Published in final edited form as:

Clin Auton Res. 2011 December ; 21(6): 381–387. doi:10.1007/s10286-011-0126-6.

Muscle sympathetic responses during orthostasis in heat-stressed individuals

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Abstract

Purpose—Whole-body heat stress compromises the control of blood pressure during an orthostatic challenge, although the extent to which this occurs can vary greatly between individuals. The mechanism(s) responsible for these varying responses remain unclear. This study tested the hypothesis that the individuals who are best able to tolerate an orthostatic challenge while heat stressed are the ones with the largest increase in sympathetic activity during orthostasis, indexed from recordings of muscle sympathetic nerve activity (MSNA).

Methods—MSNA, arterial blood pressure, and heart rate were recorded from 11 healthy volunteers throughout passive whole-body heating and during 15 min of 60° head-up tilt (HUT) or until the onset of pre-syncope symptoms.

Results—Whole-body heating significantly increased core temperature (~0.9°C), supine heart rate and MSNA. Eight of 11 subjects developed pre-syncope symptoms resulting in early

termination of HUT. The HUT tolerance time was positively correlated ($R = 0.82$, $P = 0.01$) with the increase in MSNA by HUT.

Conclusion—These data suggest that the individuals with the largest increase in MSNA during upright tilt have the greatest capacity to withstand the orthostatic challenge while heat stressed.

Keywords

Sympathetic nervous system; Heat stress disorders; Tilt-table test; Syncope

Introduction

Humans are more susceptible to syncope during orthostasis when combined with heat stress [1, 16, 20, 33]. The effect of heat stress on attenuating orthostatic tolerance varies greatly among individuals [16, 33]. For example, Keller et al. [16] reported that while heat stressed some subjects were unable to complete 3 min of 20 mmHg lower-body negative pressure while other subjects tolerated over 50 mmHg lower-body negative pressure. The mechanisms responsible for the variability in orthostatic tolerances while heat stressed are not entirely understood.

In normothermic conditions, sympathetically mediated peripheral vasoconstriction plays a key role in defending against decreases in arterial pressure during orthostatic or hemorrhagic challenges. For example, muscle sympathetic nerve activity (MSNA) increases as a linear function with reduced central blood volume in healthy individuals [2, 14, 30]. Accordingly, one may hypothesize that the degree to which one is able to tolerate an orthostatic challenge depends on the sympathetic response to that challenge. However, sympathetically mediated vasoconstriction depends on both an appropriate increase in sympathetic nerve activity and an effective post-junctional response to the increase in sympathetic activity. This latter point is particularly important given that adrenergic vasoconstrictor responsiveness may change under some conditions. As an example, a dissociation between sympathetic activity and increases in vascular resistance was speculated to be a mechanism for orthostatic intolerance after space flight [19].

In heat stress conditions, the effectiveness of the pressor response to adrenergic stimulation is reduced in anesthetized [18, 22] and conscious [23] rats. In humans, whole-body heating attenuates cutaneous α -adrenergic vasoconstrictor responsiveness [32], as well as the elevation in arterial blood pressure to systemic infusions of the α_1 adrenergic agonist phenylephrine [8]. Moreover, heat stress attenuates the pressor response to a sympathoexcitatory stimulus and causes an apparent disassociation between MSNA and the corresponding blood pressure response [6]. Accordingly, if heat stress impairs adrenergic vasoconstrictor responsiveness, one could speculate that orthostatic tolerance may not be related to the increase in MSNA while subjects are in this thermal condition. Alternatively, if the increase in sympathetic activity is sufficient to overcome heat induced impairments in post-junctional adrenergic responsiveness, then individuals with the largest increase in sympathetic activity may have the greatest tolerance to central hypovolemia associated with orthostasis. Thus, the objective of this investigation is to identify whether there is a relationship between sympathetic activity, as indexed from MSNA, and orthostatic tolerance in heat-stressed individuals. Specifically, this study tested the hypothesis that the individuals who are best able to tolerate an orthostatic challenge while heat stressed are the ones with the largest increase in MSNA.

Methods

Subjects

Eleven healthy volunteers [7 male, 4 female, age 34 ± 6 yrs (mean $\pm$ SD); height 173 ± 10 cm; weight 74 ± 11 kg; and BMI 24.4 ± 2.5] participated in this study. Volunteers were not taking medications and had no known cardiovascular diseases. Volunteers refrained from caffeine, alcohol, and intensive exercise 24 h prior to the study. The study protocol and consent were approved by the Institutional Review Boards of the University of Texas Southwestern Medical Center and Texas Health Presbyterian Hospital Dallas and a written informed consent was obtained from each volunteer.

Measurements

Internal temperature (T_{core}) was measured from intestinal temperature via telemetric temperature pill (HQ Inc., Palmetto, FL, USA) that was swallowed by each volunteer at least 2 h prior to data collection. Mean skin temperature (T_{sk}) was obtained from the weighted electrical average of six thermocouples attached to the skin [27]. Each volunteer was dressed in a tube-lined suit that permitted the control of T_{sk} by changing the temperature of the water perfusing the suit. Skin blood flow was indexed from dorsal forearm skin using laser-Doppler flowmetry with integrating flow probes (Perimed, North Royalton, OH, USA). Forearm sweat rate was measured adjacent to this area via capacitance hygrometry (Vaisala, Woburn, MA, USA) using the ventilated capsule method (surface area 2.83 cm^2). The area from which skin blood flow and sweat rate were measured was not covered by the water perfused suit. Heart rate was monitored from an electrocardiogram interfaced with a cardi tachometer (CWE, Ardmore, PA, USA).

Arterial blood pressure was measured by auscultation of the brachial artery (SunTech Medical Instruments Inc., Raleigh, NC, USA). In addition, continuous Finometer-derived blood pressures (Finometer, Finapres Medical Systems, Amsterdam, The Netherlands) were obtained to aid in the identification of the onset of syncopal symptoms during head-up tilt (HUT). Unless indicated, reported blood pressures are from brachial artery auscultation. Respiratory frequency was monitored using piezoelectric pneumography. Multifiber recordings of MSNA were obtained with a tungsten microelectrode inserted in the peroneal nerve. A reference electrode was placed subcutaneously 2–3 cm from the recording electrode. The signal was amplified, filtered with a bandwidth of 500–5,000 Hz, and integrated with a time constant of 0.1 s (Iowa Bioengineering, Iowa City, IA, USA). The recording electrode was adjusted until a site was found in which muscle sympathetic bursts were clearly identified using previously established criteria [29]. Mean voltage neurograms were displayed on a chart recorder. The nerve signal was also routed to an oscilloscope and a loudspeaker for monitoring throughout the study.

Protocols

The study was conducted in a temperature-controlled room ($\sim 25^\circ\text{C}$). Five minutes of thermal and hemodynamic data were obtained as normothermic baseline with the subject in the supine position. T_{sk} was then increased to $\sim 38^\circ\text{C}$ by perfusing the tube-lined suit with 46°C water. Once T_{core} was elevated $\sim 0.9^\circ\text{C}$, the temperature of the water perfusing the suit was slightly reduced to attenuate further increases in T_{core} . Two minutes of thermal and hemodynamic data were obtained as heat stress baseline. The multifiber MSNA recordings were well maintained in all subjects throughout whole-body heating and heat stress baseline data collection. While still heat stressed, the subjects were tilted from supine to 60° HUT and remained in this position for 15 min or until the onset of syncopal symptoms. The subject supported his/her body weight with one leg, while the leg with the microneurographic needles was not weight bearing and maintained in the same slightly

flexed position relative to when the subject was supine using pillows as support. HUT was discontinued if signs or symptoms of syncope were observed (e.g., nausea, pallor, rapid decreases in heart rate and/or blood pressure, or a sustained decrease in systolic blood pressure < 80 mmHg). Only 3 of the 11 subjects completed 15 min of HUT without syncopal symptoms during the heat stress. HUT was not discontinued if the MSNA recording was lost, which occurred well prior to the end of HUT in three subjects or in concert with the onset of syncopal symptoms (i.e., pre-syncope) immediately before termination of HUT in two subjects. Table 1 shows the number of subjects who maintained or did not maintain the MSNA recording, along with those who completed or did not complete 15 min of HUT.

Data analysis

Data were sampled at 200 Hz through a commercial data acquisition system (Biopac System, Santa Barbara, CA, USA). MSNA bursts were first identified in real time by visual inspection of data plotted on a chart recorder, coupled with the burst sound from the audio amplifier. These bursts were further evaluated via a computer software program that identified bursts based upon fixed criteria, including an appropriate latency following the R wave of the electrocardiogram [5, 7]. The amplitude of the integrated MSNA signal of the entire recording was normalized by assigning a value of 100 to the mean amplitude of the largest 10% of the bursts during the 5-min normothermic baseline period [12]. Total MSNA was identified from burst area of the integrated neurogram, which was evaluated on a beat-by-beat basis, and expressed as units/ min.

Hemodynamic variables and MSNA during the 5-min supine normothermic baseline period and during the 2-min heat stress baseline period prior to HUT were analyzed. For the non-syncopal subjects, mean hemodynamic and MSNA data during the final minute of HUT were evaluated, defined as “Tilt” data. For the syncopal subjects, the evaluated variables during the last minute of HUT prior to any sign or symptom of syncope are also defined as “Tilt” data. The evaluated variables during the final 10 s before the end of HUT for the syncopal subjects are defined as “Pre-syncope” data.

Statistical analyses were performed using commercially available software (SigmaStat 3.5, SPSS Inc.). Baseline values between normothermic and whole-body heating trials were compared via paired *t* tests. Comparison of absolute values between pre-HUT baseline, Tilt, and Pre-syncope were evaluated via a one-way repeated measures ANOVA, followed by multiple comparison post hoc (Tukey) analyses where appropriate. In the subjects whose MSNA recordings were maintained during HUT prior to the onset of syncopal symptoms (i.e., through the “Tilt” period; *N* = 8), the relationship between tilt time and the increase in MSNA from supine heat stress to the Tilt period was analyzed via Pearson product moment correlation analysis. Given that in three subjects the MSNA recording was lost well prior to the Tilt period, data from these three individuals were not included in this analysis. All values are reported as mean ± SE. *P* values of < 0.05 were considered statistically significant.

Results

Whole-body heating increased T_{core} from normothermic baseline $37.0 \pm 0.1^{\circ}\text{C}$ to $37.9 \pm 0.1^{\circ}\text{C}$ prior to HUT. This increase in T_{core} , coupled with corresponding increase in skin blood flow and sweat rate, indicate that the volunteers were sufficiently heat stressed (Table 2). Whole-body heating increased resting heart rate and MSNA, while mean arterial blood pressure (MAP) was not significantly changed (Table 2).

Temperatures, heart rate and MAP immediately prior to HUT, during Tilt, and at Pre-syncope are shown in Table 3. During HUT, 8 of 11 subjects developed pre-syncope symptoms resulting in early termination of the challenge. A representative recording of the final ~100 s of a pre-syncope subject is shown in Fig. 1. It should be noted that no subject actually fainted given that the test was terminated upon identification of symptoms of ensuing syncope. T_{sk} and T_{core} remained elevated and equivalent throughout HUT (Table 3). Prior to any pre-syncope symptoms during HUT, heart rate increased ($P < 0.001$, $N = 11$), while MAP did not change ($P = 0.23$, $N = 11$) relative to just prior to tilt. MSNA recordings were maintained in eight subjects (i.e., 2 non-syncope and 6 syncope subjects, see Table 1) during Tilt. In these eight subjects, Tilt increased MSNA, relative to just prior to HUT, whether expressed as burst frequency (28 ± 4 to 54 ± 4 bursts/min) or total activity (457 ± 51 to 1088 ± 216 units/min, both $P < 0.05$, $N = 8$). In the eight subjects who experienced pre-syncope resulting in early HUT termination ($N = 4$ who maintained MSNA recordings and $N = 4$ who did not maintain MSNA recordings through the pre-syncope period; see Table 1), at pre-syncope MAP and heart rate decreased significantly relative to the Tilt period (Table 3). In the four subjects with maintained MSNA recording through pre-syncope, MSNA was clearly suppressed at Pre-syncope in these subjects (Tilt: 49 ± 4 bursts/min and 910 ± 149 units/min; Pre-syncope: 21 ± 7 bursts/min and 367 ± 127 units/min, both $P < 0.01$).

Mean HUT time was 483 ± 90 s ($N = 11$), inclusive of the subjects who completed the 15-min HUT test. A relatively strong correlation ($R = 0.82$, $P = 0.01$) was identified between the elevation in MSNA from just prior to HUT (i.e., heat stress baseline) to the Tilt period and HUT time (Fig. 2, $N = 8$ who maintained MSNA recordings through the Tilt period). This observation suggests that the individuals with the largest increase in MSNA during HUT were the ones who generally exhibited the highest HUT tolerance while heat stressed.

Discussion

The present results suggest that individual differences in the capacity to withstand an orthostatic challenge while heat stressed can partially be explained by the magnitude of the increase in MSNA, and presumably increases in vascular resistance, during that challenge.

An orthostatic challenge in heat-stressed subjects induces large increases in MSNA and heart rate, as illustrated in the present dataset. For example, for the same orthostatic challenge (i.e., the same level of lower-body negative pressure) the increase in MSNA and heart rate were greater when subjects were heat stressed relative to normothermia [9]. Although the same gravitational stress likely causes greater unloading of baroreceptors while heat stressed, another possible mechanism for the observed accentuation in MSNA response is that the increase in sympathetic activity is less effective in increasing arterial blood pressure; that is a greater increase in sympathetic activity may be needed to evoke appropriate increases in vascular resistance necessary to maintain arterial blood pressure. The latter hypothesis is supported by our previous findings in which heat stress attenuates α -adrenergic vasoconstrictor responsiveness in some [8, 32] but not all tissues [17], and that the pressor response to the same (or greater) sympathetic activation is attenuated in heat-stressed conditions. Accordingly, if post-junctional vasoconstrictor responsiveness was severely impaired, and the accompanying heightened sympathetic response was insufficient to appropriately increase vascular resistance, orthostatic tolerance would not be related to the sympathetic neural response; however, the present data do not support this speculation.

When compensatory sympathetic activation fails during an orthostatic challenge, syncope will occur [26, 31]. Consistent with this, bradycardia and MSNA suppression are often, but not always [3, 28], observed during a gravitational challenge sufficient to cause syncope [13,

21, 31]. Sympathetic suppression associated with syncope was proposed to be related to the magnitude of the exaggerated sympathetic activation, in combination with relative ventricular hypovolemia and stimulated myocardial ventricular afferents, during central hypovolemia [25]. Based upon those observations, one might speculate that the individuals with the greatest increase in MSNA during upright tilt (i.e., the ones with the exaggerated sympathetic activation prior to suppression of sympathetic activation) would be the individuals with the shortest tolerance time to that tilt, as these individuals would be more likely to suppress sympathetic activity leading to syncopal symptoms. However, the results of the present study show the opposite; that is the increase in MSNA during the orthostatic challenge was positively correlated with tilt time (Fig. 2).

There are a number of mechanisms that may be responsible for the positive linear relationship between the increase in MSNA during HUT and tolerance time. First, elevated MSNA likely increases systemic vascular resistance to some extent, despite proposed reduced post-junctional adrenergic responsiveness, particularly if MSNA is representative of sympathetic activity to non-muscle beds such as the splanchnic and renal vascular beds. With accompanying elevations in systemic vascular resistance, the individual could tolerate a greater reduction in cardiac output, secondary to reduced venous return, prior to the onset of syncopal symptoms. Second, enhanced sympathetic activation may also increase circulating catecholamines thereby contributing to improved blood pressure control. Third, the individuals with the greatest baroreflex responsiveness may have a larger increase in MSNA for the same hypotensive challenge and thus have a higher tolerance. Fourth, the onset of sympathetic suppression associated with syncope may be triggered at different levels of hypotension between subjects, such that there is less of an increase in sympathetic activity just prior to the point of sympathetic suppression in the syncopal-prone individuals. Regardless of the mechanism(s), the present results suggest that individual differences in the magnitude of the MSNA response to an orthostatic challenge may contribute to differences in orthostatic tolerance in moderately heat-stressed individuals.

In normothermic subjects, a reduced reserve to increase sympathetic activity may contribute to individual variability in orthostatic tolerance [11]. We [4, 7, 8, 10, 15] and others [24, 34] showed that whole-body heating increases MSNA in resting supine individuals. Thus, we speculated that the higher absolute MSNA while heat stressed, or the greater the elevation in MSNA to the heat stress (i.e., the change between normothermic and the heat stress conditions), might reduce the reserve by which sympathetic activity could further increase during an orthostatic challenge and thus compromised the control of blood pressure. Counter to that speculation, tilt time was not related to either absolute MSNA during heat stress (tilt time vs. burst rate $R = -0.315$, $P = 0.35$; tilt time vs. total activity $R = 0.112$, $P = 0.74$) or the increase in MSNA from normothermia to heat stress conditions (tilt time vs. burst rate $R = -0.354$, $P = 0.286$; tilt time vs. total activity $R = -0.386$, $P = 0.241$). A possible reason for the lack of a relationship between these responses may be related to the relatively small increases in MSNA during heat stress alone (from 275 ± 29 to 465 ± 40 units/min) when compared to the large increases during Tilt ($1,088 \pm 216$ units/min). Thus, in the heat-stressed human there remains ample capacity for MSNA to subsequently increase during a hypotensive challenge.

MSNA was maintained in 8 of the 11 subjects sufficient to obtain data during the Tilt period. Despite this relatively low number of subjects, the relationship between HUT tolerance and the change in MSNA to HUT was highly significant with R values of 0.78 and 0.82 depending on the method of MSNA analysis. For concerns of safety, HUT was terminated at the onset of syncopal symptoms (i.e., pre-syncope) and thus no subject actually fainted. The reported HUT times, therefore, are clearly shorter than actual tolerance should fainting had been the end-point. However, the present study was not designed to

identify the onset of fainting, but rather to assess those factors that might contribute to the onset of symptoms of ensuing syncope. Thus, we are confident that the proposed correlations provide meaningful information pertaining to the relationship between MSNA and orthostatic tolerance.

In conclusion, the present findings suggest that the individuals who have the largest increase in MSNA to an orthostatic challenge generally exhibited the highest tolerance while moderately heat stressed. These findings suggest that although post-junctional vasoconstrictor responsiveness in some tissues is impaired while heat stressed, the accentuated sympathetic response to an orthostatic challenge [9] is sufficient to overcome such impairment while in this thermal condition.

Acknowledgments

This research project was funded in part by grants from the National Institutes of Health—National Heart, Lung, and Blood Institute (HL-61388 and HL-84072) and American Heart Association (0635245N).

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Fig. 1.

Representative tracings of MSNA, blood pressure (BP) and heart rate (HR) during 60° head-up tilt while heat stressed from one subject. The tilt was ended because of pre-syncope symptoms (i.e., rapid reductions in arterial and pulse pressures along with bradycardia). Notice the clear suppression in MSNA, HR and BP just prior to the end of tilt. Data indicated by the 60 s *solid line* are included in the “Tilt” averages, while data indicated by the 10 s *line* are included in the “Pre-syncope” averages, in Table 3

Fig. 2.

Correlation between the increase in MSNA burst rate (*left panel*, $P=0.01$) and total activity (*right panel*, $P=0.02$) due to head-up tilt and the tilt time. The increase in MSNA was calculated from the period just prior to tilt while heat stressed and the last minutes of the 15 min tilt test in the two non-fainters or the last minutes before any sign or symptom of ensuing syncope in subjects who did not complete the tilt test

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Table 1

Distribution of subjects who maintained or lost muscle sympathetic nerve activity (MSNA) recordings during head-up tilt (HUT) protocol

	HUT = 15 min		HUT < 15 min		Total
	Maintained MSNA	No MSNA	Maintained MSNA	No MSNA	Maintained MSNA
Supine	3	0	8	0	11
“Tilt” period	2	1	6	2	8
“Pre-syncope” period	–	–	4	4	4

During the HUT challenge, 8 of 11 subjects developed pre-syncope symptoms prior to 15 min of HUT (HUT < 15 min) resulting in early termination of the challenge. HUT = 15 min depicts the number of subjects who completed 15 min of HUT. “Tilt” period: 1 min prior to syncope symptoms, or the 15th minutes of HUT for the three individuals who did not experience syncope symptoms during HUT. The MSNA recording was lost in three subjects well prior to the “Tilt” period (e.g., primarily during the transition from supine to HUT), and in another two subjects in concert with the onset of syncope symptoms (i.e., pre-syncope)

Table 2

Thermal and hemodynamic baselines values while subjects were normothermic and during whole-body heating just prior to HUT

	Normothermia	Heat stress	<i>P</i>
Internal temperature (°C)	37.0 ± 0.1	37.9 ± 0.1	< 0.001
Mean skin temperature (°C)	34.5 ± 0.2	37.8 ± 0.2	< 0.001
Sweat rate (mg/cm ² /min)	–	0.49 ± 0.09	< 0.001
SkBF (% of baseline)	100	419 ± 52	< 0.001
SBP (mmHg)	121 ± 4	128 ± 5	0.03
DBP (mmHg)	76 ± 2	68 ± 1	0.02
MAP (mmHg)	91 ± 2	88 ± 1	0.20
Heart rate (beats/min)	59 ± 3	82 ± 6	< 0.001
MSNA (bursts/min)	17 ± 2	29 ± 3	< 0.001
MSNA (units/min)	275 ± 29	465 ± 40	< 0.001
Respiratory rate (cycles/ min)	15.9 ± 0.9	16.0 ± 1.2	0.97

Values are from normothermic baseline (normothermia) and while heat stressed immediately prior to head-up tilt (heat stress). Mean arterial blood pressure (MAP) was calculated as two-thirds diastolic blood pressure (DBP) plus one-third systolic blood pressure (SBP), measured by auscultation of the brachial artery. Skin blood flow (SkBF) is expressed as percent of normothermic baseline. *MSNA* muscle sympathetic nerve activity. *P* values indicated paired differences. Subject number = 11

Table 3

Thermal and hemodynamic variables prior to head-up tilt, during head-up tilt, and at pre-syncope

	Prior	Tilt	Pre-syncope	P
Internal temperature (°C)	37.9 ± 0.1	38.0 ± 0.1	37.9 ± 0.1	0.06
Mean skin temperature (°C)	37.8 ± 0.2	37.7 ± 0.2	37.7 ± 0.3	0.61
Sweat rate (mg/cm ² /min)	0.49 ± 0.11	0.56 ± 0.10	0.62 ± 0.13	0.32
MAP (mmHg)	88 ± 1	92 ± 3	67 ± 5 ^{*,#}	<0.001
Heart rate (beats/min)	82 ± 6	113 ± 7 [*]	92 ± 11 [#]	<0.001
Subject number	11	11	8	

Prior: resting baseline while heat stressed but prior to head-up tilt. Tilt: the last minute of tilt for the non-fainters, or the 1-min period prior to the onset of any pre-syncope symptoms. Pre-syncope: the last 10 s of data before the end of the tilt due to pre-syncope symptoms. Given the transient nature of blood pressure, mean arterial blood pressure (MAP) for this dataset originate from the Finometer; however, pre-tilt (i.e., Prior) Finometer values were normalized to values obtained via auscultation of the brachial artery. The P values are from the main effect comparison of the one-way repeated measures ANOVA from the 8 subjects who experienced syncope symptoms.

^{*} Significantly different from Prior ($P < 0.001$).

[#] Significantly different from Tilt ($P < 0.001$).