Dissociation Between Muscle and Skin Sympathetic Nerve Activity in Essential Hypertension, Obesity, and Congestive Heart Failure

Guido Grassi, Manuela Colombo, Gino Seravalle, Domenico Spaziani, Giuseppe Mancia

Abstract—Essential hypertension, obesity, and congestive heart failure are characterized by an increase in muscle sympathetic nerve activity. Whether in these conditions skin sympathetic nerve activity is also increased has never been systematically examined, however. In 10 untreated mild essential hypertensive, 12 untreated normotensive obese, 10 mild (New York Heart Association class II) heart failure, and 10 normotensive lean healthy control subjects, we measured beat-to-beat arterial blood pressure (Finapres technique), body mass index, and postganglionic sympathetic nerve activity in skeletal muscle and skin areas (microneurographic technique, peroneal nerve). The muscle and skin nerve measurements were made in a randomized sequence. All data were obtained with the subject supine in a quiet, semidark environment at constant temperature over two periods of 30 minutes each, separated by a 20- to 30-minute interval. Blood pressure was increased only in hypertensive and body mass index only in obese subjects. Muscle sympathetic nerve activity quantified as bursts/min was markedly and significantly ($P < .01$) greater in essential hypertensive (33.3 ± 1.7), obese (42.2 ± 2.8), and congestive heart failure subjects (55.8 ± 4.3) in comparison with control subjects (23.9 ± 1.6). This was the case also for muscle sympathetic nerve activity, quantified as bursts per 100 heart beats. In contrast, skin sympathetic nerve activity (bursts per minute) was superimposable in hypertensive, obese, heart failure, and control subjects, its ability to increase being documented in all four groups by the marked response to an acoustic stimulus. Thus, in various diseases, muscle but not skin sympathetic activity is increased, with the sympathetic activation not being uniformly distributed over the whole cardiovascular system. (Hypertension. 1998;31[part 1]:64–67.)

Key Words: hypertension, essential ■ obesity ■ heart failure ■ sympathetic nervous system ■ reflex

Microneurographic studies have provided evidence that different mechanisms are involved in the regulation of muscle sympathetic nerve activity, ie, that while the former is under baroreflex and humoral control, the latter is mainly modulated by thermoregulatory and emotional factors.1–4 This provides a physiological background to the recent finding that in severe heart failure, ie, a condition known to be characterized by a baroreflex impairment and neurohumoral abnormalities,1–7 sympathetic activation can be detected via microneurography in the muscle but not in the skin nerve areas.8 It remains unsettled, however, whether the different behavior of muscle and skin sympathetic nerve activity reported in heart failure is peculiar to this condition or is a finding commonly observed in other abnormal states characterized by muscle sympathetic activation and reflex and humoral alterations.

To obtain conclusive information on this issue, we systematically used the microneurographic technique to assess muscle and skin nerve activity in (1) essential hypertensive patients in which several,9–12 although not all,13–15 studies have shown sympathetic activation in the skeletal muscle area to be associated with abnormalities in reflex cardiovascular control16, (2) obese subjects, known to be characterized by elevated muscle sympathetic nerve activity and baroreflex impairment17,18; and (3) mild congestive heart failure patients, in which muscle sympathetic nerve activation and baroreflex impairment are less in magnitude than in those with a documented severe heart failure state.6,7 The results show muscle sympathetic activation never to be accompanied by skin sympathetic overactivity, indicating a lack of sympathetic activation to skin in the presence of sympathetic activation to muscle and presumably visceral areas.19–22

Methods

Subjects

Our study was performed on a total of 42 outpatients. Ten subjects had mild essential hypertension, ie, (1) a diastolic blood pressure between 90 and 109 mm Hg at sphygmomanometric measurements performed in the outpatient clinic and (2) no history and/or clinical evidence of hypertension-related complications or major end organ damage. Twelve subjects had a normal blood pressure (ie, a diastolic value <90 mm Hg and a systolic value <140 mm Hg) but a marked increase in body mass index (always ≥30 kg/m²). Ten subjects had mild congestive heart failure, ie, dyspnea with strenuous physical exertion (New York Heart Association class II) and a moderate...
reduction of echocardiographic left ventricular ejection fraction (42.5±3.2%, mean±SEM). The remaining 10 subjects were healthy lean normotensive controls. Control, obese, and hypertensive subjects were taking no drug treatment, whereas heart failure patients were being treated with oral furosemide (40 mg daily), the other drug treatment (digitalis and/or angiotensin-converting enzyme inhibitor) having been withdrawn 4 days before the study. All subjects gave their informed consent to the investigation, and the study protocol was approved by the ethics committee of our institutions.

Measures

Blood pressure was measured by (1) a mercury sphygmomanometer, taking the first and fifth Korotkoff sounds to identify systolic and diastolic values, respectively and (2) a finger photoplethysmographic device (Finapres, Ohmeda 2300) capable of providing accurate and reproducible beat-to-beat systolic and diastolic values.23 Heart rate was continuously monitored by a cardiotachometer triggered by the R wave of an ECG lead. Respiration rate was monitored by a strain-gauge pneumograph positioned at the mid-chest level. Multihit recordings of efferent postganglionic sympathetic nerve activity to skeletal muscle (skeletal sympathetic nerve activity, MSNA) or skin (skin sympathetic nerve activity, SSNA) areas were obtained through a tungsten microelectrode inserted into the right or left peroneal nerve, as previously described.24 The nerve signal was amplified ×70 000, fed through a bandpass filter (700 to 2000 Hz), and integrated with a custom nerve activity analyzer (Bioengineering Department, University of Iowa). Integrated nerve activity was monitored by a loudspeaker, displayed on a storage oscilloscope (model 511A, Tektronix), and recorded with blood pressure, heart rate, and respiration rate on thermic paper by an ink polygraph (Gould 3800, Gould Instruments). The muscle or skin nature of sympathetic nerve activity was assessed by the criteria detailed in previous studies.1–4,24 For MSNA the criteria were that (1) a weak electrical stimulation through the microelectrode induced an involuntary muscle contraction but not paresthesias, (2) tapping or passive stretching of the muscle supplied by the nerve caused afferent mechanoreceptive impulses, and (3) the recording consisted of spontaneous pulse-synchronous bursts that increased during held expiration. For SSNA criteria were that (1) electrical stimulation through the microelectrode induced skin paresthesias without concomitant muscle contraction, (2) light skin touching evoked afferent nerve impulses, and (3) tapping or passive stretching of the muscle supplied by the nerve did not cause afferent mechanoreceptive impulses. Neurograms were accepted only if they did not show simultaneous SSNA and MSNA activity and if the signal-to-noise ratio was above 3. MSNA was quantified over each 30-minute period either as bursts per minute or as bursts per 100 heart beats, while SSNA was quantified as bursts per minute. The SSNA response to an acoustic stimulus (see below) was quantified by the percentage change in the amplitude of the bursts following the stimulus as compared to the mean amplitude of the spontaneous bursts occurring over the 3 minutes preceding the stimulus.

Protocol and Data Analysis

All subjects were studied in the morning after a light breakfast and an overnight abstinence from alcohol, smoking, and coffee consumption. The protocol of the study was as follows. (1) The subject was placed supine and fitted with devices to measure sphygmomanometric blood pressure, finger blood pressure, heart rate, and respiration rate. (2) After blood pressure was measured twice by mercury sphygmomanometer, the microelectrode was inserted into the peroneal nerve to obtain MSNA or SSNA, which was recorded together with finger blood pressure, heart rate, and respiration rate for 30 minutes. (3) The microelectrode was repositioned in the peroneal nerve fascicles to obtain the sympathetic nerve activity (MSNA or SSNA), which had not been obtained in the previous recording period, and was also recorded together with finger blood pressure, heart rate, and respiration rate for 30 minutes. MSNA was evaluated before SSNA in 23 subjects and after SSNA in 19 subjects. (4) At the end of the SSNA recording period, a 5-second acoustic signal provided by an alarm clock was delivered to check the SSNA ability to increase.7 The delivery of the stimulus was not anticipated by the subjects. Each

### Results

As shown in the Table, hypertensive and congestive heart failure subjects were somewhat older than control and obese subjects. Body mass index was increased only in obese subjects, and sphygmomanometric or finger blood pressures were increased only in hypertensive subjects. Heart rate was not significantly different in control, obese, and hypertensive subjects but slightly although significantly increased in heart failure patients. The respiration rate was superimposable in all four groups.

![Graph showing MSNA and SSNA average data](image)

**Fig 1.** Shows MSNA and SSNA average data. Compared with control values, MSNA was significantly greater in subjects with hypertension, obesity, and congestive heart failure, the

<table>
<thead>
<tr>
<th>Variable</th>
<th>C (n=10)</th>
<th>EH (n=10)</th>
<th>O (n=12)</th>
<th>CHF (n=10)</th>
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<tr>
<td>Age, yr</td>
<td>38.1±4.0</td>
<td>47.8±6.4*</td>
<td>39.0±3.1</td>
<td>48.0±4.9*</td>
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<td>BMI, kg/m²</td>
<td>25.3±1.1</td>
<td>26.1±1.3</td>
<td>37.8±2.2†</td>
<td>25.6±2.1</td>
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<td></td>
<td></td>
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<tr>
<td>Systolic</td>
<td>134.0±3.1</td>
<td>141.3±3.3*</td>
<td>136.5±3.4</td>
<td>132.7±2.4</td>
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<td>Diastolic</td>
<td>80.5±2.6</td>
<td>99.1±3.0†</td>
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<td>82.5±2.7</td>
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<tr>
<td>Finger BP, mm Hg</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>132.5±3.5</td>
<td>138.9±3.2</td>
<td>135.5±3.2</td>
<td>130.8±3.1</td>
</tr>
<tr>
<td>Diastolic</td>
<td>79.4±2.9</td>
<td>96.6±1.9†</td>
<td>81.7±3.0</td>
<td>80.7±3.3</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; Sphyg BP, sphygmomanometric blood pressure. Data are shown as mean±SEM. *P<.05, †P<.01 vs C.

Average of two measurements.
increase being minimal in the hypertensive, intermediate in the obese, and maximal in the congestive heart failure individuals.

In contrast, SSNA was not significantly different in the four groups. In each group, however, SSNA increased to a similarly marked extent in response to the acoustic stimulus. The increase was +105.5±24% in control subjects; +113.6±21% in hypertensive subjects; +117.2±30% in obese subjects, and +101.9±28% in heart failure patients.

Discussion

Our study agrees with previous data5,7,9–12,17,18 that in essential hypertensive, normotensive obese, and heart failure patients, (1) MSNA is increased compared with controls and (2) the increase is progressively greater from the hypertensive subjects to those with obesity and heart failure. It also shows, however, that SSNA is similar in these three conditions and that despite the ability to markedly raise in response to an appropriate stimulus, in no condition is this activity different from that of control subjects. This confirms the results obtained by Middlekauff et al16 by measuring MSNA and SSNA in patients with severe congestive heart failure. It further documents, however, that a pattern characterized by muscle but not skin sympathetic activation is not typical of just a single condition but is common to different conditions or diseases.

Our study does not clarify why sympathetic activation so often occurs in muscle areas while sparing the skin. We can speculate, however, that various mechanisms are involved. For example, in congestive heart failure and obesity, a mechanism could be the impairment of the arterial baroreflex associated with these conditions,6,7,16 because baroreflex restrains MSNA but has no effect on SSNA, which depends on emotional and thermoregulatory influences.3,4,28 In hypertension, on the other hand, the ability of baroreceptor stimulation and deactivation to respectively inhibit and enhance MSNA is largely unaltered.12,15 Thus, the mechanism could be the reflex originating from cardiac volume receptors, which was impaired in several patients with chronic blood pressure elevation,26 restraining MSNA without influencing SSNA.27 Finally, a common mechanism could be hyperinsulinemia because (1) insulin stimulates MSNA but has no effect on SSNA20 and (2) insulin resistance (ie, a condition leading to increased plasma insulin levels) is frequently detected in obesity, hypertension, and congestive heart failure.29–31

Two further questions should be addressed. First, does the sympathetic activity to the skin subserved by the peroneal nerve reflect the sympathetic activity to other skin areas? The sympathetic activity to most skin areas escapes measurement, but SSNA behavior has been shown to be similar when taken from the peroneal and brachial nerves.32 This indicates that the sympathetic activity to a single skin site reflects the sympathetic activity to other sites as well. Second, in hypertension, obesity, and heart failure does the sympathetic nerve activity to visceral areas reflect the increased MSNA or the unchanged SSNA? In congestive heart failure, the former is likely to be the case because when cardiac function declines the spillover rate of norepinephrine from the sympathoeffectector junctions soon increases in the general circulation, the renal vein, the coronary sinus, and the brain.19,21,33 In hypertension, on the other hand, some areas may behave like the skeletal muscle while others may behave like the skin, because in subjects with a blood pressure elevation, an increased spillover rate of norepinephrine from the sympathoeffectector junctions has been demonstrated from the kidney, the heart, and the brain, but not from the splanchic area.20,34 This appears to be the case also for obesity, in which an increase in norepinephrine spillover in the renal but not in the coronary circulation has been recently reported.22

References


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Hypertension. 1998;31:64-67
doi: 10.1161/01.HYP.31.1.64

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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