Independent Control of Skin and Muscle Sympathetic Nerve Activity in Patients With Heart Failure

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Background Sympathetic excitation characterizes heart failure, but the underlying mechanisms remain unknown. Abnormal baroreflex restraint of sympathetic neural outflow has been proposed, since baroreflexes are known to be abnormal in heart failure. The purpose of this study was to determine if sympathetic activation in humans with heart failure is limited to regions governed by the baroreflexes or is generalized to other regions free from baroreflex control.

Methods and Results We report the first direct recordings of skin sympathetic nerve activity (free from baroreflex control) in humans with heart failure and compare simultaneous skin and muscle (baroreflex-dependent) sympathetic peroneal nerve activity in six patients with severe heart failure (mean left ventricular ejection fraction, 0.19±0.06) and in six age-matched normal control subjects. Although muscle sympathetic nerve activity was markedly increased in heart failure patients (heart failure versus controls, 69±3 versus 21±2 bursts per minute; \(P<.001\)), skin sympathetic nerve activity was not increased (heart failure versus controls, 12±1 versus 15±1 bursts per minute; \(P=NS\)).

Conclusions The finding that skin sympathetic nerve activity in contrast to muscle sympathetic nerve activity is not increased in heart failure supports the concept that an altered reflex system, such as the baroreflexes, with nonuniform effects on muscle and skin sympathetic nerve activity, underlies sympathoexcitation in heart failure. (Circulation. 1994;90:1794-1798.)

Key Words • heart failure • baroreceptors • reflex

Sympathetic activation in patients with heart failure was first recognized over 30 years ago, but the mechanisms underlying this sympathoexcitation remain poorly understood. Initially adaptive, activation of the sympathetic nervous system may lead to adverse sequelae, including progressive heart failure and increased mortality. Increased central sympathetic outflow in patients with heart failure has been documented in skeletal muscle, cardiac, and renal beds, each of which is subject to baroreflex control. These uniform findings of sympathetic activation directed to tissues governed by the baroreflexes have prompted the concept that impaired baroreflex restraint underlies sympathetic activation. It is unknown if increased sympathetic neural outflow in heart failure is limited to regions governed by the baroreflexes or is generalized to all tissues—a distinction with mechanistic implications.

Skin sympathetic nerves that mediate vasoconstriction and sweating differ from skeletal muscle, cardiac, and renal sympathetic nerves in that they are not governed by the baroreflexes but are subject to other regulatory mechanisms such as thermoregulatory influences and central (or cognitive) stimuli. The determination of sympathetic nerve activity directed to skin would clarify whether sympathetic activation in heart failure is limited to regions subject to baroreflex restraint or is more generalized, implicating a nonbaroreflex-mediated mechanism.

We report the first direct recordings of skin sympathetic nerve activity in humans with heart failure and compare simultaneous skin and muscle sympathetic peroneal nerve activity in patients with severe heart failure and in age-matched normal control subjects.

Methods

After written informed consent was obtained, six heart failure patients and six age-matched normal control subjects were studied. The study protocol was approved by the UCLA Human Subjects Protection Committee. All studies were performed with subjects in the supine, postabsorptive state in a quiet, semidark, thermoneutral room (22°C). Control subjects were healthy as confirmed by normal physical examinations and were not taking medications. In heart failure patients, medications including vasodilators, diuretics, and digoxin were discontinued 24 to 36 hours before the study. All heart failure patients were hospitalized at the UCLA Medical Center for heart transplantation evaluation, which included echocardiography, cardiopulmonary exercise testing, and pulmonary artery catheterization performed within 24 hours of the research study.

Microneurography

Multiunit postganglionic sympathetic nerve activity was recorded using tungsten microelectrodes inserted selectively into skin or muscle fascicles of the peroneal nerve. The signals were amplified by a factor of 50,000 to 100,000 and bandpass-filtered (700 to 2000 Hz) (Nerve Traffic Analyzer,
model 662C-3, University of Iowa, Bioengineering). For recording and analysis, nerve activity was rectified and integrated (time constant, 0.1 second) to obtain a mean voltage display of sympathetic nerve activity that was recorded on paper (EVR-16 recorder, PPG).

A recording of skin sympathetic nerve activity was acceptable when (1) weak electrical stimulation through the electrode produced muscle twitch without paresthesias and (2) the mean voltage neurogram revealed narrow-based bursts (signal to noise ratio >2:1) that were not pulse synchronous and increased during arousal stimuli (eg, loud noise).10,19,21

A recording of muscle sympathetic nerve activity was acceptable when (1) weak electrical stimulation through the electrode produced muscle twitch without paresthesias and (2) the mean voltage neurogram revealed broad-based bursts (signal to noise ratio >2:1) that showed postextrasystolic potentiation but did not increase during arousal stimuli.10,19,21 Mixed skin and muscle sympathetic recordings were not accepted for analysis.

Sympathetic bursts were identified by inspection of the mean voltage neurogram. The data are presented as bursts per minute. Since muscle (in contrast to skin) sympathetic nerve bursts are pulse synchronous, exhibiting cardiac rhythmicity (attributed to baroreflex influences), and patients with heart failure tend to have a faster heart rate than healthy subjects, muscle sympathetic nerve activity is also reported as bursts per 100 heartbeats.10,19,21

Protocol
Subjects rested in the supine position. ECG leads were positioned on the chest, and an automated sphygmomanometer was placed on the upper arm (Dinamap, Criticon). The leg was positioned for microneurography. After identification of an acceptable skin or muscle sympathetic nerve recording site and a 5-minute rest period, sympathetic nerve activity was recorded for 5 to 10 minutes. Immediately after this recording, the microelectrode was repositioned in a different nerve fascicle innervating the other (skin or muscle) tissue bed, and the recording procedure was repeated. Muscle and skin sympathetic recordings were obtained in random order.

Statistical Analysis
Statistical analysis was performed using unpaired Student’s t tests. Probability values of <.05 were considered statistically significant. Values are presented as mean±SEM.

Results
Clinical Characteristics
Ages of heart failure patients and control subjects did not differ significantly (heart failure patients versus control subjects, 43±7 versus 35±6 years; P=NS). All patients had advanced (New York Heart Association class III-IV) heart failure. Etiology of heart failure was coronary artery disease in three patients and idiopathic dilated cardiomyopathy in three patients. As measured by echocardiography (n=6), quantified mean left ventricular ejection fraction was 0.19±0.06 and mean left ventricular end diastolic dimension was 79±6 mm. Pulmonary artery catheterization (n=6) revealed mean right atrial pressure of 8±3 mm Hg, mean pulmonary wedge pressure of 24±8 mm Hg, mean cardiac index of 2.1±0.4 L/min/m², and mean systemic vascular resistance of 1496±338 dyne·s/cm⁵. Mean peak oxygen consumption measured by cardiopulmonary exercise testing (n=5) was 11.7±1.7 mL/kg.

Microneurography Studies
Mean heart rate, blood pressure, and skin and muscle sympathetic nerve activity are compared between heart failure and control groups in the Table. Heart failure patients had higher resting heart rates compared with control subjects.

Values for skin and muscle sympathetic nerve activity in individual heart failure patients and control subjects are displayed in Fig 1. Muscle sympathetic nerve activity was markedly increased in heart failure patients compared with control subjects (heart failure patients versus control subjects, 69±3 versus 21±2 bursts per minute; P<.001). Similar results were found when muscle sympathetic nerve activity was calculated as bursts per 100 heartbeats (Table). There was no overlap for values of muscle sympathetic nerve activity between heart failure patients and control subjects (Fig 1).

In marked contrast to muscle sympathetic nerve activity, skin sympathetic nerve activity was not increased in heart failure patients compared with control subjects (heart failure patients versus control subjects, 12±1 versus 15±1 bursts per minute; P=NS; Fig 1 and Table). The minute-to-minute individual variation of skin sympathetic nerve activity as estimated by the standard deviation was low in both normal control subjects (range, 2.1 to 4.7 bursts per minute) and heart failure patients (range, 0.7 to 3.1 bursts per minute).

Representative skin and muscle neurograms from two heart failure patients and two control subjects are shown in Fig 2. During skin sympathetic recordings, an arousal stimulus such as a loud noise reproducibly increased heart rate, blood pressure, heart failure patients (bursts per minute) directed to muscle and skin compared in heart failure patients and in control subjects. Muscle sympathetic nerve activity is markedly increased in heart failure patients compared with control subjects (P<.001). In contrast, skin sympathetic nerve activity is not increased (P=NS). C represents control; HF, heart failure; and SNA, sympathetic nerve activity.

| Comparison of Hemodynamics and Sympathetic Activity in Heart Failure Patients and Control Subjects |
|-------------------------------------------------|-----------------|--------|
| HF Control | | P |
| Heart rate, beats per minute | 89±4 | 66±3 | .02 |
| Mean arterial pressure, mm Hg | 85±2 | 89±2 | NS |
| Muscle SNA, bursts per minute | 69±3 | 21±1 | <.001 |
| Muscle SNA, bursts per 100 heartbeats | 77±3 | 35±3 | .003 |
| Skin SNA, bursts per minute | 12±1 | 15±1 | NS |

HF indicates heart failure; SNA, sympathetic nerve activity. Values are mean±SEM.

Fig 1. Graph shows individual values of muscle and skin sympathetic nerve activity (bursts per minute) directed to muscle and skin compared in heart failure patients and in control subjects. Muscle sympathetic nerve activity is markedly increased in heart failure patients compared with control subjects (P<.001). In contrast, skin sympathetic nerve activity is not increased (P=NS). C indicates control; HF, heart failure; and SNA, sympathetic nerve activity.
elicited a burst of sympathetic neural activity in both heart failure patients and in normal control subjects. The ratio of muscle sympathetic nerve activity to skin sympathetic nerve activity (bursts per minute) was significantly greater in heart failure patients than in control subjects (heart failure patients versus control subjects, 6.8±0.5 versus 1.6±0.1; \( P=.01 \)).

**Discussion**

The major new finding in this study was that skin sympathetic nerve activity, in dramatic contrast to muscle sympathetic nerve activity, is not increased in patients with severe heart failure. This finding, which is consistent with intact central partitioning of skin and muscle sympathetic neural outflow in heart failure, supports the concept that baroreflex dysfunction underlies the sympathoexcitation in heart failure.

In normal humans, arterial and cardiopulmonary baroreflex regulation of skin and muscle sympathetic nerve activity is independent: Muscle sympathetic nerve activity is tightly controlled by the baroreflexes, whereas skin sympathetic nerve activity is largely free from baroreflex influences.\(^{17,20-24}\) Bini and colleagues\(^{25}\) reported that in normal subjects exposed to hyperthermic conditions, skin sympathetic nerve activity directed to sweat glands exhibited cardiac rhythmicity, a characteristic generally attributed to baroreflex influences. However, in further experiments in which the baroreflexes were engaged, no cardiac rhythmicity or baroreflex modulation of either skin sudomotor or vasomotor sympathetic activity was detectable.\(^{25}\) The investigators concluded that skin sympathetic nerve activity is not influenced by the baroreflexes and speculated that a common central pacemaker under certain conditions may influence both the heart and skin sympathetic activity. Vissing and colleagues\(^{24}\) investigated the cardiopulmonary baroreflex control of skin sympathetic nerve activity in normal subjects. No cardiac rhythmicity or baroreflex modulation of skin sympathetic nerve activity was observed, and these investigators concluded that skin sympathetic nerve activity is not subject to cardiopulmonary baroreflex regulation.\(^{24}\)

Substantial evidence in humans and animals with heart failure supports the concept that the baroreflexes are impaired in heart failure.\(^{13,15,16}\) Our findings of normal resting skin sympathetic activity but markedly increased muscle sympathetic activity provide direct evidence that sympathoexcitation in heart failure is not generalized. These findings of regional differences in sympathetic nerve activation in heart failure are in agreement with norepinephrine kinetic data, which show increased norepinephrine spillover in muscle, cardiac, and renal beds but not in the pulmonary bed in patients with heart failure.\(^4\) Our results are consistent with the concept of diminished baroreflex restraint underlying the sympathetic excitation characteristic of heart failure.

Although our findings support the hypothesis that an impairment of the arterial and cardiopulmonary baroreflexes leads to sympathoexcitation in heart failure, other reflex systems and humoral substances have nonuniform effects on muscle and skin sympathetic nerve activity and may also be contributory. For example, activation of the metaboreflex during exercise increases sympathetic nerve activity directed to muscle but not to skin.\(^{19}\) Similarly, hyperinsulinemia increases muscle but not skin sympathetic nerve activity.\(^{23}\) Skin and muscle sympathetic neural responses to other reflex systems such as the lung inflation reflex, chemoreflexes, and visceral reflexes or to other humoral substances such as angio-
tensin II are not fully delineated but may also be nonuniform.9,22,26 Further studies are necessary to identify which reflex system(s) or humoral substances contribute significantly to resting sympathetic excitation in heart failure.

Neurohormonal activation in heart failure appears to occur in stages and grades, with sympathetic activation preceding the activation of the renin-angiotensin system and greater activation of the sympathetic nervous system correlating with greater severity of heart failure.3,27-29 We studied patients referred for heart transplantation who had severe heart failure as indicated by their markedly abnormal resting hemodynamics, uniformly depressed left ventricular ejection fraction, New York Heart Association functional class III-IV symptoms, and poor exercise capacity. Even in this population with advanced heart failure, skin sympathetic nerve activation was not present.

Although skin sympathetic nerve activity is not increased at rest in normothermic heart failure patients, it remains unknown whether underlying control mechanisms of skin sympathetic outflow are intact. We did observe, however, that a brief arousal stimulus elicited a burst of skin sympathetic activity, which was reproducible and not obviously different in heart failure patients and normal control subjects.

In the present study, we made no attempt to determine if the skin sympathetic nerve activity is directed to cutaneous blood vessels, sweat glands, or both. Further investigations of these responses in heart failure would be of interest, since the clinical impression of cutaneous vasoconstriction in heart failure appears discrepant with our findings of normal skin sympathetic nerve activity. Possible explanations include an increased cutaneous sensitivity to circulating norepinephrine in heart failure or alternatively, nonsympathetically mediated mechanisms of cutaneous vasoconstriction in heart failure. Nonetheless, the nature of the neuroeffector responses do not impact on the implications of the findings in this study, since neither cutaneous vasoconstrictor nor sudomotor sympathetic activity is subject to baroreflex influences in resting, normothermic individuals.23,24 and the purpose of this study was to compare sympathetic nerve outflow directed to tissues that normally exhibit independent sympathetic control. We recorded skin sympathetic nerve activity from one region, a nonacral area of the lower extremity. It remains unknown whether our finding of normal skin sympathetic nerve activity in heart failure applies to all cutaneous regions.

Summary

Direct recordings of skin sympathetic nerve activity in humans with heart failure provide strong direct evidence that sympathetic activation in humans with heart failure is not uniform, sparing tissues free from baroreflex restraint. Identification and characterization of the abnormalities of regulation of sympathetic nerve activity, with attention focused on reflex systems or humoral substances that elicit nonuniform muscle and skin sympathetic neural responses, may provide further insights into the underlying mechanism of resting sympathoexcitation in humans with heart failure.

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