

Detection of low- and high-frequency rhythms in the variability of skin sympathetic nerve activity

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Cogliati, Chiara, Renata Magatelli, Nicola Montano, Krzysztof Narkiewicz, and Virend K. Somers. Detection of low- and high-frequency rhythms in the variability of skin sympathetic nerve activity. *Am J Physiol Heart Circ Physiol* 278: H1256–H1260, 2000.—Spectral analysis of skin blood flow has demonstrated low-frequency (LF, 0.03–0.15 Hz) and high-frequency (HF, 0.15–0.40 Hz) oscillations, similar to oscillations in R-R interval, systolic pressure, and muscle sympathetic nerve activity (MSNA). It is not known whether the oscillatory profile of skin blood flow is secondary to oscillations in arterial pressure or to oscillations in skin sympathetic nerve activity (SSNA). MSNA and SSNA differ markedly with regard to control mechanisms and morphology. MSNA contains vasoconstrictor fibers directed to muscle vasculature, closely regulated by baroreceptors. SSNA contains both vasomotor and sudomotor fibers, differentially responding to arousals and thermal stimuli. Nevertheless, MSNA and SSNA share certain common characteristics. We tested the hypothesis that LF and HF oscillatory components are evident in SSNA, similar to the oscillatory components present in MSNA. We studied 18 healthy normal subjects and obtained sequential measurements of MSNA and SSNA from the peroneal nerve during supine rest. Measurements were also obtained of the electrocardiogram, beat-by-beat blood pressure (Finapres), and respiration. Spectral analysis showed LF and HF oscillations in MSNA, coherent with similar oscillations in both R-R interval and systolic pressure. The HF oscillation of MSNA was coherent with respiration. Similarly, LF and HF spectral components were evident in SSNA variability, coherent with corresponding variability components of R-R interval and systolic pressure. HF oscillations of SSNA were coherent with respiration. Thus our data suggest that these oscillations may be fundamental characteristics shared by MSNA and SSNA, possibly reflecting common central mechanisms regulating sympathetic outflows subserving different regions and functions.

autonomic; power spectra

MICRONEUROGRAPHIC MEASUREMENT of peripheral sympathetic nerve discharge has enabled direct intraneural recordings of sympathetic traffic to muscle blood ves-

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sels (muscle sympathetic nerve activity, MSNA) and to skin [skin sympathetic nerve activity, SSNA (12, 25)]. MSNA reflects the vasoconstrictor signal to the skeletal muscle vasculature. SSNA contains both vasoconstrictor and sudomotor fibers (11). Moreover, it has been reported recently that peroneal SSNA contains a vasodilator component, synchronous with vasomotor activity (21).

MSNA is acutely sensitive to blood pressure changes and is closely regulated by the arterial and cardiopulmonary baroreflexes (25). Hence the duration of each burst is limited by the cardiac cycle. SSNA bursts are broad based, sensitive to thermal stimuli, and regulate peripheral vasoconstriction or perspiration; mental stress and sensory stimuli elicit SSNA bursts with constant latency. The responses to environmental stimuli differ with respect to the target district, i.e., glabrous or hairy skin. In particular, it may be that SSNA from the tibial nerve is mainly mentally responsive, whereas SSNA from the peroneal nerve is partly thermally dependent and partly mentally responsive (11). Absolute measurements of SSNA are not altered by either arterial or cardiopulmonary baroreflexes (5, 8, 24). In pathophysiological conditions characterized by high MSNA, such as heart failure and hypertension, SSNA is not increased (6, 13).

MSNA and SSNA nevertheless have certain common characteristics. Cigarette smoking increases both MSNA and SSNA (16). During sleep, burst properties of MSNA resemble those of SSNA. Arousal stimuli during wakefulness activate SSNA but not MSNA. During sleep both SSNA and MSNA increase in response to an arousal stimulus. Both MSNA and SSNA are suppressed during light sleep. Based on these sleep-related characteristics, Takeuchi et al. (22) suggested that SSNA and MSNA may share common origins in the central nervous system.

Power spectral analysis of MSNA has provided important insights into central mechanisms governing MSNA variability (15, 18). Spectral analysis of MSNA revealed low frequency (LF, 0.03–0.15 Hz) and high frequency (HF, 0.15–0.40 Hz), almost identical to the oscillatory components present in the variability patterns of R-R interval and blood pressure (18). Although the LF oscillation in cardiovascular variability is modulated

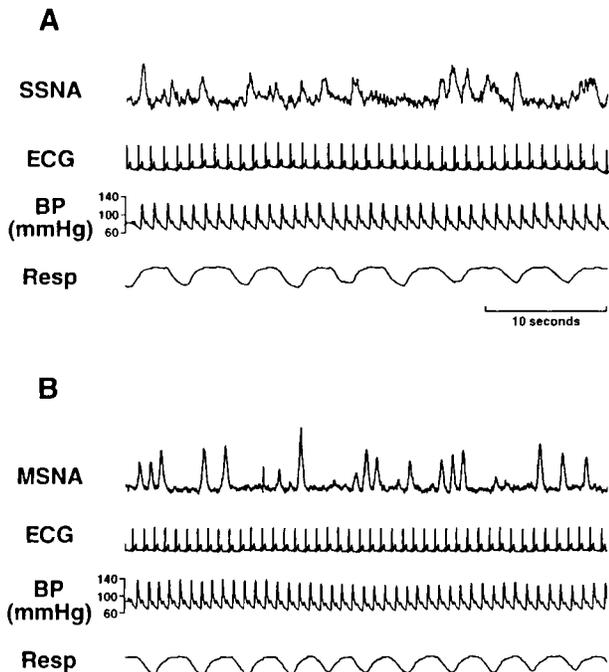


Fig. 1. *A*: recordings of skin sympathetic nerve activity (SSNA), electrocardiogram (ECG), blood pressure (BP), and respiration (Resp) in single subject during supine rest. *B*: measurements of muscle sympathetic nerve activity (MSNA), ECG, BP, and Resp in same subject. Spectral analyses of each of these recordings are shown in Fig. 2, *A* and *B*.

significantly by the arterial baroreflex, there is emerging evidence of an important central contribution to the LF oscillation (4, 14). The HF component of cardiovascular variability is dependent on the respiratory frequency.

A central contribution to the genesis of LF cardiovascular oscillations suggests the possibility that an LF component may conceivably be evident in SSNA variability. Because SSNA is also influenced by breathing (3, 8), with bursts of SSNA occurring during deep inspiration, an HF component may also be present in SSNA. Although LF and HF oscillations in skin blood flow have been described (2), it is not known whether these oscillations are secondary to the oscillatory properties of arterial pressure or a reflection of LF and HF oscillatory patterns in SSNA. Spectral analysis of SSNA has not been reported previously. We therefore tested the hypothesis that LF and HF oscillatory components are evident in SSNA, similar to the oscillatory components of MSNA.

METHODS

We studied 18 healthy male volunteers aged 30 ± 3 yr (range 22–35 yr). All volunteers were nonsmokers and were not on medications. These studies were approved by the Institutional Committee on Human Subjects in Research. Informed written consent was obtained from all subjects.

Subjects were studied during supine rest. We recorded electrocardiogram (ECG), beat-by-beat arterial pressure (Finapres), and respiration (strain gauge pneumotachometer). MSNA and SSNA were recorded from a sympathetic nerve fascicle in the peroneal nerve using sterile tungsten microelec-

trodes (microneurography) (12, 25). The electrodes were connected to a preamplifier, and the nerve signal was fed through a band-pass filter (range 700–2,000 Hz) and routed through an amplitude discriminator to a storage oscilloscope and loudspeaker. For recordings and analysis, the filtered neural signal was fed through a resistance-capacitance integrating network (RC circuit time constant, 0.1 s) to obtain a mean voltage display of the neural activity. Data were stored via an FM tape recorder (TEAC).

Both MSNA and SSNA signals were recorded on the same day in a quiet room at an ambient temperature of 25°C, in resting conditions with the subject breathing spontaneously, during two consecutive periods of 10 min each. MSNA was recognized as narrow-based sympathetic bursts that were absolutely linked to the cardiac cycle on a beat-by-beat basis, unaffected by a startle response, and increased during apnea. Eliciting SSNA afferent activity by gentle touching of the appropriate skin area was used to help in the identification of skin nerve fascicles. SSNA recordings were further identified as broad-based neural activity unrelated to the cardiac cycle, increased during arousal stimuli and deep inspiration, and unchanged by apnea.

Data were analyzed off-line after analog-to-digital conversion at a rate of 300 Hz per channel by use of a 12-bit converter (Data Translation; Marlboro, MA). The methodology and the software for data acquisition and spectral analysis have been described previously (10, 17). From the ECG signal a derivative-threshold algorithm provided the continu-

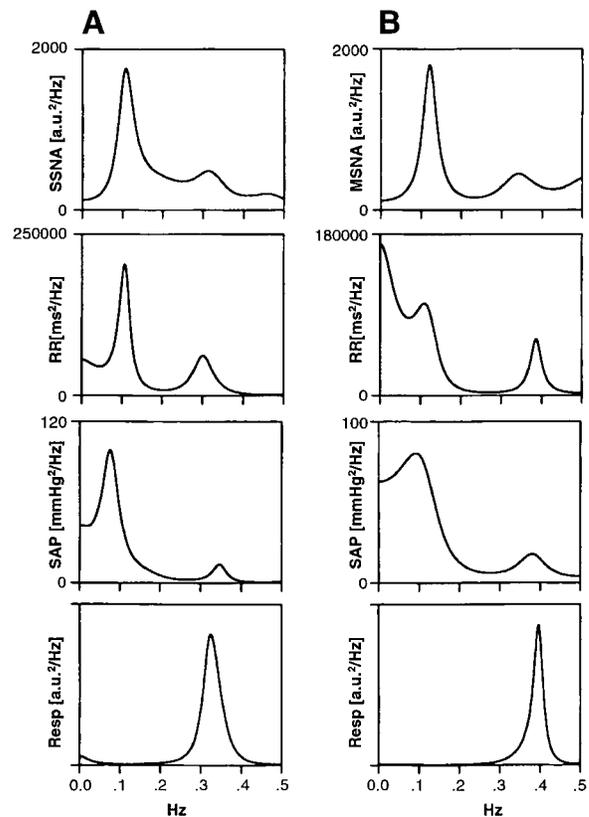


Fig. 2. *A*: spectral analysis of SSNA, R-R interval (R-R), systolic arterial pressure (SAP), and respiratory (Resp) variability. *B*: spectral analysis of MSNA, R-R, SAP, and Resp variability in same subject. Notice presence of 2 major oscillatory components (low frequency, around 0.1 Hz; high frequency, synchronous with the respiratory rate) in SSNA as well as in MSNA variability spectra. Absolute measurements of SSNA, MSNA, and hemodynamics for the 2 sessions in this subject are shown in Fig. 1, *A* and *B*.

Table 1. Spectral components of MSNA and SSNA variability. R-R interval and SAP variability are reported for each recording session

	LF, Hz	LF, nu	HF, Hz	HF, nu	LF/HF
MSNA	0.09 ± 0.006	36 ± 3	0.26 ± 0.019	43 ± 4	1.0 ± 0.25
R-R	0.09 ± 0.005	53 ± 5	0.26 ± 0.016	43 ± 5	1.7 ± 0.37
SAP	0.08 ± 0.006	59 ± 4	0.27 ± 0.016	35 ± 4	3.3 ± 1.29
SSNA	0.10 ± 0.007	33 ± 3	0.27 ± 0.01	50 ± 4	0.84 ± 0.14
R-R	0.10 ± 0.007	57 ± 5	0.27 ± 0.011	38 ± 5	2.38 ± 0.57
SAP	0.09 ± 0.004	55 ± 5	0.27 ± 0.009	36 ± 5	2.46 ± 0.76

Values are means ± SE; n = 18 volunteers. MSNA and SSNA, muscle and skin sympathetic nerve activity; SAP, systolic arterial pressure; LF, low frequency; HF, high frequency; nu, normalized units.

ous series of R-R intervals (tachogram). Systogram and diastogram were calculated from continuous arterial pressure signal, and the signal of respiration was sampled once for every cardiac cycle.

All variability series were analyzed by means of autoregressive parametric spectral and cross-spectral algorithms (17), which can automatically provide the number, central frequency, and associated power of each relevant oscillatory component. The very low-frequency component (VLF, 0.00–0.03 Hz) requiring specific algorithms and long data series was not addressed in this study and accordingly was considered to be a direct current component. Power in absolute as well as in normalized units was calculated for each oscillatory component of the signal. Normalized units were obtained by dividing the power of each component by the total variance from which the VLF had been subtracted and multiplying this value by 100 (22a).

Cross-spectral analysis was performed by means of bivariate autoregressive identification (1) and was used to compute a squared coherence function. Coherence (K^2) is a measure of the statistical link between two variability series at any given frequency and is expressed as a number between 1 and 0; only values of $K^2 \geq 0.5$ were considered significant.

RESULTS

Absolute measurements during the MSNA recording session and during the SSNA recording session in the same subject, together with spectral analysis of these recordings, are shown in Figs. 1 and 2, respectively. Average MSNA burst frequency was 27 ± 5 bursts/min, mean R-R interval was 973 ± 45 ms, and mean systolic arterial pressure (SAP) was 115 ± 2 mmHg. Spectral analysis of MSNA variability revealed LF and HF components in all subjects (Fig. 2, Table 1). Similar spectral profiles were also present in R-R and SAP

variability (Fig. 2). Consistent with earlier studies (1), cross-spectral analysis between MSNA and both R-R interval and SAP oscillatory components revealed a significant coherence ($K^2 > 0.5$) in the LF range for all except one subject. HF_{MSNA} oscillations correlated significantly with HF_{R-R} , HF_{SAP} , and HF of respiration in 16 of 18 subjects.

Average SSNA burst frequency was 12 ± 1 bursts/min; mean R-R interval and systolic blood pressure were 972 ± 40 ms and 113 ± 2 mmHg, respectively. In all subjects LF (0.1 ± 0.007 Hz) and HF (0.27 ± 0.01 Hz) spectral components were detectable in SSNA variability. Similar spectral profiles were present in R-R interval and SAP variabilities (Fig. 2, Table 1). Coherence function indicated a constant significant link ($K^2 > 0.5$) between LF oscillations of SSNA and the corresponding LF components of R-R interval and SAP variabilities, in all except one subject (Fig. 3). Similar results were observed for coherence between HF_{SSNA} and HF_{R-R} , whereas a significant coherence was observed between HF_{SSNA} and HF_{SAP} in 16 of the 18 subjects. In all but one subject HF_{SSNA} was coherent with respiratory HF.

DISCUSSION

The novel finding in this study is the detection of clear LF and HF rhythms in the variability of discharge of skin sympathetic outflow, similar to the LF and HF oscillations observed in MSNA variability and coherent with oscillations in R-R interval and systolic pressure. The presence of an HF component coherent with respiration is consistent with the reported loose coupling between SSNA and respiration (3, 8) and with the respiratory HF component observed in skin blood flow (2). The LF oscillatory component in SSNA is coherent with the LF in R-R interval and SAP and comparable to the LF oscillation in MSNA.

SSNA differs markedly from MSNA in terms of control mechanisms and function. Indeed, whereas MSNA is constituted by vasoconstrictor fibers, mostly regulated by baroreceptor and other related cardiovascular reflex mechanisms, SSNA contains vasomotor and sudomotor fibers responding to mental and thermal stimuli (11). Regional changes in SSNA in response to heat stress are not secondary to baroreflex regulation of blood pressure, because arterial and cardiopulmonary baroreceptor denervation does not alter vasomotor responses (19). A recent paper by Grassi et al. (7) reported that the alerting reaction associated with an

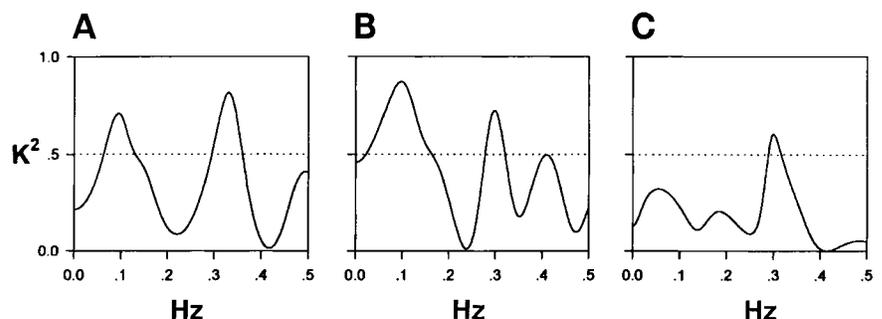


Fig. 3. Cross-spectral analysis between SSNA and R-R interval (A), SAP (B), and Resp (C) variability. Notice significant coherence ($K^2 > 0.5$) between major oscillatory components in SSNA-R-R, SSNA-SAP, and SSNA-Resp cross-spectra.

increase in blood pressure was characterized by MSNA inhibition and SSNA excitation. It also has been reported recently that SSNA recorded from the peroneal nerve contains a vasodilatory component synchronous with sudomotor nerve activity (21). Thus, whereas MSNA subserves a primary role in the regulation of cardiovascular variables, SSNA function is mainly related to thermoregulation.

Additional experiments providing simultaneous measurements of MSNA and SSNA and provocative stimuli are necessary to characterize the different mechanisms determining LF and HF oscillations in the two sympathetic outflows. It may be that the similarities in oscillatory characteristics we report in sequential measures of MSNA and SSNA may have been even more striking in terms of coherence had these measurements been obtained simultaneously. We speculate that the presence of an oscillatory pattern common to both neural pathways may act as a mechanism linking sympathetic outflows having different peripheral effects and thus contributing to a functional interaction between cardiovascular and thermoregulatory responses.

Important strengths of this study include the use of direct intraneural recordings of SSNA and MSNA in humans. Measurements of SSNA especially avoid the potential effects of systemic arterial pressure oscillations on skin blood flow measurements. Thus the LF and HF oscillations in SSNA represent fluctuations in the neural traffic per se and are not a manifestation of the oscillatory characteristics of R-R interval or arterial pressure.

With specific regard to the oscillatory components, whereas the HF component of SSNA may conceivably be explained by reflex or central effects of ventilation on SSNA, the LF component of SSNA cannot be explained as secondary to the arterial baroreflex, because baroreflex mechanisms do not alter SSNA (24). Indeed, even though baroreflex mechanisms are important in regulating MSNA and the LF component of cardiovascular variability (18), there is emerging evidence of an important central contribution to the LF cardiovascular oscillation (4). Although SSNA does not contribute to R-R interval or to blood pressure, the LF and HF components of SSNA are similar to and coherent with LF and HF oscillations in R-R interval and blood pressure. Thus common central mechanisms may contribute to the similarities in morphology and regulation of MSNA and SSNA, which are evident during sleep (22).

Our findings of oscillatory modulation in skin sympathetic neural traffic provides new insight into earlier studies of skin blood flow. The range and center frequency of the LF component of SSNA evident from the present study are compatible with physiological studies of the optimal frequency response of skin blood flow to SSNA stimulation. During SSNA stimulation, maximal responses of skin blood flow occur in the frequency range between 0.075 and 0.1 Hz (20). Thus the oscillations evident on spectral analysis of SSNA likely repre-

sent an important functional characteristic of neural vasomotor control of skin blood flow.

Because central command and arousal stimuli are potent mechanisms for increasing sympathetic outflow to skin (5, 7, 8, 23), it is reasonable to suppose that central mechanisms contribute importantly to SSNA and that the LF oscillations present in skin blood flow may be dependent not only on local oscillatory mechanisms (2) but also on central autonomic modulation. Prior studies of MSNA and SSNA have indeed identified several conditions where both MSNA and SSNA are increased, probably because of central activation (16, 22). Our data support the concept that these oscillations represent fundamental characteristics of neural mechanisms regulating efferent peripheral sympathetic nerve traffic.

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