental design. This query resulted in 79 pairs of observations from 60 different subjects. Given the focus on inter-individual variability, for the subjects with more than one pair of normothermic/hyperthermic trials, only one data set was included. In such instances, the paired trial that was included in the analysis was randomly decided via a coin toss. Therefore, the analysis comprised 60 pairs of observations from 60 different subjects (53 males). The subject characteristics were (mean \pm SD): age 35 ± 8 years, height 178 ± 8 cm, and weight 83.7 ± 15.8 kg. All subjects were free of any known cardiovascular, neurological, or metabolic diseases. Each study protocol from which these data were obtained received institutional approval from the University of Texas Southwestern Medical Center and Texas Health Presbyterian Hospital Dallas, and all subjects signed an approved informed consent form.

Under most circumstances ($n = 41$ pairs, 7 females), the order of the normothermic and hyperthermic trials were randomized, with the second trial being undertaken at least 24 h after the first (mean 33 ± 32 days), but at the same time of day. However, in a subset of trials ($n = 19$ pairs, all males), both the normothermic and hyperthermic trials were conducted on the same day, with the normothermic trial occurring first, separated by 140 ± 37 min. These data were included in the analysis given that the magnitude of the hyperthermia-induced reductions in LBNP tolerance in this group ($-67 \pm 16\%$) were not different ($P = 0.768$) to that occurring in the group in which the trials were conducted on separate days ($-69 \pm 24\%$), and the evidence indicating that plasma volume and leg interstitial fluid pressures are fully restored within 30 min following LBNP [1]. For the females, both trials were undertaken in the same phase of their menstrual cycle. Subjects arrived at the laboratory euhydrated, confirmed via urine specific gravity (1.013 ± 0.007), and having refrained from strenuous exercise, alcohol, and caffeine for 24 h. All procedures were undertaken in a temperature-controlled laboratory ($\sim 25^\circ\text{C}$).

Instrumentation and measurements

Approximately 90 min prior to experimental testing, each subject swallowed a temperature pill (HQ Inc., Palmetto, FL, USA) to measure intestinal temperature. Mean skin temperature was measured from the weighted average of six thermocouples attached to the skin [27]. Body temperature was controlled via a water-perfused tube lined suit (Med-Eng, Ottawa, ON, Canada) that covered the entire body except the head, hands, and the feet. Heart rate was continually recorded from an electrocardiogram (HP Patient Monitor, Agilent, Santa Clara, CA, USA) interfaced with a cardi tachometer (CWE, Ardmore, PA, USA). Beat-to-beat arterial pressure was continuously measured via the Penaz method (Finometer Pro, FMS, Amsterdam, The Netherlands or NexFin HD, BMEYE B.V., Amsterdam, The Netherlands), with its readings confirmed intermittently via auscultation of the brachial artery by electrospigmomanometry (Tango+, SunTech, Raleigh, NC, USA). During all experimental trials the subjects were placed into an LBNP box that was sealed at the level of the iliac crest, remaining supine for the duration of the protocol.

Experimental protocol

Following instrumentation and either a normothermic period or whole-body passive heat stress, all subjects underwent progressive LBNP to pre-syncope. During normothermia, 34°C water perfused the suit throughout the experiment. During the hyperthermic trial, the subjects underwent whole-body passive heat stress by perfusing $46\text{--}50^\circ\text{C}$ water through the suit, with the LBNP test commencing when intestinal temperature was $\sim 1.4^\circ\text{C}$ above baseline temperature. Under most circumstances ($n = 48$ pairs, 3 females), the progressive LBNP test started at 20 mmHg for 3 min, with the LBNP increasing by 10 mmHg every 3 min until the onset of syncopal signs and symptoms. In a subset of tests ($n = 12$ pairs, 4 females), the starting LBNP was 10 mmHg, and likewise increased by 10 mmHg every 3 min. These trials were included in the analysis given the repeated measures study design and that the magnitude of the hyperthermia-induced reductions in LBNP tolerance were not different ($P = 0.689$) whether the trials commenced at 10 mmHg LBNP ($-66 \pm 19\%$) or 20 mmHg LBNP ($-69 \pm 22\%$). In the event the LBNP level reached 100 mmHg, that stage was continued without further increasing LBNP until the onset of syncopal signs and symptoms.

The criteria for LBNP termination were: continued self-reporting by the subject of feeling faint, sustained nausea, rapid and progressive decreases in blood pressure resulting in sustained systolic blood pressure being <80 mmHg, and/or relative bradycardia accompanied with a narrowing of pulse pressure. Notably, every LBNP trial, save one, was terminated due to hemodynamically identified syncopal signs, with one trial being terminated due to syncopal symptoms expressed by the subject.

Data analysis

Data were sampled at a minimum of 50 Hz via a data acquisition system (Biopac System, Santa Barbara, CA, USA). Steady-state data (60 s average) were analyzed at normothermic baseline (i.e., pre-thermal perturbation; Baseline) and just prior to commencing LBNP (i.e., post-thermal perturbation during hyperthermia trials; Pre-LBNP). Data (10 s average) were also analyzed upon the attainment of the peak heart rate during the final 2 min of LBNP (Peak-LBNP) [12] and during the final 10 s of LBNP (Pre-Syncope). Heart rate data at Peak-LBNP and Pre-Syncope were also evaluated as the change () from Pre-LBNP. LBNP tolerance was quantified using the cumulative stress index (CSI) [22], which is calculated by summing the product of LBNP and the time at each level of LBNP across the trial until the test was terminated (i.e., 20 mmHg × 3 min + 30 mmHg × 3 min, etc.).

Given that hyperthermia unanimously reduces LBNP tolerance [19, 28], CSI data were 'standardized' to quantitatively identify whether those trials deemed highly tolerant during normothermia remained tolerant, relative to the entire data set, during hyperthermia. Therefore, a *Z*-score was calculated for each subject's LBNP trial in both thermal conditions as follows: $CSI\ Z\text{-score} = (CSI_{\text{subject}} - CSI_{\text{mean}}) / CSI_{SD}$, where CSI_{subject} is a subject's CSI, CSI_{mean} is the mean CSI of all subjects in a given thermal condition, and CSI_{SD} is the standard deviation of the CSI in the same thermal condition. Thus, within a given thermal condition an individual's CSI *Z*-score of '0' represents the average CSI of the data set, while a CSI *Z*-score of ±1.0, ±2.0, ±3.0, etc. indicates CSI values that are 1, 2, 3, etc. standard deviations greater (+) or lower (-) than the mean CSI value. Subsequently, the 20 trials with the highest normothermic CSI *Z*-scores (designated as HIGH) and the 20 observations with the lowest normothermic CSI *Z*-scores (designated as LOW) were identified. The CSI *Z*-scores during the hyperthermic LBNP challenge were statistically compared between the 20 HIGH normothermic observations and the 20 LOW normothermic observations, irrespective of their ranking in the hyperthermic LBNP trial. The 'middle' 20 observations were not included in this sub-analysis.

Statistical analysis

Relationships between normothermic LBNP tolerance and hyperthermic LBNP tolerance across all subjects were identified via Pearson product moment correlation analysis. Data at Baseline, Pre-LBNP, Peak-LBNP, and Pre-Syncope, irrespective of group (i.e., HIGH or LOW), were analyzed using repeated measures analysis of variance (ANOVA; main effects temperature × time). Subject characteristics of the HIGH and LOW groups were compared using independent sample *t* tests. All other data in this HIGH vs. LOW analysis were analyzed using mixed-model repeated measures ANOVA (main effects group × temperature). Where appropriate, post hoc, pair-wise, comparisons were made incorporating

a Bonferroni adjustment. Data were analyzed using SigmaPlot (v.12, Systat Software Inc., Chicago, IL, USA) with a priori statistical significance set at $P = 0.05$. All data are reported as mean \pm SD.

Results

Complete data set analysis

Baseline (i.e., pre-perturbation) internal (36.9 ± 0.3 °C) and mean skin (34.3 ± 0.5 °C) temperatures were similar ($P = 0.513$) between thermal conditions. Hyperthermia increased intestinal (to 38.3 ± 0.3 °C; $P < 0.001$) and mean skin (to 38.5 ± 0.8 °C; $P < 0.001$) temperatures, which remained elevated and stable throughout LBNP. LBNP time to tolerance (normothermia 19.8 ± 5.3 min, hyperthermia 9.1 ± 4.23 min) and the final LBNP stage reached (normothermia 80 ± 20 mmHg, hyperthermia 40 ± 10 mmHg) were higher ($P < 0.001$ for both) during normothermia. Consistent with those values, LBNP tolerance, as assessed with CSI, was unanimously higher during normothermia (997 ± 437 mmHg min) compared to hyperthermia (303 ± 213 mmHg min; $P < 0.001$). Furthermore, normothermic CSI was correlated ($R^2 = 0.380$; $P < 0.001$) with hyperthermic CSI (Fig. 1).

Hyperthermia slightly decreased ($P < 0.001$) mean arterial pressure and profoundly elevated ($P < 0.001$) heart rate (Fig. 2). However, in both thermal conditions heart rate progressively increased ($P < 0.001$) during LBNP, but the magnitude of the elevation in heart rate to LBNP, prior to any bradycardia associated with pre-syncope, was less ($P < 0.001$) during the hyperthermic trial (Fig. 2).

Assessment of HIGH vs. LOW groups

Subject characteristics of the LOW and HIGH groups are presented in Table 1. Intestinal and mean skin temperatures did not differ ($P = 0.319$) at any time points, inclusive of LBNP, between the LOW and HIGH groups and were similar to those values reported for the complete data set (see above). Normothermic LBNP time to tolerance (HIGH 25.3 ± 2.6 min, LOW 14.2 ± 3.1 min), the final LBNP stage reached (HIGH 90 ± 10 mmHg, LOW 60 ± 10 mmHg), and CSI (HIGH $1,467 \pm 356$ mmHg min, LOW 565 ± 166 mmHg min) were higher ($P < 0.001$ for all comparisons) in the HIGH group. Hyperthermia decreased, in both groups ($P < 0.001$), LBNP tolerance time (HIGH 12.6 ± 3.6 min, LOW 5.9 ± 2.9 min), the final LBNP stage reached (HIGH 60 ± 10 mmHg, LOW 30 ± 10 mmHg), and CSI (HIGH 474 ± 226 mmHg min, LOW 160 ± 115 mmHg min), with the hyperthermic value for each of these variables being lower ($P < 0.001$) in the LOW group. Notably, the HIGH group had a greater absolute reduction in LBNP tolerance from normothermia to hyperthermia (HIGH -992 ± 362 mmHg min, LOW -406 ± 193 mmHg min; $P < 0.001$).

Calculating the CSI Z -scores standardized the data such that CSI Z -scores for the complete data set ($n = 60$ pairs) during normothermia (0.0 ± 1.0 a.u.) and hyperthermia (0.0 ± 1.0 a.u.) were not different ($P = 0.495$; Fig. 3). By design, in normothermia the LOW group's CSI Z -score (-1.0 ± 0.4 a.u.) was lower ($P < 0.001$) than the HIGH group's CSI Z -score (1.1 ± 0.8 a.u.; Fig. 3). That during hyperthermia the CSI Z -score remained significantly lower in the LOW group (-0.7 ± 0.5 a.u.) compared to the HIGH group (0.8 ± 1.1 a.u.; $P < 0.001$).

indicates that the LOW group remained relatively intolerant and the HIGH group remained relatively tolerant to LBNP while hyperthermic.

During normothermic LBNP trials, the HIGH group had a greater increase in heart rate ($P = 0.022$), despite no difference ($P = 0.395$) in mean arterial pressures between groups (Fig. 4). By contrast, during hyperthermic LBNP, heart rate and the magnitude of the increase in heart rate were not different ($P = 0.161$) between groups. Except for Pre-LBNP ($P = 0.020$), mean arterial pressure during hyperthermia was not different ($P = 0.347$) between LOW and HIGH groups (Fig. 4).

Discussion

The primary objective of this study was to test the hypothesis that hyperthermic LBNP tolerance is related to normothermic LBNP tolerance, and by extension that a group observed to have high normothermic LBNP tolerance will also have a relatively high hyperthermic LBNP tolerance. The data presented in this study support this hypothesis. Specifically, hyperthermic LBNP tolerance was moderately related to normothermic LBNP tolerance (Fig. 1), and a subset of observations deemed to have a high normothermic LBNP tolerance were also relatively tolerant to LBNP during hyperthermia (Fig. 3). These findings suggest that normothermic LBNP tolerance may be a predictor of hyperthermic tolerance and that the physiological mechanisms underlying variations in LBNP tolerance during normothermia may also be relevant during hyperthermia.

Relationships between normothermic and hyperthermic LBNP tolerance

Although hyperthermia decreases LBNP tolerance in every subject, LBNP tolerance while hyperthermic varies widely between individuals [3, 12, 19, 20]. Those individuals exhibiting relatively high hyperthermic LBNP tolerance do not have a greater cutaneous vasoconstrictor response [12], nor do they have attenuated hyperthermia-induced reductions in central venous pressure [3] or cerebral perfusion [20]. Thus, what makes someone more tolerant to LBNP during hyperthermia, relative to others, is unclear. In this regard, the present study identified that normothermic LBNP tolerance accounts for ~38 % of the variance observed in hyperthermic LBNP tolerance (Fig. 1). Related to this observation, a group observed to be highly tolerant during normothermia was also found to have high tolerance during hyperthermia (Fig. 3). Thus, both approaches strongly suggest that a high hyperthermic LBNP tolerance is associated with a high normothermic LBNP tolerance.

Mechanisms underlying variations in hyperthermic LBNP tolerance

Mechanisms responsible for elevated LBNP tolerance while normothermic vary and include differences in the release of vasoactive hormones [9, 16], enhanced vasoconstriction and increases in heart rate [7, 8, 26], augmented protection of cardiac output and cerebral perfusion [21], greater oscillations in arterial pressure and cerebral perfusion [25], and a higher capacity to increase sympathetic nerve activity [7]. The present study confirms that high LBNP tolerance during normothermia is associated with an augmented heart rate response, despite similar mean arterial pressures (Fig. 4). By contrast, this study demonstrates that the heart rate response to LBNP is not enhanced in those who are

relatively tolerant to LBNP while hyperthermic (Fig. 4). Thus, an enhanced increase in heart rate is associated with higher LBNP tolerance during normothermia, but not during hyperthermia.

Mechanisms of hyperthermic LBNP intolerance

The mechanisms by which hyperthermia impairs LBNP tolerance are numerous and include insufficient increases in peripheral resistance [12, 15, 24], hyperthermia-induced decreases in ventricular filling pressures [14, 29] (likely occurring subsequent to reductions in the central blood volume [13, 14]), impaired arterial baroreflex control of blood pressure [11], and reductions in cerebral perfusion [4, 23, 28]. The present study indicates that, although heart rate is elevated by hyperthermia itself, there is an attenuated increase in heart rate during LBNP while in this thermal condition (Fig. 2). That is, the magnitude of the elevation in heart rate during LBNP is greater when individuals are normothermic relative to when hyperthermic. This observation is likely related to hyperthermia-induced tachycardia prior to LBNP (Fig. 2), which may limit the range by which heart rate can further increase during LBNP. Notably, however, it remains uncertain whether, and the extent to which, attenuated increases in heart rate potentially contribute to reductions in hyperthermic LBNP tolerance. Thus, the implications of this observation remain unclear.

Considerations

Critical to the conclusions drawn from these data is the test–retest reliability of LBNP tolerance. Notably, LBNP tolerance during normothermia elicits repeatable results [18]. Unfortunately, however, no such investigation has been undertaken with regard to hyperthermic LBNP tolerance. Nevertheless, given that hyperthermia unanimously reduces LBNP tolerance (by upwards to 60–70%), it is likely that the observed magnitude of the effect of hyperthermia in reducing LBNP tolerance far outweighs any test–retest variability in LBNP tolerance while hyperthermic.

A limitation of the present study is the lack of ‘mechanistic’ insights that would help to further explain the present data. For instance, it would have been beneficial to compare how LBNP changed central blood volume, peripheral resistance, or baroreflex function in the high vs. the low tolerance groups during hyperthermia, as has been done previously during normothermia [7–9, 16, 21, 26]. However, given the retrospective nature of this study, which permitted the evaluation of a very large number of subjects ($n = 60$), such analyses were not possible. Nevertheless, the heart rate and blood pressure observations presented in the current study remain novel and clinically relevant.

Conclusions

The present study demonstrates that LBNP tolerance while hyperthermic is related to normothermic tolerance, and that those who have high normothermic tolerance are relatively tolerant during hyperthermia. These data suggest that normothermic LBNP tolerance may be a predictor of hyperthermic tolerance, and thus the physiological mechanisms underlying variations in LBNP tolerance during normothermia are likely relevant during hyperthermia.

Perspectives

The data presented have implications for conditions in which individuals (e.g., soldiers [5], miners [2], and firefighters [6]) are often hyperthermic and at an increased risk of central hypovolemia; as occurs during a hemorrhagic injury [10]. Specifically, these data suggest that, should an individual with high normothermic tolerance to central hypovolemia encounter a similar circumstance when hyperthermic, they will, theoretically, endure such an insult for a longer period of time prior to cardiovascular collapse, when compared to an individual with low normothermic tolerance. Further research is required to understand the mechanisms of these observations.

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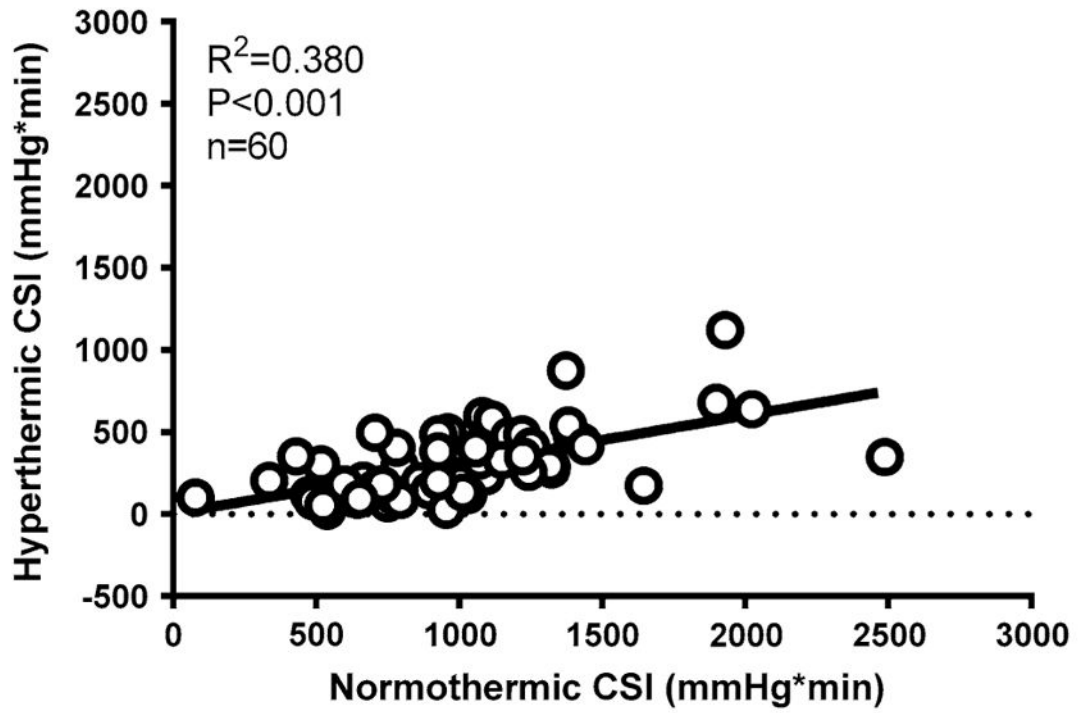


Fig. 1. Correlation between normothermic lower body negative pressure (LBNP) tolerance [i.e., the cumulative stress index (CSI)] and hyperthermic LBNP tolerance

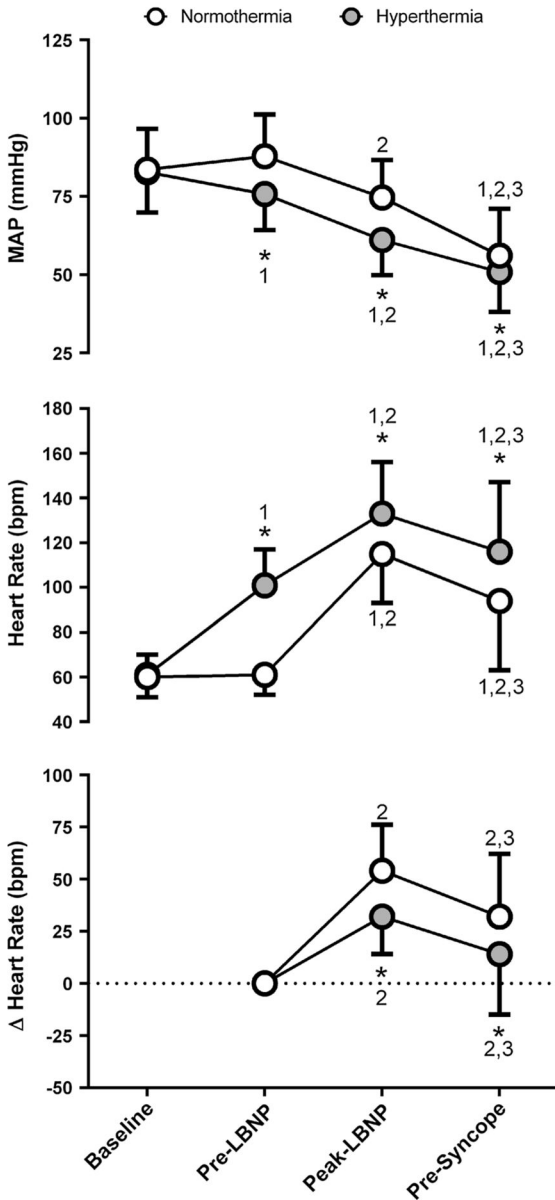


Fig. 2. Mean arterial pressure (MAP; *top*), heart rate (*middle*), and the change (Δ) in heart rate from Pre-LBNP (*bottom*) during normothermic and hyperthermic LBNP at Baseline, Pre-LBNP, Peak-LBNP, and immediately prior to LBNP termination (Pre-Syncope) (mean \pm SD). *Asterisks* indicate different from normothermia ($P < 0.029$); *1, 2, and 3* indicate different from Baseline, Pre-LBNP, and Peak-LBNP, respectively ($P < 0.018$). Peak-LBNP is the period with the highest heart rate achieved during the final 2 min of LBNP (i.e., prior to any bradycardia associated with progressive LBNP)

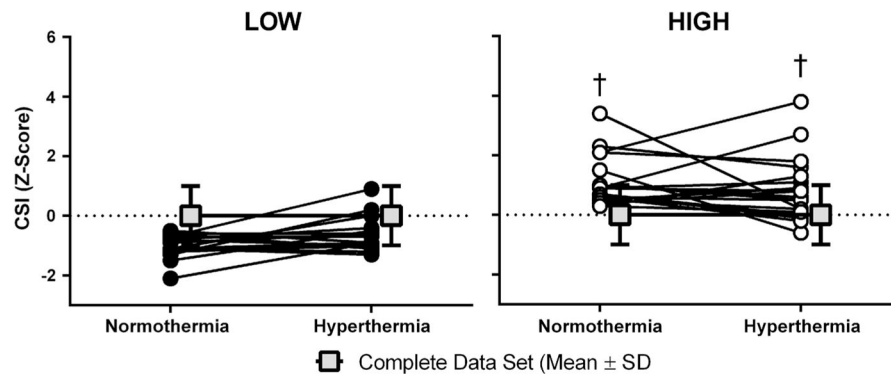


Fig. 3. Individual changes in standardized (i.e., Z -score) LBNP tolerance [indexed from the cumulative stress index (CSI)] from normothermia to hyperthermia in the 20 observations with the lowest (LOW) and highest (HIGH) normothermic tolerance. The mean data from the complete data set are also depicted ($n = 60$ pairs; *gray squares*). These data indicate that during hyperthermia the HIGH group remained relatively tolerant (mean value above 0), while the LOW group remained relatively intolerant (mean value below 0). *Dagger* indicates HIGH group is different from LOW group ($P < 0.001$). Mean (\pm SD) for each group within each condition is reported in text. An explanation of the Z -score, its interpretation, and how it was calculated is presented in “Methods”

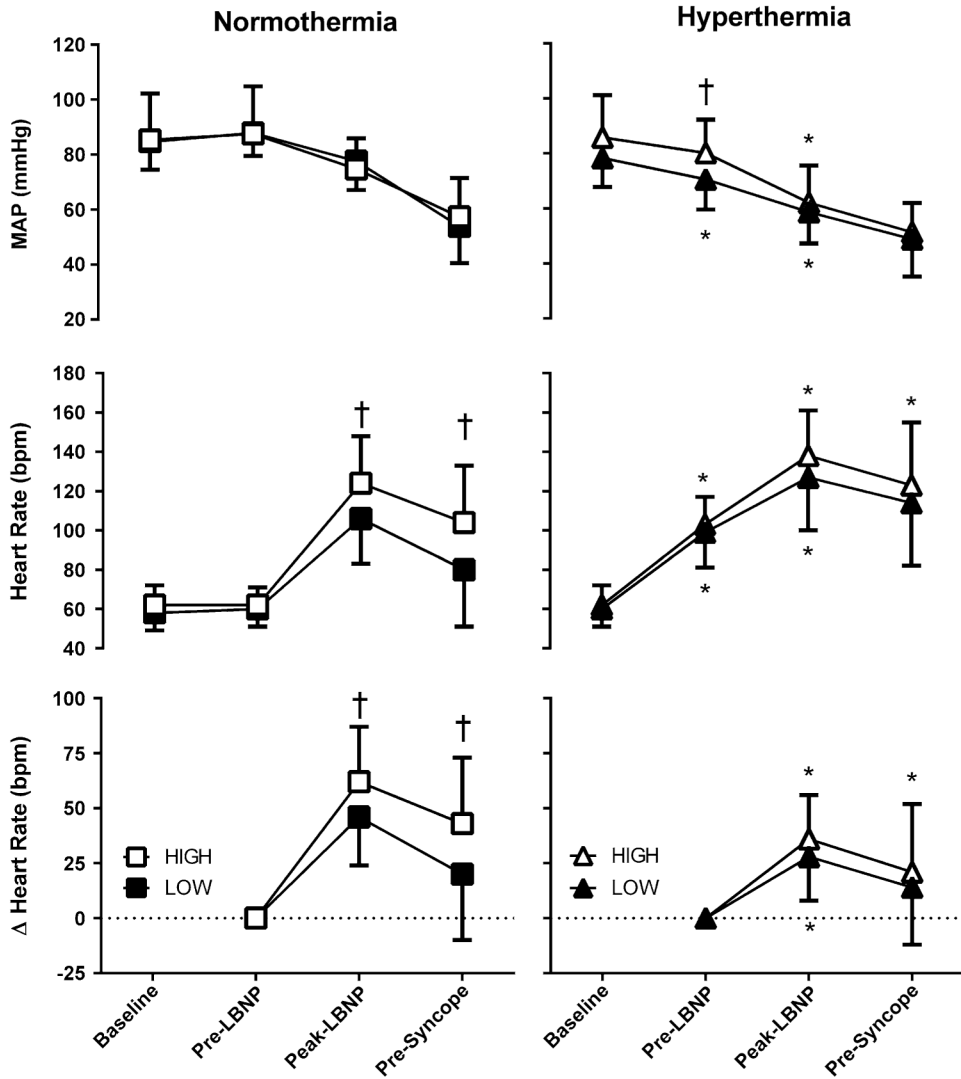


Fig. 4. Mean arterial pressure (MAP; *top*), heart rate (*middle*), and the change () in heart rate from Pre-LBNP (*bottom*) at Baseline, Pre-LBNP, Peak-LBNP, and immediately prior to LBNP termination (Pre- Syncope) in the 20 observations with the lowest (LOW) and highest (HIGH) normothermic tolerance during normothermia (*on left*) and hyperthermia (*on right*) (mean ± SD). *Dagger* indicates different from LOW ($P < 0.022$); *asterisks* indicate different from normothermia for the respective group ($P < 0.013$). Peak-LBNP is the period with the highest heart rate achieved during the final 2 min of LBNP (i.e., prior to any bradycardia associated with progressive LBNP)

Table 1HIGH vs. LOW subject characteristics (mean \pm SD)

	LOW	HIGH
Age (years)	37 \pm 9	36 \pm 9
Height (cm)	178 \pm 7	179 \pm 8
Weight (kg)	87.5 \pm 18.3	83.9 \pm 17.4
Sex (male/female)	17/3	17/3

HIGH 20 observations with the highest normothermic lower body negative pressure tolerance, *LOW* 20 observations with the lowest normothermic lower body negative pressure tolerance

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