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RESEARCH ARTICLE

Autonomic mechanisms associated with heart rate and vasoconstrictor reserves

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Abstract
Introduction Hemorrhage is accompanied by baroreflex-mediated tachycardia and vasoconstriction. The difference between baseline and maximum responses is defined as the heart rate (HR) and vasoconstrictor 'reserve'.
Objective To test the hypothesis that higher HR and vasoconstrictor reserves in subjects with high tolerance (HT) to central hypovolemia is associated with greater reserve for sympathoexcitation and vagal withdrawal compared with low tolerant (LT) subjects.
Methods R R intervals (RRI), systolic arterial pressure (SAP), estimated stroke volume, and muscle sympathetic nerve activity (MSNA) were measured during lower body negative pressure (LBNP) designed to induce pre-syncope. Subjects with tolerance $\leq$60 mmHg LBNP were classified as LT ($n = 22$) while subjects who tolerated LBNP levels >60 mmHg were classified as HT ($n = 56$). Spontaneous cardiac baroreflex sensitivity (BRS) was assessed via RRI-SAP down down sequences.
Results HR reserve in HT subjects (+52 $\pm$ 2 bpm) was twofold greater ($P < 0.001$) than that in LT subjects (+27 $\pm$ 3 bpm). Vasoconstrictor reserve in the HT group (+3.4 $\pm$ 0.5 pru) was greater ($P = 0.04$) than that of the LT group (+1.9 $\pm$ 0.3 pru). HT subjects demonstrated greater ($P \leq 0.03$) BRS reserve (−14.2 $\pm$ 1.8 ms/mmHg) and MSNA reserve (+41 $\pm$ 2 bursts/min) compared with LT subjects (−7.4 $\pm$ 1.7 ms/mmHg and +26 $\pm$ 7 bursts/min).
Interpretation Our data support the hypothesis that greater physiological reserve capacity for tachycardia and vasoconstriction related to high tolerance to central hypovolemia is associated with greater reserves for sympathoexcitation and cardiac vagal withdrawal.

Keywords Lower body negative pressure · Hemorrhage · Sympathetic nerve activity · Cardiac vagal control

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Introduction

Hemorrhage is the leading cause of death in civilian and military trauma [39]. Elevated heart rate (HR) and peripheral vasoconstriction reflect autonomically mediated compensatory responses to hypotension secondary to the reduction in central blood volume that accompanies bleeding and act to maintain adequate perfusion of vital organs during the acute phase of blood loss. It is well documented in the trauma literature, however, that a cohort of patients respond to severe bleeding with a relative bradycardia, i.e., the inability to mount a robust elevation in heart rate [1, 3, 23, 30, 40, 42, 44, 45]. Within this construct, clinicians have been cautioned that the lack of elevated HR during hemorrhage is not a necessary indication of the absence of significant blood loss after trauma [44, 45]. Most importantly, relative bradycardia in hypotensive patients can be associated with increased mortality [31].

The challenge of understanding the physiological compensatory responses to progressive hemorrhage in trauma patients may be due, in part, to the existence of two subpopulations with distinctly different physiological

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capacities to respond to blood volume loss. The clinical literature hints at such a cohort of trauma patients, identifying relative bradycardia in 29 44% of hypotensive (systolic pressure <100 mmHg) patients [23, 31, 43, 45]. We, and others, define the maximum response from baseline levels (e.g., HR, peripheral vasoconstriction) to a reduction in central blood volume as the physiological 'reserve' [24, 27]. Using an experimental model of progressive hemorrhage in humans [15, 20] that is designed to induce hemodynamic decompensation (i.e., severe hypotension and pre-syncope) has revealed that subjects with high tolerance (HT) to reduced central blood volume display higher HR [16] and peripheral vasoconstriction [17, 38] than low tolerant (LT) subjects [16, 38]. These observations suggest that greater physiological reserve is associated with greater tolerance to central hypovolemia. However, the 'reserve' for autonomic responses associated with greater HR and vasoconstrictor reserves has not been reported in HT and LT subjects. In this investigation, we tested the hypothesis that a higher HR and vasoconstrictor reserve in subjects with HT to central hypovolemia would be associated with greater reserve for sympathetic activation and vagal withdrawal compared with LT subjects.

Materials and methods

Subjects and ethical approval

Seventy-eight non-smoking male volunteers participated in this study (age 30 ± 1 years; height 179 ± 1 cm; weight 84.6 ± 1.4 kg). Females were excluded from this study because of the inability to obtain muscle sympathetic nerve activity in LT women. All experimental procedures were conducted under a protocol reviewed and approved by the Brooke Army Medical Center Institutional Review Board, and in accordance with the approved protocol. Data from these subjects are also reported as a subgroup of a larger cohort in a related study [36]. Prior to inclusion, all subjects underwent a medical history and physical examination by a physician to ensure that they had no previous or current medical conditions that might preclude their participation. Subjects were instructed to maintain their normal sleep patterns, refrain from exercise, and abstain from caffeine and other autonomic stimulants including prescription or non-prescription drugs for at least 24 h prior to the study. Subjects received a verbal briefing and written descriptions of all procedures and risks associated with the study, and were made familiar with the laboratory, the protocol, and procedures. Subjects were encouraged to ask questions of the investigators, and then gave their written informed consent to participate in the study.

Experimental protocol

Subjects were instrumented with a standard 4-lead ECG to record cardiac electrical potentials, and an infrared finger photoplethysmograph (Finometer® Blood Pressure Monitor, TNO-TPD Biomedical Instrumentation, Amsterdam, The Netherlands) to record beat-by-beat finger arterial pressure. The Finometer® blood pressure cuff was placed on the middle finger of the left hand, which in turn was laid at heart level.

Progressive reduction in central blood volume was induced by application of lower body negative pressure (LBNP) in order to simulate, as closely as possible in healthy human volunteers, the hemodynamic challenges associated with severe hemorrhage [20]. Subjects assumed the supine position within an airtight chamber and were sealed at the level of the iliac crest by way of a neoprene skirt. Each subject underwent exposure to a protocol designed to test their LBNP tolerance. The LBNP protocol consisted of a 5-min rest period (baseline) followed by 5 min of chamber decompression at -15, -30, -45, and -60 mmHg, and then additional increments of -10 mmHg every 5 min until the onset of hemodynamic decompensation or the completion of 5 min at -100 mmHg. Hemodynamic decompensation was identified in real time by the attending investigator by a precipitous fall in systolic arterial pressure (SAP) greater than 15 mmHg concurrent with the onset of pre-syncopal symptoms such as bradycardia, grey-out (loss of color vision), tunnel vision, sweating, nausea or dizziness. No subject completed 5 min at -100 mmHg, and all subjects expressed one or more subjective pre-syncopal symptoms that coincided with a target SAP <90 mmHg.

Based on the results from previous experiments [16, 33, 38], 56 subjects were categorized into the group with high tolerance (HT) to reduced central blood volume based upon entrance into the -70 mmHg LBNP level while the remaining 22 subjects were categorized into the low tolerance (LT) group because of their failure to complete -60 mmHg of LBNP.

Data analysis

Data were sampled at 500 Hz, digitized to computer (WinDAQ, Dataq Instruments, Akron, OH), and then imported into commercially available data analysis software (WinCPRS, Absolute Aliens, Turku, Finland). Individual R-waves from the ECG were marked at their occurrence in time and used for subsequent identification of systolic (SAP, mmHg) and diastolic arterial pressures (DAP, mmHg) generated from the Finometer®. R R intervals (RRI, ms) were used to calculate heart rate (HR, beats/min). Mean arterial pressure (MAP, mmHg) was

automatically calculated as the area under the arterial blood pressure waveform. Using the arterial pressure waveform as an input, stroke volume (SV, ml) was estimated on a beat-by-beat basis using the pulse contour method as previously outlined [29]. Changes in the measurement of baseline thoracic electrical bioimpedance (Z_0) have been demonstrated to reflect proportional changes in central blood volume and filling of the heart during LBNP [5]. In a separate group of subjects ($N = 20$), we have demonstrated in our laboratory that the average relative changes in SV estimated from the pulse contour method during progressive central hypovolemia (LBNP from 0 to 60 mmHg) correlated with percent changes in Z_0 (amalgamated $r^2 = 0.97$; Fig. 1). We chose to use reductions in stroke volume during LBNP as representative of the magnitude of central blood volume because of the relationship between SV and measured blood volume [5, 7] and cardiac filling [5, 7] during progressive LBNP, and that the average change in SV ($-43 \pm 8\%$, $N = 20$) produced a more physiological correlate than Z_0 ($+5.9 \pm 2.3\%$, $N = 20$). Cardiac output (Q, l/min) was estimated by multiplying SV by HR. Total peripheral vascular resistance [PVR, mmHg/(min l)] was calculated by dividing MAP by Q.

Measure of cardiac vagal baroreflex response

Vagal baroreflex sensitivity (BRS) was assessed via the sequence method [37]. The WinCPRS software was used to automatically detect potential sequences between the RRI and SAP signals. A valid sequence was defined as at least three sequentially decreasing SAPs with at least a 1 mmHg change per beat and associated RRIs with at least a 4 ms change per beat [37]. Baroreflex gain was then estimated via linear regression [37].

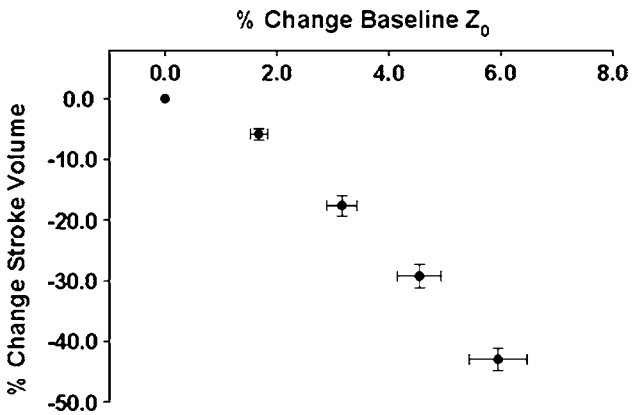

Fig. 1 Relationship between the percent (%) change in baseline thoracic electrical bioimpedance (Z_0) and stroke volume (amalgamated r^2 0.97). *Dots* represent the mean (N 20) and *bars* represent ±1 SEM

Measure of sympathetic nerve activity

Muscle sympathetic nerve activity (MSNA) was measured directly from the peroneal nerve via microneurography, according to the procedures previously described in detail [18]. Sympathetic bursts occurring during the final 3 min of baseline and 3 min of each LBNP level were divided by 3 to derive an average MSNA in bursts/min for each LBNP level. Although efforts were made to obtain MSNA in most subjects included in the current analysis, the high negative pressures applied to induce hemodynamic decompensation dislodged the recording electrode in all but a small cohort of subjects prior to this point, and so we only report complete MSNA datasets across all levels of LBNP in nine HT subjects and five LT subjects.

Statistical analysis

The reserve for a specific physiological response to central hypovolemia (e.g., vagal withdrawal, MSNA) has been defined as the difference between the measured maximum response and the baseline level [24, 27]. We used this concept to calculate HR reserve, vasoconstrictor (PVR) reserve, BRS reserve, and MSNA reserve in our subject groups. We determined the maximum response of each physiological parameter by calculating the average from the final 1 min of data prior to the highest or lowest value (depending on the variable) obtained in the data record. To identify the MAP at which pre-syncope occurred, the final 1 min of data were used. A t test statistic for unpaired measures was used to compare subject demographic data and each measure of reserve capacity between subjects in the HT and LT groups. Since the reserves and maximal levels for HR and PVR reserve have been shown a priori to be higher in HT subjects [16, 17, 38], a one-tailed statistical comparisons were used to determine differences between HT and LT groups. A two-way repeated measures ANOVA was performed to compare differences between groups (HT vs. LT) across time (baseline vs. pre-syncope) for all other variables. The probabilities of observing chance effects on the dependent variables of interest are presented as exact P values. All data are expressed as mean ± SEM.

Results

The HT and LT groups were statistically similar in age, height, weight, and gender distribution (Table 1). By design, maximum tolerance to progressive LBNP was an average of 46% higher in the HT compared to the LT subjects (Table 1). Responses to LBNP of MAP, SV, Q, and PVR at baseline rest and decompensation (pre-syncope) are presented in Fig. 2. MAP was similar

(approximately 98 mmHg) in both groups at baseline rest, and was reduced ($P < 0.001$) at the point of hemodynamic decompensation, but was not statistically distinguishable ($P = 0.510$) between the HT group (78 ± 2 mmHg) and LT group (77 ± 1 mmHg). HT subjects were able to tolerate a greater ($P < 0.001$) reduction in SV ($\Delta SV = -61 \pm 3$ ml) than the LT subjects ($\Delta SV = -46 \pm 4$ ml). Average Q was decreased by LBNP ($F = 39.411$; $P < 0.001$), but these responses were statistically indistinguishable ($F = 0.011$; $P = 0.916$) between HT and LT subjects (Fig. 2). Average PVR was elevated by LBNP ($F = 8.760$; $P = 0.004$; Fig. 2), with the average reserve (maximum ΔPVR) being 78% greater in the HT subjects compared with the LT group ($F = 3.121$; $P = 0.041$; Table 2).

The responses of HR and spontaneous cardiac BRS are presented in Fig. 3. HR was elevated ($F = 257.6$; $P < 0.001$) with LBNP (Fig. 3), but the HR reserve (maximum ΔHR) in the HT group was twofold greater than the HR reserve in the LT group (Table 2). The average spontaneous cardiac BRS at baseline rest was 20% higher ($P = 0.016$) in the HT subjects (17.5 ± 1.8 ms/mmHg)

Table 1 Demographic data for high (HT) and low (LT) tolerant subjects

	High tolerant (HT)	Low tolerant (LT)	*P* value
N	56	22	
LBNP tolerance time (s)	1,861 ± 27	1,277 ± 31	<0.0001
Age (years)	30 ± 1	29 ± 2	0.57
Height (cm)	179 ± 1	180 ± 2	0.59
Weight (kg)	83.9 ± 1.4	86.3 ± 3.5	0.46

Values are mean ± 1 SEM

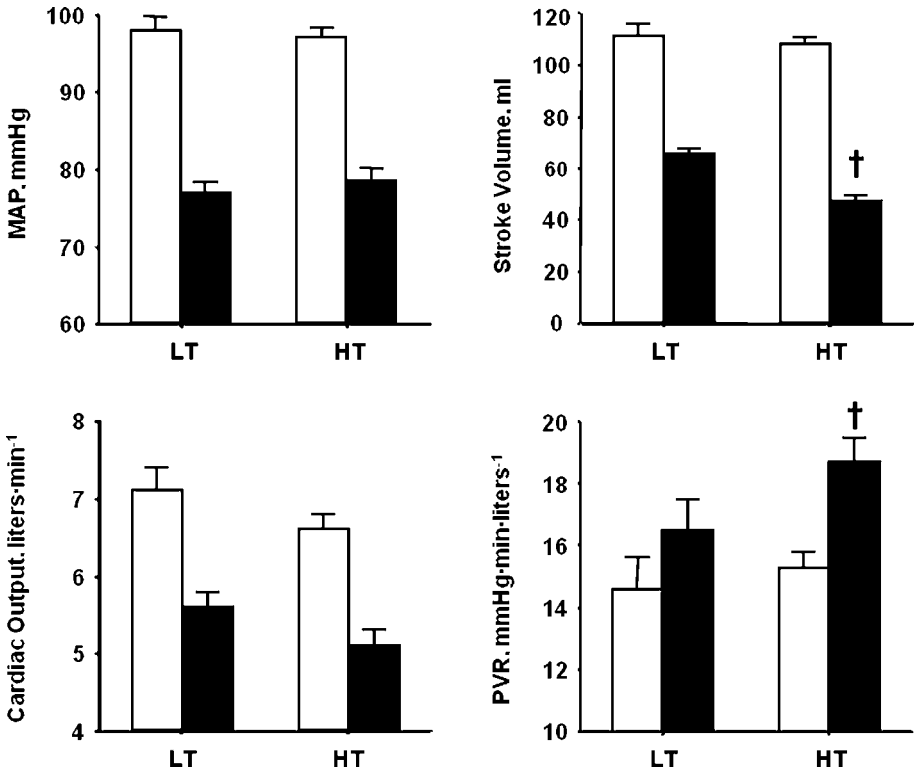

Fig. 2 Mean arterial pressure (*MAP*), stroke volume, cardiac output and peripheral vascular resistance (*PVR*) at baseline (*open bars*) and pre syncope (*closed bars*) in high tolerant (*HT*) and low tolerant (*LT*) subject groups. Bars and lines represent mean ± 1 SEM
$^{\dagger}P \leq 0.044$ compared with corresponding LT value

Table 2 Physiological 'reserves' for vasoconstriction (ΔPVR), tachycardia (ΔHR), sympathetic activation (ΔMSNA), and vagal withdrawal (ΔBRS) for high (HT) and low (LT) tolerant subjects measured from baseline to the point of hemodynamic decompensation (pre syncope)

	High tolerant (HT)	Low tolerant (LT)	*t* value	*P* value
ΔPVR [mmHg/(min l)]	+3.4 ± 0.5	+1.9 ± 0.3	3.121	0.041
ΔHR (beats/min)	+52 ± 2	+27 ± 3	44.162	<0.001
ΔMSNA (bursts/min)	+41 ± 2	+26 ± 7	6.113	0.029
ΔBRS (ms/mmHg)	14.2 ± 1.8	7.4 ± 1.7	6.495	0.014

Values are mean ± 1 SEM

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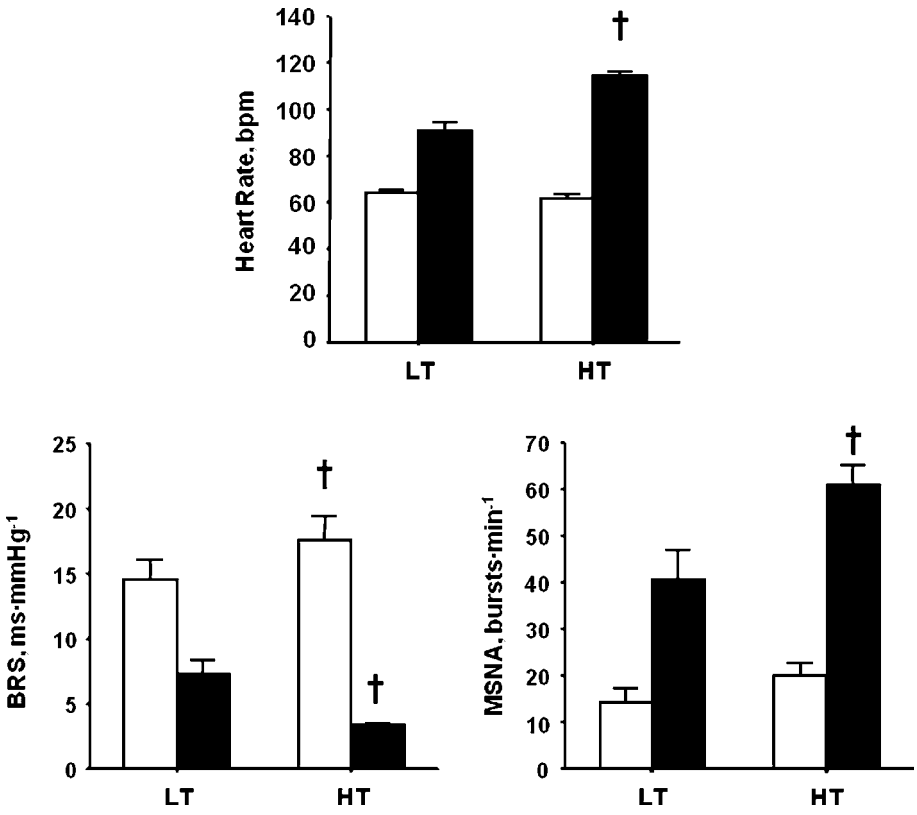

Fig. 3 Heart rate, muscle sympathetic nerve activity (*MSNA*) and spontaneous baroreflex sensitivity (*BRS*) at baseline (*open bars*) and pre syncope (*closed bars*) in high tolerant (*HT*) and low tolerant (*LT*) subject groups. *Bars and lines* represent mean ± 1 SEM. $^{\dagger}P \leq 0.041$ compared with corresponding LT value

than the LT subjects (14.5 ± 1.5 ms/mmHg). LBNP reduced ($F = 61.2$; $P < 0.001$) BRS (Fig. 3), but the reserve for vagal baroreflex withdrawal (maximum ΔBRS) was nearly twofold greater ($P = 0.014$) in the HT subjects (Table 2).

MSNA at baseline rest and at pre-syncope for LT and HT groups are presented in Fig. 3. Average MSNA was statistically similar at baseline ($P = 0.360$) between HT and LT groups, and increased ($F = 11.01$; $P < 0.001$) with LBNP. However, the group average MSNA at pre-syncope in the HT subjects (61 ± 6 bursts/min) was ~50% higher than that measured in the LT subjects (41 ± 6 bursts/min). Consequently, the average MSNA reserve (maximum ΔMSNA) was ~55% greater ($P = 0.029$) in the HT subjects (41 ± 2 bursts/min) compared to the LT subjects (26 ± 7 bursts/min) (Table 2). When expressed as bursts per 100 heart beats, MSNA at pre-syncope in the HT subjects (53.2 ± 5.0 bursts/100HB) was statistically indistinguishable ($P = 0.477$) from that calculated in the LT subjects (47.0 ± 6.8 bursts/100HB).

Discussion

We sought to better define the contributions of autonomic mechanisms involved in the control of HR and peripheral vasoconstriction, and their role in defending against hemodynamic decompensation during progressive reduction in central blood volume. We used LBNP as a model of hemorrhage in healthy humans [15, 20]. Like hemorrhage, LBNP induces a reduction in venous return to the heart which leads to reduced SV, Q, arterial blood pressure, and perfusion of vital organs [15, 28, 41, 46], and ultimately, hemodynamic decompensation. Using this model, we defined subjects with high and low tolerance to central hypovolemia and examined physiological responses associated with vagal and sympathetic control of HR and peripheral vasoconstriction. We reaffirmed previous findings [16, 38] that lower heart rate reserve (i.e., relative bradycardia) is associated with individuals having low tolerance to the reduction of central blood volume. Our results indicate that these individuals with lower maximal HR reserve during progressive LBNP represent approximately one-third of the normal healthy population, consistent with clinical observations that have identified relative bradycardia in 29 44% of hypotensive patients [23, 31, 43, 45].

Tolerance and sympathetically mediated mechanisms

Our hypothesis that higher HR in HT subjects during progressive reduction in central blood volume would be associated with higher sympathetic activity compared to LT subjects was supported by several new observations.

Our large experimental population of humans ($N = 78$) who underwent LBNP to the point of hemodynamic decompensation (pre-syncope) provided the unique opportunity to obtain complete MSNA recordings in cohorts of both HT and LT subjects ($N = 14$). Due to the challenge of collecting MSNA recordings in this experimental model, we are unaware of similar datasets in which comparisons of directly measured sympathetic nerve activity in HT and LT subjects have been accomplished. Since MSNA was statistically indistinguishable at baseline, it is clear that the twofold greater elevation in MSNA at pre-syncope observed in HT subjects represented a greater MSNA reserve when compared to LT subjects (Table 2). This higher reserve capacity in HT subjects was associated with a greater reserve for generating a tachycardic response. This close relationship between the reserves for increasing HR and sympathetic nerve activity is further reinforced by the absence of a group difference when MSNA is expressed as bursts per 100 heart beats. In the absence of a robust MSNA and HR reserve, LT subjects could only tolerate a reduction in SV of approximately 40% before the failure of compensatory mechanisms, leading to cardiovascular decompensation. In contrast, a greater MSNA and HR reserve allowed HT subjects to compensate for a 56% reduction in stroke volume (Fig. 3) and to maintain cardiac output and blood pressure during higher levels of central hypovolemia (level of LBNP tolerance). These responses are supported by recent findings of greater tolerance (absence of hypotension) during hemorrhage in exercise-trained rats, associated with higher HR and sympathetic drive, indirectly assessed using metrics of HR variability [2].

Although there are studies suggesting that higher PVR does not always account for differences in tolerance to central hypovolemia [8, 9, 16], there is compelling evidence that individuals with high tolerance to acute reductions in central blood volume display greater vasoconstriction than low tolerant subjects [4, 17, 26, 34, 38, 47]. When vasoconstrictor reserve (i.e., change in PVR from baseline to maximal vasoconstriction) is reduced by lower circulating blood volume in the same subjects (e.g., via dehydration), their tolerance to central hypovolemia is decreased [11, 24, 27]. Like these previous findings, we observed in the present investigation that HT subjects displayed greater increases in PVR than LT subjects reflected by a greater vasoconstrictor reserve.

Hypoadrenergic responsiveness has been hypothesized as a possible mechanism underlying low tolerance as evidenced by a relationship between low plasma norepinephrine concentrations and less vascular resistance [17, 26, 34, 47]. However, methodological limitations [11] and large inter-subject variability [17] make it difficult to confirm that reduced peripheral resistances observed during conditions of reduced central blood volume are a consequence of lower sympathetic traffic. Although limited to a cohort of a larger subject population, the present study is the first to provide comparative data regarding the association between directly measured MSNA and PVR reserve in HT and LT subjects. We hypothesized that the larger vasoconstrictor reserve exhibited in HT subjects would be associated with a greater MSNA reserve. Consistent with this expectation, we found that an average 58% higher MSNA reserve in HT subjects compared to LT subjects was associated with a 79% greater PVR reserve. The results of the present investigation are consistent with the notion that the ability to distinguish HT from LT subjects by their PVR response underscores the importance of sympathetically mediated vasoconstriction in addition to tachycardia as a compensatory mechanism for defending systemic blood flow (cardiac output) and dictating individual tolerance to central hypovolemia. We are unaware of any other data with direct measures of MSNA reserve that associates higher tolerance to reduced central blood volume with proportionally elevated HR and PVR reserves.

Tolerance and vagally mediated cardiac mechanisms

Our results corroborate those of previous investigations that demonstrated a dynamic reduction in BRS with decreased central blood volume (via LBNP in humans and actual hemorrhage in both humans and animals) [14, 15, 19, 25, 32, 35, 48]. Our finding that baseline spontaneous BRS was greater in HT subjects than in LT subjects (Fig. 3) is also consistent with previous observations that high integrated cardiac BRS ($\Delta HR/\Delta AP$) is associated with high tolerance to conditions of central hypovolemia [2, 8 10, 12, 16, 24]. Since acute reductions in BRS during conditions of lowered central blood volume reflect baroreflex-mediated cardiac vagal withdrawal [19], we hypothesized that a greater tachycardia response observed in the HT compared with LT subjects would be associated with larger reductions in spontaneous BRS during progressive LBNP (i.e., greater BRS reserve). Indeed, our observations support the notion that a greater reserve for baroreflex-mediated vagal withdrawal in addition to higher sympathetic activation may contribute to greater elevations in heart rate in individuals with high tolerance to hypovolemic hypotension.

Clinical perspectives (translational physiology)

There has been significant effort to identify an early marker for detection of the severity of blood loss. Reasonably, HR has received significant attention because it is easily obtained from standard monitors and tachycardia represents a typical reflex response to reduced central blood volume. However,

the HR response to trauma that includes hemorrhage has proven to be insensitive in distinguishing those who died from those who lived [21, 22], or those who did or did not receive a life-saving intervention [6]. The inclusion of data from trauma patients who display a relative bradycardia in response to hypotension with data from patients who elicit significant tachycardia can contribute to the apparent non-specificity of HR as an indicator of clinical outcome, particularly during hemorrhage. As a result of the reported relative bradycardia in bleeding patients, clinicians have been cautioned that the lack of tachycardia with hemorrhage following trauma can mask the diagnosis of severe bleeding [44, 45]. Not only does the present study provide underlying autonomic mechanisms associated with the blunted HR response during hemorrhage, but more significantly indicates that approximately one-third of the patients at greatest risk for developing overt circulatory shock are individuals with relative bradycardia. A greater reserve for elevating HR and subsequently defending cardiac output may reflect a more effective maintenance of cerebral perfusion and delay the onset of shock. This notion may be supported by our recent observation that the delay in the onset of pre-syncopal symptoms in HT subjects is associated with greater oscillatory patterns of cerebral blood velocity [36]. Although not presented in the present paper, relationships between progressive hypovolemia induced by LBNP (time/pressure effects) prior to the development of pre-syncope and parameters generated from heart rate and blood pressure responses reveal that there is no one parameter that can predict early group differences (i.e., specificity) since HT subjects can display higher or lower values of MAP, HR, SV, Q, and PVR during pre-syncope [36]. As such, adequate monitoring of bleeding patients should include specific and sensitive physiological measurements other than HR. We have recently demonstrated that real-time arterial waveform feature extraction using advanced machine-learning methodologies can provide early and continuous blood loss capable of distinguishing individuals at higher risk for hemodynamic decompensation [13]. Using such an approach can promote early identification of high/low tolerance in hemorrhaging trauma patients, with significant improvement in triage and treatment capabilities, particularly in a mass casualty scenario.

Conclusion

We have identified autonomic mechanisms associated with a cohort of humans whose 'reserve' to compensate are relatively attenuated when challenged with a reduction in central blood volume similar to that experienced with hemorrhage leading to cardiovascular decompensation. The primary finding of this study is that individuals with more reserve for sympathetic activation and vagal-cardiac withdrawal have greater tachycardic and vasoconstrictor responses, allowing them to maintain systemic blood flow (cardiac output) and perfusion (arterial) pressure for a longer period of time, and ultimately tolerate a greater reduction in central blood volume.

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Conflict of interest No conflicts of interest, financial or otherwise, are declared by the authors.

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