PATHOPHYSIOLOGY AND NATURAL HISTORY
CONGESTIVE HEART FAILURE

Direct evidence from intraneural recordings for increased central sympathetic outflow in patients with heart failure

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ABSTRACT Patients with heart failure have increased vascular resistance and evidence for increased neurohumoral drive. High levels of circulating norepinephrine are found in patients with heart failure, but it is not known whether they reflect increased sympathetic neural activity or result from altered synthesis, release, or metabolism of norepinephrine. We used microneurography (peroneal nerve) to directly record sympathetic nerve activity to muscle (mSNA) and also measured plasma norepinephrine levels in patients with heart failure and in normal control subjects. Our goal was to determine whether sympathetic nerve activity is increased in patients with heart failure and whether plasma norepinephrine levels correlate with levels of mSNA in heart failure. Resting muscle sympathetic nerve activity in 16 patients with moderate to severe heart failure (54 ± 5 bursts/min, mean ± SE) was significantly higher (p < .01) than the levels of activity in either nine age-matched normal control subjects (25 ± 4 bursts/min) or 19 "young" normal control subjects (24 ± 2 bursts/min). We found a significant correlation between plasma norepinephrine levels and mSNA (r = .73, p < .05). Neither mSNA nor plasma norepinephrine levels correlated with total systemic vascular resistance, cardiac index, left ventricular ejection fraction, or heart rate. However, both mSNA and plasma norepinephrine levels showed significant positive correlations (p < .05) with left ventricular filling pressures (r = .80, mSNA vs filling pressures; r = .82, norepinephrine levels vs filling pressures) and mean right atrial pressure. The results of the study provide the first direct evidence of increased central sympathetic nerve outflow in patients with heart failure and the first direct evidence that plasma norepinephrine levels show a reasonable correlation with sympathetic nerve activity to muscle in these patients. Furthermore, the data suggest that preload is an important determinant of SNA in these patients. Circulation 73, No. 5, 913-919, 1986.

A HALLMARK of advanced heart failure is high peripheral vascular resistance. Several neurohumoral factors may contribute to the increased vascular resistance, including increased activity of the renin-angiotensin system, elevated levels of arginine vasopressin, and increased activity of the sympathetic nervous system. The elevated plasma norepinephrine levels seen in patients with heart failure have been interpreted as evidence for a high sympathetic drive, and most studies have relied on measurements of plasma norepinephrine levels to monitor levels of sympathetic nerve activity in these patients. However, because of potential neurohumoral interactions in patients with heart failure it is not known whether the high levels of circulating norepinephrine result from increased sympathetic nerve activity, from facilitated release of norepinephrine from peripheral adrenergic nerve endings, or from altered synthesis or metabolism of norepinephrine.

We used microneurography of the peroneal nerve to directly record sympathetic nerve activity to muscle (mSNA) in patients with advanced heart failure and in normal control subjects to determine whether resting mSNA was increased in patients with heart failure. Plasma norepinephrine levels were also measured to...
determine whether they correlate with measured sympathetic nerve traffic in patients with heart failure. In addition, hemodynamic variables and indexes of cardiac function were measured to evaluate whether levels of sympathetic nerve activity reflect the severity of cardiac dysfunction in these patients.

Methods

Subjects

Patients. Sixteen patients with moderate-to-severe heart failure were studied. There were 11 men and five women, ages 24 to 79 years (55 ± 4 years, mean ± SE). In 14 of the 16 patients, microneurography was performed at the time of or immediately after cardiac catheterization. In the other two patients, microneurography was performed within 2 days after the catheterization. The patients were studied after they had been hospitalized for several days and were stable. Severity of cardiac disease ranged from class II and class IV by New York Heart Association functional classification. Table 1 shows the clinical characteristics and resting hemodynamic values for these 16 patients. Complete hemodynamic data are not available for patients A. R., J. V., and S. H., but these three patients had significant left ventricular dysfunction as evidenced by a cardiac index of 1.9 liter/min/m² for patient J. V. and S. H. and a left ventricular ejection fraction of 9% for patient A. R. Moderate-to-severe impairment of resting cardiac performance for the group of patients is indicated by the measured variables summarized in Table 1 (left ventricular ejection fraction 19 ± 2%, cardiac index 2.2 ± 0.1 liter/min/m², left ventricular filling pressure 22 ± 3 mm Hg, systemic vascular resistance 1626 ± 102 dyne·sec·cm⁻²; mean ± SE).

Ten patients had idiopathic dilated cardiomyopathy and six patients had secondary cardiomyopathy (one from hypertension, one from valvular heart disease, and four from ischemic heart disease). No patient was studied within 1 month of a myocardial infarction. Six patients had not received digitalis glycosides for at least 2 weeks, and in all patients other medications had been stopped at least 18 hr before the study. Four patients receiving digitalis glycosides at study had atrial fibrillation. All other subjects had normal sinus rhythm. All patients had normal electrolytes and blood counts.

Normal control subjects. Levels of resting sympathetic nerve activity were obtained in 28 normal subjects who were divided into two groups. Because of a previously reported slight tendency for increasing resting mSNA with age, nine subjects were age-matched controls. There were eight men and one woman in this group, ages 25 to 67 years (47 ± 5.0 years, mean ± SE). The second group comprised 19 "young" normal controls, ages 22 to 40 years (29 ± 1.3 years, mean ± SE). All control subjects had normal medical histories and normal physical examinations and none were receiving medications.

The research protocol was approved by the Human Subjects Review Committee and informed written consent was obtained from all patients and subjects.

Measurements. The left ventricular ejection fraction was determined by a resting gated radionuclide ventriculogram in 13 patients and by left ventricular angiography in one patient. During the microneurographic studies, the subjects were studied in the supine position. Heart rates (electrocardiogram), blood pressure (brachial or radial arterial cannula in the patients with heart failure and sphygmomanometry in normal control subjects), respiration (pneumograph), and resting mSNA (microneurography) were recorded on a direct-writing or ink jet recorder.

### TABLE 1
Clinical characteristics and resting hemodynamics of the patients with heart failure

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>NYHA functional class</th>
<th>LV ejection fraction (%)</th>
<th>HR (beats/min)</th>
<th>MAP (mm Hg)</th>
<th>CO (l/min)</th>
<th>CI (l/min/m²)</th>
<th>LV filling pressure (mm Hg)</th>
<th>SVR (dyne·sec·cm⁻²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. R.</td>
<td>69</td>
<td>IV</td>
<td>9</td>
<td>95</td>
<td>95</td>
<td>3.8</td>
<td>1.9</td>
<td>—</td>
<td>37⁸</td>
</tr>
<tr>
<td>J. V.</td>
<td>61</td>
<td>III</td>
<td>—</td>
<td>54</td>
<td>85</td>
<td>3.8</td>
<td>1.9</td>
<td>—</td>
<td>1536</td>
</tr>
<tr>
<td>S. H.</td>
<td>65</td>
<td>II</td>
<td>—</td>
<td>59</td>
<td>78</td>
<td>3.7</td>
<td>1.9</td>
<td>10⁶</td>
<td>1622</td>
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<tr>
<td>I. B.</td>
<td>67</td>
<td>III</td>
<td>25</td>
<td>99</td>
<td>88</td>
<td>3.1</td>
<td>2.0</td>
<td>29¹</td>
<td>1729</td>
</tr>
<tr>
<td>P. M.</td>
<td>51</td>
<td>II</td>
<td>10</td>
<td>77</td>
<td>78</td>
<td>5.0</td>
<td>2.8</td>
<td>13⁹</td>
<td>1168</td>
</tr>
<tr>
<td>B. K.</td>
<td>59</td>
<td>III</td>
<td>17</td>
<td>92</td>
<td>90</td>
<td>4.2</td>
<td>2.7</td>
<td>20⁴</td>
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<tr>
<td>B. M.</td>
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<td>III</td>
<td>20</td>
<td>72</td>
<td>89</td>
<td>4.2</td>
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<td>10⁴</td>
<td>1638</td>
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<td>D. S.</td>
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<td>14</td>
<td>95</td>
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<td>2.5</td>
<td>1.4</td>
<td>35⁶</td>
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<td>A. W.</td>
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<td>25</td>
<td>73</td>
<td>76</td>
<td>4.1</td>
<td>2.1</td>
<td>25⁴</td>
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<tr>
<td>T. M.</td>
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<td>III</td>
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<td>97</td>
<td>86</td>
<td>3.8</td>
<td>2.1</td>
<td>30⁶</td>
<td>1453</td>
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<td>K. K.</td>
<td>28</td>
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<td>20</td>
<td>82</td>
<td>72</td>
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<td>1.9</td>
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<tr>
<td>W. G.</td>
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<td>III</td>
<td>20</td>
<td>100</td>
<td>89</td>
<td>3.1</td>
<td>1.5</td>
<td>21⁴</td>
<td>2270</td>
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<tr>
<td>L. M.</td>
<td>75</td>
<td>IV</td>
<td>20</td>
<td>69</td>
<td>102</td>
<td>3.2</td>
<td>1.9</td>
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<td>1750</td>
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<td>34</td>
<td>121</td>
<td>122</td>
<td>4.2</td>
<td>2.4</td>
<td>40⁴</td>
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<tr>
<td>H. M.</td>
<td>45</td>
<td>II</td>
<td>15</td>
<td>112</td>
<td>84</td>
<td>5.9</td>
<td>2.7</td>
<td>18⁶</td>
<td>1052</td>
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<tr>
<td>J. J.</td>
<td>38</td>
<td>II</td>
<td>21</td>
<td>87</td>
<td>99</td>
<td>6.8</td>
<td>3.2</td>
<td>6⁴</td>
<td>1141</td>
</tr>
<tr>
<td>Mean</td>
<td>55</td>
<td>19</td>
<td>85</td>
<td>89</td>
<td>4.1</td>
<td>2.2</td>
<td>22</td>
<td>1626</td>
<td></td>
</tr>
<tr>
<td>SE</td>
<td>4.1</td>
<td>1.72</td>
<td>4.12</td>
<td>2.99</td>
<td>0.29</td>
<td>0.13</td>
<td>2.67</td>
<td>101</td>
<td></td>
</tr>
</tbody>
</table>

HR = heart rate; MAP = mean arterial pressure; CO = cardiac output; CI = cardiac index; SVR = systemic vascular resistance.

Filling pressure as pulmonary capillary wedge pressure.

Filling pressure as left ventricular end-diastolic pressure.
For the patients with heart failure, right heart catheterizations were performed via the subclavian vein or the groin. Cardiac output was measured by the thermodilution technique in 13 patients and by green dye curves in two patients. Baseline hemodynamic values were recorded and systemic vascular resistance (dyne-sec-cm⁻²) was calculated as (mean arterial pressure minus right atrial pressure)/(cardiac output) × 80. In 12 patients left ventricular filling pressures were determined by a balloon catheter positioned in the pulmonary wedge position and in three patients by a catheter in the left ventricle.

Venous blood samples for norepinephrine levels were obtained from 10 patients via the proximal port of a triple-lumen Swan-Ganz catheter, positioned with its distal tip in the pulmonary artery, while simultaneous sympathetic nerve recordings were being obtained. The samples were collected in prechilled heparinized tubes and immediately placed on ice, then centrifuged at 4°C. Norepinephrine levels were assayed with the high-pressure liquid chromatographic technique with an electrochemical detector (SmithKline Bio-Science Laboratories, Van Nuys, CA). For this laboratory, duplicate measurements of plasma norepinephrine showed a coefficient of variation of 10.0% for a mean level of 162 pg/ml and a coefficient of variation of 9.1% for a mean level of 662 pg/ml. The assay is sensitive to 10 pg/ml. Normal laboratory values for norepinephrine in supine subjects are 110 to 410 pg/ml.

Microneurography. Multunit recordings of sympathetic nerve activity were obtained from a muscle fascicle in the right or left peroneal nerve posterior to the fibular head. The recordings were made with tungsten microelectrodes 200 μm in diameter in the shaft, tapering to an uninsulated tip of 1 to 5 μm. A reference electrode was inserted subcutaneously 1 to 3 cm from the recording electrode. The electrodes were connected to a preamplifier with a gain of 1000 and an amplifier with a gain of 50. The neural activity was fed through a bandpass filter (700 to 2000 Hz). For audio monitoring during the experiment, the filtered neurogram was passed into an amplitude discriminator to improve signal-to-noise ratio. For recording and analysis, the filtered neurogram was fed through a resistance-capacitance integrating network (time constant 0.1 sec) to obtain a mean voltage display of neural activity.

Figure 2 shows representative mean voltage neurograms from three normal subjects. The neurograms represent multifiber recordings. Nerve action potentials from the multifiber recordings were rectified and then integrated to produce the mean voltage display. A burst therefore represents a summation of nerve action potentials from multiple fibers.

Three criteria were used for identification of an acceptable recording of sympathetic nerve activity from a nerve fascicle to muscle. First, weak electrical stimulation (1 to 3 V, 0.2 msec, 1 Hz) through the electrode in the peroneal nerve elicited involuntary muscle contraction but not paresthesias. Second, tapping or stretching the muscles and tendons supplied by the impaled fascicle elicited afferent mechanoreceptor discharges, whereas stroking the skin in the distribution of the peroneal nerve did not evoke afferent discharges. Third, the neurogram revealed spontaneous, pulse-synchronous bursts characteristic of mSNA. Evidence that such activity represents efferent sympathetic nerve activity has been obtained from earlier studies and includes (1) interruption of the activity by local nerve block proximal but not distal to the recording site, (2) elimination of the activity by ganglionic blockade, and (3) conduction velocity approximating 1 m/sec, which is characteristic of sympathetic C fibers.

Data analysis. After determining that a suitable and stable recording site had been obtained, recordings of resting mSNA were obtained and analyzed. Sympathetic bursts were identified by inspection of the mean voltage neurogram. Four to 6 min of resting mSNA were averaged for each subject. Sympathetic nerve activity is expressed as bursts per minute and bursts per 100 heart beats.

Analysis of 29 microneurographic tracings independently by two of the authors (W. N. L. and A. L. M.) revealed an interobserver variability of 5.0 ± 1.7% (mean ± SE). The intraobserver variability for this technique is 4.3 ± 5.2%. Previous studies have shown that microneurographic recordings of mSNA are reproducible. Simultaneous recordings from two muscle nerves showed a remarkable similarity, with average differences in burst frequency of less than 6%. Values of resting mSNA during an experimental session and values for resting mSNA for a given subject studied on different days were quite similar, with an average variability in both cases of less than 10%.

Statistical analysis. Two-tailed t tests and analysis of variance for the three groups were used for determination of group differences. Analysis by two-variable linear regression was used to evaluate correlations between resting sympathetic nerve activity or plasma norepinephrine levels and hemodynamic variables and between sympathetic nerve activity and plasma norepinephrine levels. All statistical analyses were performed with the Clinical Research Center’s CLINFO computer statistical software package (BBN Software Products Corp. Cambridge, MA). Differences were considered significant for p < .05. Data are presented as mean ± SE.

Results

Resting mSNA was elevated in patients with heart failure compared with either the age-matched normal control group or the “young” normal control group. Resting mSNA for the patients with heart failure was 54 ± 5 bursts/min in contrast to 25 ± 4 bursts/min for the age-matched control subjects (p < .01) and 24 ± 2 bursts/min for the “young” control subjects (p < .01, figure 1). Figures 2 and 3 show representative recordings from normal control subjects and patients with heart failure and illustrate the striking differences observed in resting mSNA between the groups. Whereas the sympathetic bursts occurred intermittently in normal subjects, patients with heart failure frequently had a burst of sympathetic activity with almost every heart beat.

Differences in resting sympathetic nerve activity between the patients with heart failure and the normal control subjects could not be attributed to differences in heart rates. Although as a group the patients with heart failure had higher heart rates than control subjects (85 ± 4 vs 71 ± 4 vs 65 ± 2 beats/min, heart failure vs age-matched control vs “young” normal control), when the sympathetic nerve activity was expressed in bursts per 100 heart beats for each group, it was still significantly higher in patients with heart failure as compared with either control group (65 ± 6 vs 36 ± 7 vs 38 ± 3 bursts/100 beats, heart failure vs age-matched control vs “young” normal control, p < .05 heart failure vs either control, figure 1).

Analysis of resting levels of mSNA for the patients
with heart failure in relation to their heart rate, blood pressure, cardiac index, or left ventricular ejection fraction failed to identify any significant correlations. However, mSNA showed a significant positive correlation with indexes of cardiac preload. Figure 4 shows a significant correlation between mSNA and left ventricular filling pressures (n = 15, r = .798, p < .001). Mean right atrial pressures also showed a correlation with sympathetic nerve activity (mSNA vs right atrial pressure, n = 16, r = .595, p < .05). A linear regression of total systemic vascular resistance in relation to resting mSNA in the patients with heart failure failed to show a significant correlation (n = 15, r = .375, p = .17).

A significant correlation between plasma norepinephrine levels and resting mSNA was found in the patients with heart failure (norepinephrine = -219 + 14.4 × mSNA, n = 10, r = .726, p = .02, figure 5). Like mSNA, plasma norepinephrine levels also failed to correlate with heart rate, blood pressure, cardiac index, or left ventricular ejection fraction in the patients with heart failure. However, as with mSNA, plasma norepinephrine levels did correlate with left ventricular filling pressures and right atrial mean pressures (norepinephrine vs filling pressure, n = 10, r = .818, p < .01; norepinephrine vs right atrial pressure, n = 16, r = .595, p < .05).

**Discussion**

This study provides the first direct evidence that central sympathetic nerve outflow is increased in patients with heart failure. The study illustrates several points. First, the differences in resting mSNA between patients with heart failure and normal control subjects were striking and not subtle. Second, the level of resting mSNA correlated with ventricular filling pressures in the patients with heart failure but not with other indexes of cardiac dysfunction. Third, resting levels of mSNA failed to correlate with elevated levels of total systemic vascular resistance in the patients with heart failure. Fourth, in the resting state in patients with heart failure, plasma norepinephrine levels correlated with levels of mSNA.

The increased vascular resistance in patients with advanced heart failure is associated with increased circulating levels of renin, vasopressin, and norepinephrine. The circulating norepinephrine levels have been interpreted as a marker of increased sympathetic nerve activity. Additional indirect evidence for increased sympathetic activity in patients with heart failure is provided by the finding that α-adrenergic blockade results in a greater increase in limb blood flow at rest in patients with cardiac failure than in normal subjects and that patients with chronic heart
PATHOPHYSIOLOGY AND NATURAL HISTORY—CONGESTIVE HEART FAILURE

The recordings of mSNA in our patients with heart failure provide direct evidence for increased central sympathetic outflow in these patients. The mechanisms for the increase in sympathetic nerve activity were not established in this study and we can only speculate on potential mechanisms. First, mSNA is normally under baroreceptor modulation, and studies have found evidence of baroreceptor dysfunction in patients with heart failure. Therefore, one could speculate that the increased sympathetic activity in heart failure is in part secondary to impairment of the normal inhibitory baroreceptor modulation of central sympathetic outflow. Second, studies in animals indicated exaggerated sympathoadrenal responses to exercise.

However, it is not known whether the high levels of circulating norepinephrine in patients with heart failure truly reflect increased sympathetic neural activity. In normal subjects, Wallin et al. demonstrated a correlation between plasma levels of norepinephrine and resting mSNA as measured by microneurography. However, this correlation between sympathetic nerve activity and plasma norepinephrine levels cannot be assumed for patients with heart failure because of potential interactions between the humoral and peripheral neural mechanisms. For example, angiotensin II stimulates the synthesis of norepinephrine in nerve terminals and facilitates norepinephrine release. Because there is increased activity of the renin-angiotensin system in patients with heart failure, the increased circulating norepinephrine levels could represent increased release of transmitter from peripheral adrenergic nerve endings rather than increased sympathetic nerve activity. In addition, plasma concentrations of norepinephrine are determined in part by its rate of clearance from the circulation and not solely by the rate of norepinephrine release. Decreased cardiac output in patients with heart failure may alter clearance rates for norepinephrine.

The recordings of mSNA in our patients with heart failure provide direct evidence for increased central sympathetic outflow in these patients. The mechanisms for the increase in sympathetic nerve activity were not established in this study and we can only speculate on potential mechanisms. First, mSNA is normally under baroreceptor modulation, and studies have found evidence of baroreceptor dysfunction in patients with heart failure. Therefore, one could speculate that the increased sympathetic activity in heart failure is in part secondary to impairment of the normal inhibitory baroreceptor modulation of central sympathetic outflow. Second, studies in animals indicated exaggerated sympathoadrenal responses to exercise.
cate that activation of arterial chemoreceptors by hypoxemia is a potent stimulus to sympathetic activity. However, it is unlikely that increased chemoreceptor stimulation for hypoxemia played a significant role in the increased mSNA in these patients, since arterial blood samples during the study revealed oxygen saturations of greater than 93% in six patients with high mSNA. Third, activation of chemically sensitive muscle afferents during muscle contraction is a potent stimulus to mSNA. However, muscle afferents are probably not responsible for increases in sympathetic drive in these patients, since they were studied at rest. Fourth, central neural actions of central humoral agents such as angiotensin II could be a possible mechanism for the increased sympathetic nerve activity.

In this study, the severity of left ventricular dysfunction did not correlate with the level of mSNA. Several studies have demonstrated a modest correlation between circulating norepinephrine levels and the degree of ventricular dysfunction, although a recent study found no significant correlation between plasma norepinephrine levels and indexes of cardiac function in 63 patients with heart failure. We did not find a significant correlation between resting mSNA and indexes of left ventricular function such as left ventricular ejection fraction or cardiac index, but we did find a significant positive correlation between mSNA and left ventricular filling pressures (figure 4). The mechanism and significance of this finding is not clear. Recently a positive correlation was found between muscle sympathetic activity and the relative central blood volume in normal subjects (Manting, Sundlöf, and Wallin: unpublished observations). The interpretation of the two sets of findings (which may be related) is unclear, but one could speculate that the degree of distention of cardiopulmonary vascular structures is related to the level of muscle sympathetic activity at rest. However, although one could speculate that higher filling pressures may be a factor contributing to the higher levels of muscle sympathetic activity, conversely one could also argue that increased sympathetic activity and high circulating catecholamine levels are responsible for decreased venous capacitance and a secondary rise in filling pressures.

We did not find a significant correlation between resting mSNA and total systemic vascular resistance. The lack of correlation between mSNA and systemic vascular resistance may relate to our sample size or it may reflect the variability in regional vascular resistances and/or the multifactorial basis for the high total systemic vascular resistance. Further insight into these issues will require correlation of mSNA and limb vascular resistance in a large number of patients with heart failure.

Because most studies of sympathetic mechanisms in heart failure have relied on measurements of plasma norepinephrine levels, we might comment on the relative merits and limitations of using norepinephrine levels vs microneurography for the evaluation of sympathetic activity. Microneurography provides a direct measure of sympathetic nerve activity and is particularly valuable for dynamic measurements of sympathetic nerve activity. Sympathetic outflow to different tissues is not homogeneous. Sympathetic nerve recordings from skin and muscle sites show clear differences in the temporal patterns of sympathetic bursts in both the resting state and in the reflex mechanisms controlling the amount of neural activity. For example, a given maneuver may cause opposite responses in skin and muscle sympathetic nerve activity. Because sympathetic outflow is differentiated, the nerve recordings are particularly useful to study impulse traffic to either skin or muscle nerve branches, thereby providing insight into specific sympathetic control mechanisms for these regional circulations. However,
microneurography does not differentiate neural influences from prejunctional and postjunctional neural and hormonal interactions.

Norepinephrine levels, on the other hand, do not measure sympathetic activity directly but instead reflect the net effects of both central and peripheral influences on the sympathetic nervous system and are influenced by neuronal uptake and metabolic degradation rates. The importance of these factors vary from tissue to tissue, and measured norepinephrine spillover rates and clearance rates vary considerably between different organ circuits. Thus plasma levels of norepinephrine represent a complex index of sympathetic activity that is best interpreted in combination with sympathetic nerve recordings. The reasonable correlation between resting mSNA and plasma norepinephrine levels in our patients with heart failure is consistent with the suggestion that a large percentage of the circulating norepinephrine comes from skeletal muscle.

In summary, we employed direct intraneural recordings to demonstrate that central sympathetic nerve outflow to muscle is increased in patients with heart failure. Plasma norepinephrine levels demonstrated a reasonable correlation to levels of mSNA in these patients. Levels of mSNA showed a positive correlation with ventricular preload, suggesting that ventricular preload may be a determinant of sympathetic nerve activity in patients with heart failure. The mechanisms responsible for the increased sympathetic nerve activity in patients with heart failure are still speculative, and the relative importance of the neural vs humoral factors responsible for the high vascular resistance has not been clearly established.

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References
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