



Spectral analysis of muscle sympathetic nerve activity in heat-stressed humans

Jian Cui, Rong Zhang, Thad E. Wilson and Craig G. Crandall

AJP - Heart 286:1101-1106, 2004. First published Nov 20, 2003; doi:10.1152/ajpheart.00790.2003

You might find this additional information useful...

This article cites 32 articles, 27 of which you can access free at:

<http://ajpheart.physiology.org/cgi/content/full/286/3/H1101#BIBL>

Updated information and services including high-resolution figures, can be found at:

<http://ajpheart.physiology.org/cgi/content/full/286/3/H1101>

Additional material and information about *AJP - Heart and Circulatory Physiology* can be found at:

<http://www.the-aps.org/publications/ajpheart>

This information is current as of May 20, 2005 .

Spectral analysis of muscle sympathetic nerve activity in heat-stressed humans

Jian Cui,¹ Rong Zhang,^{1,2} Thad E. Wilson,¹ and Craig G. Crandall^{1,2}

¹Institute for Exercise and Environmental Medicine, Presbyterian Hospital of Dallas, Dallas 75231;

and ²Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas 75390

Submitted 18 August 2003; accepted in final form 12 November 2003

Cui, Jian, Rong Zhang, Thad E. Wilson, and Craig G. Crandall. Spectral analysis of muscle sympathetic nerve activity in heat-stressed humans. *Am J Physiol Heart Circ Physiol* 286: H1101–H1106, 2004. First published November 20, 2003; 10.1152/ajpheart.00790.2003.—Whole body heating increases muscle sympathetic nerve activity (MSNA); however, the effect of heat stress on spectral characteristics of MSNA is unknown. Such information may provide insight into mechanisms of heat stress-induced MSNA activation. The purpose of the present study was to test the hypothesis that heat stress-induced changes in systolic blood pressure variability parallel changes in MSNA variability. In 13 healthy subjects, MSNA, electrocardiogram, arterial blood pressure (via Finapres), and respiratory activity were recorded under both normothermic and heat stress conditions. Spectral characteristics of integrated MSNA, R-R interval, systolic blood pressure, and respiratory excursions were assessed in the low (LF; 0.03–0.15 Hz) and high (HF; 0.15–0.45 Hz) frequency components. Whole body heating significantly increased skin and core body temperature, MSNA burst rate, and heart rate, but not mean arterial blood pressure. Systolic blood pressure and R-R interval variability were significantly reduced in both the LF and HF ranges. Compared with normothermic conditions, heat stress significantly increased the HF component of MSNA, while the LF component of MSNA was not altered. Thus the LF-to-HF ratio of MSNA oscillatory components was significantly reduced. These data indicate that the spectral characteristics of MSNA are altered by whole body heating; however, heat stress-induced changes in MSNA do not parallel changes in systolic blood pressure variability. Moreover, the reduction in LF component of systolic blood pressure during heat stress is unlikely related to spectral changes in MSNA.

sympathetic nervous system; autonomic; cardiovascular; variability

PRONOUNCED WHOLE BODY HEATING is a potent activator of the sympathetic nervous system (24), as evidenced by large increases in heart rate and muscle sympathetic nerve activity (MSNA) (4, 6, 7, 20). Both mean values and variability of cardiovascular parameters are altered by heat stress in animals (25) and humans (5). For example, we (5) previously showed that whole body heating reduces heart rate and blood pressure variability within the low-frequency (LF) and high-frequency (HF) ranges and increases the ratio of LF to HF (LF/HF) heart rate variability. These changes in LF and HF oscillations may reflect alterations in autonomic regulation of heart rate and blood pressure during hyperthermic exposure (5).

However, controversy exists with respect to the origin of heat stress-induced changes in spectral patterns of cardiovascular variables. For example, heat stress reduces systolic blood pressure (SBP) variability within the LF range (5). A reduction

in LF oscillation of SBP has been reported to reflect a reduction in sympathetic modulation of vasomotor tone (16, 21, 23). However, heat stress increases MSNA when analyzed either as burst rate or total activity (4, 6, 7, 20). Reduced vascular responsiveness to adrenergic agonists (7, 15, 17, 34) might be one mechanism to explain the apparent uncoupling between the aforementioned index of sympathetic activation and direct recordings of MSNA in heat-stressed humans. Another possible explanation for reduced LF blood pressure oscillations in heat-stressed subjects could be a parallel reduction in LF oscillations of MSNA, even though mean MSNA increases during heat stress. However, to our knowledge, the effects of heat stress on oscillatory characteristics of MSNA are unknown.

Spectral analysis of MSNA variability has been used to investigate autonomic control in healthy individuals (11, 18, 23, 29) and patients (1, 30, 31). These findings show that stimulation of the autonomic nervous system via baroreceptor perturbations (10, 11, 23) as well as cardiovascular diseases (1, 30, 31) alter MSNA spectral characteristics. Thus spectral characteristics of MSNA during heating may provide insight into the mechanisms of heat stress-induced MSNA activation. To investigate this question, the present study was undertaken to test the hypothesis that heat stress-induced changes in SBP variability parallel changes in MSNA variability.

METHODS

Subjects. Thirteen healthy subjects (7 male, 6 female) participated in this study. The subjects' average age was 33 ± 3 yr (SE), and all were of normal height (168 ± 3 cm) and weight (69 ± 3 kg). All subjects were normotensive (supine blood pressures $<140/90$ mmHg), were not taking medications, and did not have any known cardiopulmonary, neurological, or metabolic diseases. A written informed consent from each subject was obtained before participation in this institutionally approved study.

Measurements. Each subject was instrumented for the measurement of sublingual temperature (T_{sl}) with a thermistor placed in the sublingual sulcus. Mean skin temperature (T_{sk}) was obtained from the electrical average of six thermocouples attached to the skin (27). The subject was dressed in a tube-lined suit that permitted control of T_{sk} by changing the temperature of the water-perfusing suit. Forearm skin blood flow was indexed by laser-Doppler flowmetry (Perimed; N. Royalton, OH) from an area not covered by the tube-lined suit. Forearm sweat rate was measured via capacitance hygrometry adjacent to the laser-Doppler flow probe (Viasala; Woburn, MA).

Multifiber recordings of MSNA were obtained with a tungsten microelectrode inserted in the peroneal nerve. A reference electrode

Address for reprint requests and other correspondence: C. G. Crandall, Institute for Exercise and Environmental Medicine, Presbyterian Hospital of Dallas, 7232 Greenville Ave., Dallas, TX 75231 (E-mail: CraigCrandall@texashealth.org).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Table 1. Thermal and hemodynamic response to heat stress

	Normothermia	Heat Stress
T _{sk} , °C	34.3±0.1	37.6±0.2*
T _{sl} , °C	36.6±0.1	37.2±0.1*
SkBF, %max	11.6±1.7	51.6±2.9*
Sweat rate, mg·cm ⁻² ·min ⁻¹		0.55±0.08*
Heart rate, beats/min	56.7±0.9	78.3±1.4*
SBP, mmHg	116.4±2.0	116.9±3.7
DBP, mmHg	71.7±1.7	68.1±2.3
MAP, mmHg	86.6±1.6	84.4±2.8
MSNA, bursts/min	15.4±1.8	26.2±3.1*
MSNA, au/min	301±39	561±84*
MSNA, bursts/100 heartbeats	27.1±3.2	33.0±3.4*
Respiratory rate, breaths/min	16.8±0.9	19.0±1.6*

Values are means ± SE. T_{sl}, sublingual temperature; T_{sk}, mean skin temperature; SR, sweat rate; MSNA, muscle sympathetic nerve activity. Mean arterial blood pressure (MAP) was calculated as one-third systolic blood pressure (SBP) plus two-third diastolic blood pressure (DBP), which was measured by auscultation of brachial artery. Skin blood flow (SkBF) was normalized relative to maximum skin blood flow and expressed as percentage of maximum (% max). *P < 0.05, significantly different from normothermia condition.

was placed subcutaneously 2 to 3 cm from the recording electrode. The recording electrode was adjusted until a site was found in which muscle sympathetic bursts were clearly identified using previously established criteria (28). The nerve signal was amplified, passed through a band-pass filter with a bandwidth of 500–5,000 Hz, and integrated with a time constant of 0.1 s (Iowa Bioengineering; Iowa City, IA). Mean voltage neurograms were displayed together with blood pressure on a chart recorder. The nerve signal was also routed to an oscilloscope, loudspeaker, and computer for monitoring throughout the study.

Blood pressure was recorded on a beat-by-beat basis from a finger via a Finapres device (Ohmeda; Louisville, CO). Resting blood pressures obtained from the Finapres device were verified during the experiment by auscultation of the brachial artery (SunTech Medical Instruments; Raleigh, NC). Respiratory excursions were monitored with piezoelectric pneumography (UFI; Morro Bay, CA).

Protocol. All parameters were recorded for 6 min with the subject resting in the supine condition and T_{sk} clamped by perfusing 34°C water through the tube-lined suit. After normothermic data collection, T_{sk} was increased to ~38°C by perfusing the tube-lined suit with 46°C water. Once T_{sl} increased ~0.5–0.7°C, the temperature of the water was reduced to 44–45°C to reduce the rate of rise of internal temperature throughout the ensuing data-collection period. In this heat stress condition, data were collected for an additional 6 min. Respiratory frequency was not controlled in either thermal condition.

On completion of heat stress data collection, cool water was perfused through the suit. A 3-cm diameter heater element (Perimed), which housed the laser-Doppler flow probe, was then engaged to elevate local skin temperature to 42°C. Local temperature was held at this level for 30 min to elicit maximal cutaneous vasodilation. Skin blood flow was then normalized relative to maximal vasodilation for each site.

Data analysis. Data were sampled at 200 Hz via a data acquisition system (Biopac System; Santa Barbara, CA). 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 on fixed criteria, including an appropriate latency after the R wave of the electrocardiogram. Integrated MSNA was normalized by assigning a value of 100 to the mean amplitude of the large sympathetic bursts during the 6-min normothermic baseline period (13, 26). Normalization of the MSNA signal was performed to reduce variability between subjects attributed to several factors, including needle placement and signal amplification. Importantly, this

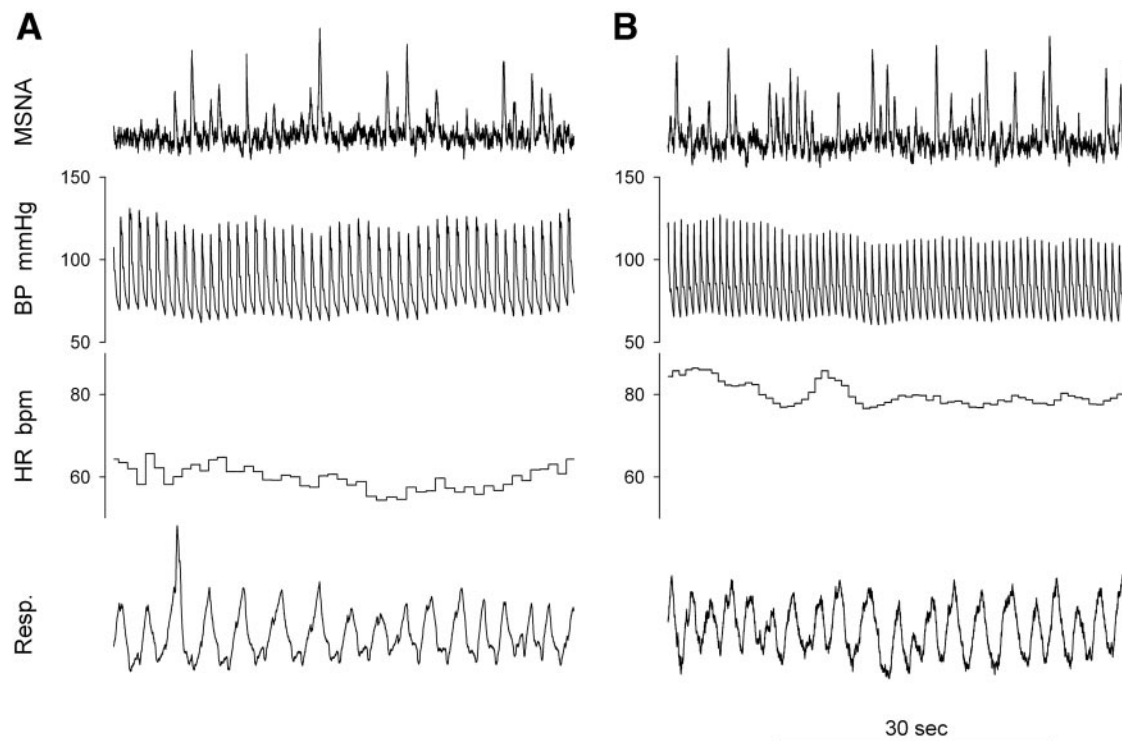


Fig. 1. Representative tracing of muscle sympathetic nerve activity (MSNA), arterial blood pressure (BP), heart rate (HR), and respiratory excursion (Resp) in normothermic (A) and heat stress (B) conditions.

method of normalization does not affect the spectral characteristics of MSNA and thus would not impact the interpretation of the present findings (26). Total MSNA was identified from burst area of the integrated neurogram and was measured on a beat-by-beat basis. If no MSNA burst was detected for a particular cardiac cycle, a zero value was assigned for this cardiac cycle. Beat-by-beat SBP and R-R interval were also recorded during the two periods of data collection. The respiratory trace was normalized when a value of 100 was assigned to the mean amplitude during the 6-min normothermic baseline period.

Beat-by-beat data series of R-R interval, SBP, and MSNA were interpolated (cubic spline) and resampled at 2 Hz. The respiratory trace in the same data segment was resampled at 2 Hz. The autopower spectra of the interpolated and resampled data were estimated via the Welch method (33). In both thermal conditions, data were subdivided into 256-point segments (128 s) with 50% overlap, windowed (Hanning method), transformed, and averaged. The LF spectral power

(0.03 to 0.15 Hz) and HF spectral power (0.15 to 0.45 Hz) of MSNA, R-R interval, and SBP were calculated from the autospectra. The LF/HF ratio of MSNA oscillatory components is a previously used and widely accepted index of MSNA power distribution that is independent of the units used to express MSNA (10, 11, 18, 22, 23). Moreover, this LF/HF ratio in resting normothermic subjects is highly reliable in repeated measurements (32). The frequency at the maximum point of the spectral density curve in the LF and HF ranges for the aforementioned variables was also identified.

Paired *t*-tests were used to assess differences between normothermic and heat stress conditions for all variables. *P* values <0.05 were considered significant. Values are expressed as means \pm SE.

RESULTS

Whole body heating significantly increased T_{sl} , skin blood flow, sweat rate, and heart rate (Table 1). These data verify the

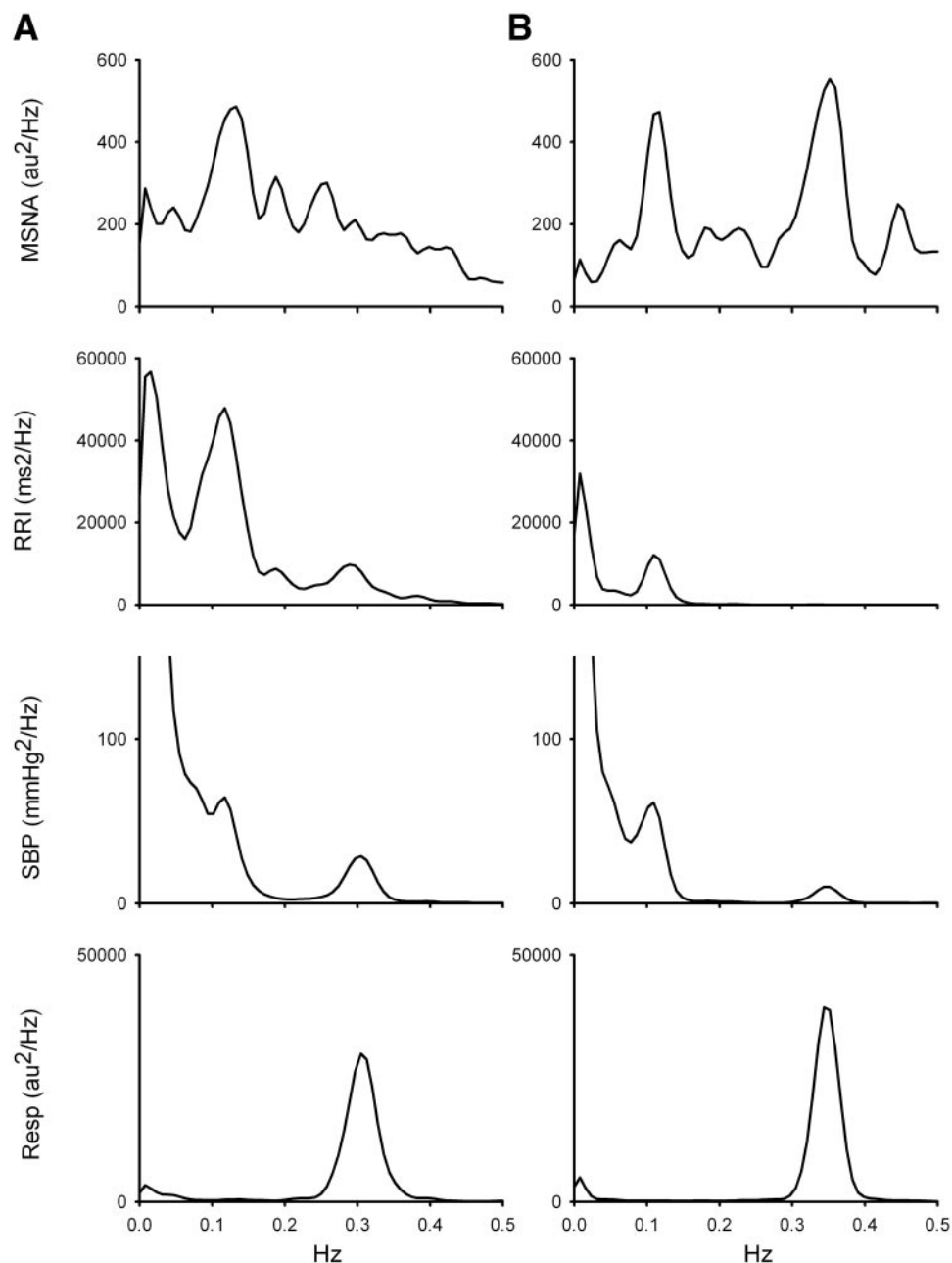


Fig. 2. Examples of autospectra of MSNA, R-R interval (RRI), systolic BP (SBP), and Resp in normothermic (A) and heat stress (B) conditions in a representative subject. See Table 2 for average heat stress-induced changes in spectral power of these variables.

Table 2. Spectral measurements of MSNA and hemodynamic variability in normothermia and heat stress conditions

	Normothermia	Heat Stress
MSNA		
Total power, au ²	63.5±8.3	80.6±9.0
LF, au ²	18.3±1.8	21.1±2.0
Freq, Hz	0.10±0.01	0.11±0.01
HF, au ²	40.5±6.5	55.1±6.7*
Freq, Hz	0.27±0.01	0.32±0.02*
LF/HF	0.49±0.04	0.41±0.04*
RR interval		
Total power, ms ²	2,509±364	803±135*
LF, ms ²	1,511±285	608±106*
Freq, Hz	0.09±0.01	0.10±0.01
HF, ms ²	908±162	156±35*
Freq, Hz	0.29±0.01	0.33±0.02*
LF/HF	1.71±0.30	6.08±1.38*
Systolic pressure		
Total power, mmHg ²	17.2±2.6	11.0±1.6*
LF, mmHg ²	14.6±2.5	9.4±1.5*
Freq, Hz	0.09±0.01	0.10±0.01
HF, mmHg ²	2.2±0.4	1.3±0.2*
Freq, Hz	0.29±0.01	0.33±0.02*
Respiration		
HF, au ²	1,177±85	1,532±120*
Freq, Hz	0.28±0.01	0.34±0.02*

Values are means ± SE. LF, low frequency; HF, high frequency. The absolute value of each component was computed as the integral of oscillatory components in LF (0.03–0.15 Hz) and HF (0.15–0.45 Hz) ranges. LF/HF, LF to HF ratio; Freq, the peak frequency for the component. **P* < 0.05, significantly different from normothermia condition.

subjects were in a heat-stressed condition. In addition, MSNA (expressed either as burst rate or total activity) increased significantly during whole body heating (Table 1 and Fig. 1). Mean blood pressure was unaffected by heat stress whereas respiratory rate was slightly, but significantly, elevated (Table 1).

Examples of the autospectra of MSNA, R-R interval, SBP, and respiratory activity from a representative subject are shown in Fig. 2. Whole body heating did not change total power or the LF oscillatory component of MSNA, whereas HF oscillatory component of MSNA was significantly elevated (Table 2). The combination of these responses resulted in the LF/HF ratio of MSNA oscillatory components being significantly reduced by the heat stress.

For R-R interval variability, the spectral power of both LF and HF oscillatory components, as well as total power, were significantly reduced by whole body heating, whereas the LF/HF ratio was elevated (Table 2). Moreover, spectral power of the LF and HF oscillatory components of SBP was significantly attenuated by the heat stress (Table 2).

The peak frequency of the LF spectral component for MSNA, R-R interval, and SBP was not altered by whole body heating, whereas the peak frequency of the HF oscillatory components of these variables increased in the heat stress condition. This elevated HF component is a reflective of the slight elevated respiratory rate during the heat stress.

DISCUSSION

The primary purpose of this study was to identify the effects of whole body heating on spectral characteristics of MSNA relative to spectral characteristics of SBP. The present data show that whole body heating increases the HF oscillatory

component of MSNA, does not change the LF component, and significantly decreases the LF/HF ratio of this variable. In contrast, whole body heating significantly reduced the LF and HF components of SBP. Taken together, these data show that heat stress-induced changes in MSNA do not parallel changes in SBP variability.

Consistent with previous observations (4, 6, 7, 20), in the present study, MSNA increased during the heat stress (see Table 1). In addition, heat stress reduced both R-R interval and SBP variability within the LF and HF ranges and increased the LF/HF components of R-R interval variability, which is consistent with our prior observation (5). Combined with the increase in MSNA, prior and present data suggest the sympathetic outflow to muscle and heart is elevated under heat stress conditions. However, it should be emphasized that effects of heat stress on spectral characteristics of recorded sympathetic nerve activity are limited to sympathetic activity innervating muscle. It is possible that spectral characteristics of sympathetic nerve activity to other organs, such as the heart, may respond differently to heat stress relative to direct recordings of MSNA.

As evident by this and our prior study (5), whole body heating reduces SBP variability within the LF range. Because heat stress increases mean MSNA, when expressed either as burst rate or total activity, the reduction in LF oscillation of SBP is unlikely to reflect a reduction in sympathetic modulation of vasomotor tone, as proposed by others (16, 21, 23). A possible mechanism for reduced LF oscillations in SBP could be due to reduced LF oscillations in MSNA despite an increase in mean MSNA with heating. However, in the present study, the LF component of MSNA variability did not significantly change after whole body heating. Therefore, the reduction in LF oscillation of SBP was not due to reduced LF oscillations of MSNA.

Under normothermic conditions, the LF component of SBP variability shows close correlation with the LF component of MSNA variability (23). However, during heat stress, this correlation deteriorates because there is an uncoupling between the LF components of MSNA and SBP variability under heat stress condition (see Table 2). One possible mechanism for this observation may be related to the effects of heat stress on postsynaptic adrenergic responsiveness. Previous studies (15, 17) demonstrated that vasoconstrictor responses to constant and bolus infusions of adrenergic agonists are impaired in heat stressed rats. Consistent with these findings, in humans, whole body heating attenuates systemic (7) and cutaneous (34) α -adrenergic vasoconstrictor responsiveness. Thus heat stress-induced impairment of vasoconstrictor responsiveness for a given neural signal (i.e., MSNA) may result in a reduction in LF spectral power of blood pressure despite a lack of change in LF spectral power of MSNA.

Whole body heating significantly decreased the ratio of LF/HF components of MSNA variability. The mechanism(s) resulting in the observed changes in MSNA spectral characteristics during the heat stress remain unknown. Previous studies (11, 23) show that sympathetic activation induced by vasoactive agents (e.g., nitroprusside) or head-up tilt is accompanied by a shift in the MSNA spectral power distribution toward the LF range, whereas sympathetic inhibition induced by phenylephrine infusion is accompanied by a MSNA spectral power shift toward the HF range (23). These findings led to the

conclusion that changes in LF component of MSNA variability are positively correlated with the change in sympathetic activity (11). However, in contrast to these observations, in the present study increases in mean MSNA due to whole body heating were not associated with increases in LF spectral power of MSNA, while HF spectral power of MSNA increased. Moreover, patients with heart failure have elevated MSNA (14) and reduced, or even absent, LF oscillations (1, 31). Thus it is likely that the aforementioned positive correlation between mean MSNA and LF spectral power (11, 23) is limited to acute baroreceptor loading and unloading in healthy individuals. Importantly, differences in the relationship between LF spectral power and mean MSNA in the present study relative to the aforementioned studies (11, 23) suggest that elevations in MSNA during heat stress are likely mediated by mechanisms other than baroreflexes; a finding consistent with our prior observation (4).

The present results show that whole body heating increases MSNA variability within the HF range. A possible mechanism resulting in this occurrence may be related to heat stress-induced alterations in respiration (3, 19). Respiratory rate increased slightly but significantly as a result of whole body heating (Table 1). Although tidal volume was not measured, spectral power of normalized respiratory trace increased significantly with the heat stress. Moreover, a prior study demonstrated that tidal volume increases in heated subjects (12). Thus both frequency and tidal volume is likely enhanced in heat stress conditions (3, 12, 19). Because respiration affects oscillations in MSNA via central mechanisms (2), changes in respiratory responses during heating may lead to the observed increase in HF spectral power of MSNA. Another possible explanation for this observation may be related to respiratory gating of sympathetic outflow (8, 9). This gating phenomenon is most apparent when sympathetic outflow is at an “usual level,” whereas it is weak or absent at the extremes of stimulation (8). In the normothermic condition, when MSNA burst frequency is relatively low, respiratory rhythms in MSNA may be weak or even absent in some individuals. However, when baseline MSNA increases, as is the case for the heat stress, the gating of MSNA by respiration may be intensified resulting in an elevated HF power of the MSNA.

In conclusion, this study shows that whole body heating does not alter the LF spectral component of MSNA, despite significant reductions in the LF spectral component of SBP and increases in mean MSNA. Moreover, heat stress increases the HF MSNA spectral component resulted in a significant reduction in the LF/HF ratio of MSNA variability. These changes in MSNA variability do not parallel changes in either SBP or heart rate variability. Two conclusions can be derived from these observations. First, the reduction in LF spectral component of SBP during a heat stress is unlikely related to spectral changes in MSNA. Second, when combined with the findings of others (11, 23), the present data support the hypothesis that increases in MSNA during a heat stress is unlikely to be entirely due to baroreceptor unloading.

ACKNOWLEDGMENTS

Present address for T. E. Wilson: Department of Biomedical Sciences, Southwest Missouri State University, 901 South National Avenue, Springfield, MO 65804.

GRANTS

This research project was funded by National Heart, Lung, and Blood Institute Grants HL-61388, HL-67422, and HL-10488 and by American Heart Association Grant 0225036Y.

REFERENCES

1. Ando S, Dajani HR, and Floras JS. Frequency domain characteristics of muscle sympathetic nerve activity in heart failure and healthy humans. *Am J Physiol Regul Integr Comp Physiol* 273: R205–R212, 1997.
2. Badra LJ, Cooke WH, Hoag JB, Crossman AA, Kuusela TA, Tahvanainen KU, and Eckberg DL. Respiratory modulation of human autonomic rhythms. *Am J Physiol Heart Circ Physiol* 280: H2674–H2688, 2001.
3. Cooper KE and Veale WL. Effects of temperature on breathing. In: *Handbook of Physiology. The Respiratory Section. Control of Breathing*. Bethesda, MD: Am. Physiol. Soc., 1986, sect. 3, pt. 2, chapt. 20, p. 691–702.
4. Crandall CG, Etzel RA, and Farr DB. Cardiopulmonary baroreceptor control of muscle sympathetic nerve activity in heat-stressed humans. *Am J Physiol Heart Circ Physiol* 277: H2348–H2352, 1999.
5. Crandall CG, Zhang R, and Levine BD. Effects of whole body heating on dynamic baroreflex regulation of heart rate in humans. *Am J Physiol Heart Circ Physiol* 279: H2486–H2492, 2000.
6. Cui J, Wilson TE, and Crandall CG. Baroreflex modulation of sympathetic nerve activity to muscle in heat-stressed humans. *Am J Physiol Regul Integr Comp Physiol* 282: R252–R258, 2002.
7. Cui J, Wilson TE, and Crandall CG. Phenylephrine-induced elevations in arterial blood pressure are attenuated in heat-stressed humans. *Am J Physiol Regul Integr Comp Physiol* 283: R1221–R1226, 2002.
8. Eckberg DL. The human respiratory gate. *J Physiol* 548: 339–352, 2003.
9. Eckberg DL, Nerhed C, and Wallin BG. Respiratory modulation of muscle sympathetic and vagal cardiac outflow in man. *J Physiol* 365: 181–196, 1985.
10. Furlan R, Magatelli R, Palazzolo L, Rimoldi A, Colombo S, and Porta A. Orthostatic intolerance: different abnormalities in the neural sympathetic response to a gravitational stimulus. *Auton Neurosci* 90: 83–88, 2001.
11. Furlan R, Porta A, Costa F, Tank J, Baker L, Schiavi R, Robertson D, Malliani A, and Mosqueda-Garcia R. Oscillatory patterns in sympathetic neural discharge and cardiovascular variables during orthostatic stimulus. *Circulation* 101: 886–892, 2000.
12. Gaudio R Jr and Abramson N. Heat-induced hyperventilation. *J Appl Physiol* 25: 742–746, 1968.
13. Halliwill JR. Segregated signal averaging of sympathetic baroreflex responses in humans. *J Appl Physiol* 88: 767–773, 2000.
14. Kingwell BA, Thompson JM, Kaye DM, McPherson GA, Jennings GL, and Esler MD. Heart rate spectral analysis, cardiac norepinephrine spillover, and muscle sympathetic nerve activity during human sympathetic nervous activation and failure. *Circulation* 90: 234–240, 1994.
15. Kregel KC and Gisolfi CV. Circulatory responses to vasoconstrictor agents during passive heating in the rat. *J Appl Physiol* 68: 1220–1227, 1990.
16. Malliani A, Pagani M, Lombardi F, and Cerutti S. Cardiovascular neural regulation explored in the frequency domain. *Circulation* 84: 482–492, 1991.
17. Massett MP, Lewis SJ, and Kregel KC. Effect of heating on the hemodynamic responses to vasoactive agents. *Am J Physiol Regul Integr Comp Physiol* 275: R844–R853, 1998.
18. Montano N, Cogliati C, Porta A, Pagani M, Malliani A, Narkiewicz K, Abboud FM, Birkett C, and Somers VK. Central vagotonic effects of atropine modulate spectral oscillations of sympathetic nerve activity. *Circulation* 98: 1394–1399, 1998.
19. Mortola JP and Gautier H. Metabolic-ventilatory interaction. In: *Regulation of Breathing*, edited by Dempsey JA and Pack AI. New York: Dekker, 1994, p. 1032–1045.
20. Niimi Y, Matsukawa T, Sugiyama Y, Shamsuzzaman AS, Ito H, Sobue G, and Mano T. Effect of heat stress on muscle sympathetic nerve activity in humans. *J Auton Nerv Syst* 63: 61–67, 1997.
21. Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, Sandrone G, Malfatto G, Dell’Orto S, Piccaluga E, Turiel M, Baselli G, Cerutti S, and Malliani A. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. *Circ Res* 59: 178–193, 1986.
22. Pagani M and Malliani A. Interpreting oscillations of muscle sympathetic nerve activity and heart rate variability. *J Hypertens* 18: 1709–1719, 2000.

23. **Pagani M, Montano N, Porta A, Malliani A, Abboud FM, Birkett C, and Somers VK.** Relationship between spectral components of cardiovascular variabilities and direct measures of muscle sympathetic nerve activity in humans. *Circulation* 95: 1441–1448, 1997.
24. **Rowell LB and O'Leary DS.** Reflex control of the circulation during exercise: chemoreflexes and mechanoreflexes. *J Appl Physiol* 69: 407–418, 1990.
25. **Stauss HM, Morgan DA, Anderson KE, Massett MP, and Kregel KC.** Modulation of baroreflex sensitivity and spectral power of blood pressure by heat stress and aging. *Am J Physiol Heart Circ Physiol* 272: H776–H784, 1997.
26. **Taylor JA, Williams TD, Seals DR, and Davy KP.** Low-frequency arterial pressure fluctuations do not reflect sympathetic outflow: gender and age differences. *Am J Physiol Heart Circ Physiol* 274: H1194–H1201, 1998.
27. **Taylor WF, Johnson JM, Kosiba WA, and Kwan CM.** Cutaneous vascular responses to isometric handgrip exercise. *J Appl Physiol* 66: 1586–1592, 1989.
28. **Vallbo AB, Hagbarth KE, Torebjork HE, and Wallin BG.** Somatosensory, proprioceptive, and sympathetic activity in human peripheral nerves. *Physiol Rev* 59: 919–957, 1979.
29. **Van De Borne P, Montano N, Narkiewicz K, Degaute JP, Malliani A, Pagani M, and Somers VK.** Importance of ventilation in modulating interaction between sympathetic drive and cardiovascular variability. *Am J Physiol Heart Circ Physiol* 280: H722–H729, 2001.
30. **Van de Borne P, Montano N, Narkiewicz K, Degaute JP, Oren R, Pagani M, and Somers VK.** Sympathetic rhythmicity in cardiac transplant recipients. *Circulation* 99: 1606–1610, 1999.
31. **Van de Borne P, Montano N, Pagani M, Oren R, and Somers VK.** Absence of low-frequency variability of sympathetic nerve activity in severe heart failure. *Circulation* 95: 1449–1454, 1997.
32. **Van de Borne P, Montano N, Zimmerman B, Pagani M, and Somers VK.** Relationship between repeated measures of hemodynamics, muscle sympathetic nerve activity, and their spectral oscillations. *Circulation* 96: 4326–4332, 1997.
33. **Welch PD.** The use of fast Fourier transform for the estimation of power spectra: a method based on averaging over short, modified periodograms. *IEEE Trans Audio Electroacoust* AU-15: 70–73, 1967.
34. **Wilson TE, Cui J, and Crandall CG.** Effect of whole-body and local heating on cutaneous vasoconstrictor responses in humans. *Auton Neurosci* 97: 122–128, 2002.

