Studies performed in the past few years have shown that the sympathetic activation that characterizes the essential hypertensive state is more pronounced if hypertension is associated with cardiac alterations, eg, left ventricular hypertrophy or heart failure.¹–⁵ No information exists, however, on whether this is the case also for left ventricular diastolic dysfunction. In 17 untreated hypertensive subjects with left ventricular diastolic dysfunction (age: 47.7±2.9 years, mean±SEM), we measured sympathetic nerve traffic (microneurography), heart rate (ECG), and beat-to-beat arterial blood pressure (Finapres) at rest and during baroreceptor deactivation and stimulation. Data were compared with those collected in 20 age-matched normotensive and 20 hypertensive subjects without a diastolic function impairment. Muscle sympathetic nerve traffic values were markedly and significantly greater in the 2 hypertensive groups than in the normotensive one (55.3±1.2 and 71.2±1.6 versus 41.7±1.0 bursts per 100 heartbeats, respectively; P<0.01 for both). For a similar blood pressure elevation, however, the sympathetic nerve traffic increase was significantly greater in patients with than without left ventricular diastolic dysfunction (+28.9%; P<0.05). In the population as a whole, muscle sympathetic nerve traffic was significantly and inversely related to various echocardiographic indices of diastolic function. Although baroreflex-heart rate control was significantly attenuated in the 2 hypertensive groups, baroreflex-sympathetic modulation was impaired only in those with diastolic dysfunction. These data provide the first evidence that, in hypertension, activation of the sympathetic nervous system may contribute not only at the blood pressure elevation but also at the development of left ventricular diastolic dysfunction. The sympathetic overactivity, which is likely to be related to the baroreflex impairment, may account for the increased cardiovascular risk characterizing diastolic dysfunction. (Hypertension. 2009;53:205-209.)

Key Words: nervous system, sympathetic | baroreceptors | hypertension | diastole | reflex

Sympathetic and Baroreflex Cardiovascular Control in Hypertension-Related Left Ventricular Dysfunction

Guido Grassi, Gino Seravalle, Fosca Quarti-Trevano, Raffaella Dell’Oro, Francesca Arenare, Domenico Spaziani, Giuseppe Mancia

Abstract—The sympathetic overdrive that characterizes essential hypertension is potentiated when left ventricular hypertrophy or congestive heart failure is detected. No information exists, however, on whether this is the case also for left ventricular diastolic dysfunction. In 17 untreated hypertensive subjects with left ventricular diastolic dysfunction (age: 47.7±2.9 years, mean±SEM), we measured sympathetic nerve traffic (microneurography), heart rate (ECG), and beat-to-beat arterial blood pressure (Finapres) at rest and during baroreceptor deactivation and stimulation. Data were compared with those collected in 20 age-matched normotensive and 20 hypertensive subjects without a diastolic function impairment. Muscle sympathetic nerve traffic values were markedly and significantly greater in the 2 hypertensive groups than in the normotensive one (55.3±1.2 and 71.2±1.6 versus 41.7±1.0 bursts per 100 heartbeats, respectively; P<0.01 for both). For a similar blood pressure elevation, however, the sympathetic nerve traffic increase was significantly greater in patients with than without left ventricular diastolic dysfunction (+28.9%; P<0.05). In the population as a whole, muscle sympathetic nerve traffic was significantly and inversely related to various echocardiographic indices of diastolic function. Although baroreflex-heart rate control was significantly attenuated in the 2 hypertensive groups, baroreflex-sympathetic modulation was impaired only in those with diastolic dysfunction. These data provide the first evidence that, in hypertension, activation of the sympathetic nervous system may contribute not only at the blood pressure elevation but also at the development of left ventricular diastolic dysfunction. The sympathetic overactivity, which is likely to be related to the baroreflex impairment, may account for the increased cardiovascular risk characterizing diastolic dysfunction.

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incrementally infused in an antecubital vein at doses of 0.5 and 1.0 

isovolumic relaxation time [IVRT]

flow velocity [E/A ratio]

those in whom the BP elevation was associated with a preserved left 

ventricular diastolic function (ratio of peak early:peak atrial Doppler 

flow velocity [E/A ratio] >1, deceleration time <220 ms, and 

isovolumic relaxation time [IVRT] <100 ms; n=20) or with a left 

ventricular diastolic dysfunction (E/A ratio <1, deceleration time >220 ms, and IVRT >100 ms; n=17).20 A group of age-matched 

male subjects (n=20) with normal office BP, normal 24-hour BP, 

and no structural or functional echocardiographic abnormalities of 

the left ventricle was taken as control. The study protocol was 

approved by the ethics committee of the institutions involved. All 

of the subjects agreed to participate after being informed of the study 

nature and purpose.

Measurements

Sympathetic Nerve Traffic

Multitunit recording of MSNA was obtained from a microelectrode 

inserted in a peroneal nerve posterior to the fibular head, as reported 

previously.1–4,17–19 Integrated nerve activity was monitored by a loud 

speaker, displayed on a storage oscilloscope (model 511A, Tektronix), 

and recorded with BP and heart rate on an ink polygraph. The 

muscle nature of MSNA was established according to criteria 

described in previous studies,1–4,17–19 and recording was accepted 

only if the signal:noise ratio was >3. Under baseline conditions, 

MSNA was quantified as burst incidence over time (bursts per minute) and bursts incidence corrected for heart rate values (bursts per 100 heartbeats). This quantification has been shown to provide reproducible values that differ only by 3.8% when assessed twice in the same session by a single investigator.17

Baroreflex

Baroreflex modulation of MSNA and heart rate was assessed via the 

vasoactive drug infusion technique.2,17–19 Briefly, phenylephrine was 

incrementally infused in an antecubital vein at doses of 0.5 and 1.0 

μg kg⁻¹ min⁻¹, whereas nitroprusside was incrementally 

infused at doses of 0.5 and 1.0 μg kg⁻¹ per minute. Each step was 

maintained for 5 minutes, and the drug initially infused was selected 

randomly. Mean BP (diastolic plus one third of pulse pressure), 

MSNA, and heart rate were averaged for the 20 minutes before the 

infusion and the 5-minute period of each step infusion. Baroreceptor 

modulation of MSNA and heart rate was estimated by calculating the 

percentage of changes in MSNA (integrated activity, ie, bursts per 

minute times mean burst amplitude, expressed in arbitrary units) and 

the absolute changes in heart rate in relation to the changes in mean 

BP induced by each dose of vasoactive drugs.2,17–19 In each patient, 

the ratio between MSNA or heart rate changes was analyzed 

separately for the 2-step infusions of phenylephrine and nitroprusside. Data were then further averaged to obtain MSNA- or heart rate-baroreflex sensitivity gain.

Echocardiographic Measurements

Conventional echocardiographic and tissue Doppler imaging 

measurements were performed. Conventional transthoracic 2D and 

Doppler echocardiography were performed with commercially avail-

able instruments equipped with a 2.25-MHz transducer. End-diastolic and end-systolic left ventricular internal diameters, interventricular septum thickness, and posterior wall thickness were measured on a 2D guided M-mode tracing during ≥5 cardiac cycles according to the recommendations of the Penn Convention.21,22 Left ventricular mass index was calculated by Devereux’s formula and normalized to body surface area.23 Left ventricular systolic function was assessed by midwall fractional shortening according to the standard formula.24 Left ventricular ejection fraction was measured from the 4-chamber 

apical projection by using the product area times length. Color 

Doppler and pulse Doppler were used to measure mitral flow (early 

diastolic peak flow velocity [E wave] and late diastolic peak flow 

velocity [A wave]) and flow at the left ventricular outflow tract. The 

intraobserver and the interobserver coefficients of variations for left 

ventricular diameter, E wave, A wave, and left ventricular mass 

index are 5.2% and 5.9%, 5.0% and 5.5%, 4.8% and 5.2%, and 6.8% 

and 7.9%, respectively. The apical 4-chamber view was used to 

obtain tissue Doppler imaging of the mitral annulus. A sample 

volume of the pulsed wave Doppler was positioned at the septal side 

of the mitral annulus, and then the spectral signal of the mitral 

annular velocity was recorded. Peak E’ was measured.20 As an index 

of left ventricular filling pressure, E/E’ was then calculated based on 

the average of 5 consecutive Doppler signals. The intraobserver and 

interobserver coefficients of variations were 4.4% and 5.9% for E, 

4.5% and 6.1% for E’, and 4.5% and 8.0% for E/E’, respectively.

Other Measurements

Body mass index was obtained by dividing body weight in kilograms by the square of the height in meters. Plasma norepinephrine was measured by high-performance liquid chromatography25 from a venous blood sample. During the MSNA recording and baroreflex testing, BP was monitored by a finger photoplethysmographic device (Finapres 2300, Ohmeda) capable of providing accurate beat-to-beat systolic and diastolic values.2,17–19 Heart rate was monitored beat-
to-beat during the experimental session by a cardiofotometer 

generated by the R wave of an ECG lead.

Protocol and Data Analysis

Sympathetic nerve traffic measurements were carried out in the 

morning after an overnight fasting. With the subject supine, the 

blood sample for plasma norepinephrine was withdrawn. After a 

30-minute interval, BP, heart rate, and MSNA were continuously 

measured during an initial 20-minute baseline period, the intravenous 

infusion of 1 vasoactive drug, a 30-minute recovery period 

followed by a second 20-minute baseline period, and the infusion of 

the second vasoactive drug. Data were analyzed by a single inves-

tigator unaware of the study design and the group to which the 

patient belonged. Individual values recorded in the baseline state 

or during baroreceptor manipulation were averaged for each group 

and expressed as means±SEM. Comparisons between groups were 

made by 2-way ANOVA using the Bonferroni correction for multiple comparisons. The Pearson correlation coefficient was used to determine the relationships between resting MSNA values and E/A ratio, deceleration time, IVRT, E/E’, and baroreflex sensitivity gain. A P<0.05 was taken as the minimal level of statistical 

significance.

Results

As shown in the Table, the different groups of subjects had a 

similar age and body mass index. Clinic, 24-hour, and finger 

systolic and diastolic BP values were significantly higher in 

the 2 hypertensive groups as compared with the normotensive 

group but almost superimposable in hypertensive patients 

with and without left ventricular diastolic dysfunction. Com-

pared with the normotensive-control group, resting heart rate 

values were slightly, although not significantly, greater in the 

hypertensive groups. Individual and average resting MSNA 

values are shown in Figure 1 and in the Table. Both when 

expressed as burst incidence over time and as burst incidence 

corrected for heart rate, MSNA was markedly and signifi-

cantly greater in the 2 groups of hypertensive patients than in 

the normotensive group. Compared with the hypertensives 

with a normal diastolic function, however, the increase was 

significantly greater in hypertensives with left ventricular 

diastolic dysfunction (+28.9%; P<0.05).
induced by the vasoactive drug infusion (and the related
motersive subjects, the magnitude of the MSNA changes
rate and in MSNA, whereas the 2 incremental doses of
which was accompanied by a progressive reduction in heart
rate (bs/100 hb), in normotensive subjects (NT) and in hypertensive patients without (HT) and with
left ventricular dysfunction (HTD). *P<0.05 and
**P<0.01 for all). Resting MSNA was not significantly related to E/E' ratio (r = -0.24; P = 0.07) but was inversely related to baroreflex-
MSNA sensitivity (r = -0.37; P < 0.01).

**Discussion**

The results of the present study document for the first time that, in essential hypertensive patients, the presence of a left ventricular diastolic dysfunction enhances the already elevated MSNA levels characterizing a chronic BP elevation.26,27 They also provide information on the mechanisms that may be responsible for the greater sympathetic activation characterizing a chronic BP elevation complicated by a diastolic dysfunction. First, we can rule out that the greater sympathetic activation seen when diastolic dysfunction is associated with hypertension was attributable to a greater severity of the hypertensive state, because patients selected with and without diastolic dysfunction had similar office, ambulatory, and finger BP levels. Second, we can also rule out that the greater sympathetic activation seen in patients with hypertension and diastolic dysfunction was attributable to a greater left ventricular mass, because in patients with and without diastolic dysfunction, the left ventricular mass value was similar in the 2 groups. Finally, we can rule out that the differences in sympathetic activity that we observed were because of the presence of a systolic dysfunction and/or a heart failure state, because patients did not display any symptom of cardiac insufficiency, and left ventricular ejection fraction, left ventricular diastolic diameter, fractional shortening, and, more importantly, E/E' were all normal and superimposable in the different groups. We can, thus, suggest that diastolic dysfunction, per se, is capable of causing a sympathetic activation, as also documented by the relationship between MSNA and different echocardiographic indices of diastolic function. It should be emphasized, however, that

As shown in Figure 2 (left), the 2 incremental doses of phenylephrine triggered a progressive increase in mean BP, which was accompanied by a progressive reduction in heart rate and in MSNA, whereas the 2 incremental doses of nitroprusside had opposite effects. Compared with the normotensive subjects, the magnitude of the MSNA changes induced by the vasoactive drug infusion (and the related
baroreflex-MSNA sensitivities) was not reduced in the hypotensives with a normal left ventricular diastolic function, but it was significantly attenuated in those in which there was a left ventricular diastolic dysfunction (Figure 2, top). Furthermore, the concomitant heart rate changes and baroreflex-heart rate sensitivities were smaller in the hypertensive patients with and without left ventricular dysfunction (Figure 2, bottom). In all of the subjects pooled, there was a significant inverse relationship between resting MSNA values and E/A ratio, deceleration time, and IVRT (r = -0.44, r = -0.38, and r = -0.40, respectively; P < 0.01 for all). Resting MSNA was not significantly related to E/E' ratio (r = -0.24; P = 0.07) but was inversely related to baroreflex-
MSNA sensitivity (r = -0.37; P < 0.01).

**Table.** Demographic and Clinic Variables in Normotensive Subjects and in Hypertensive Subjects Without and With Left Ventricular Diastolic Dysfunction

<table>
<thead>
<tr>
<th>Variable</th>
<th>NT (n=20)</th>
<th>HT (n=20)</th>
<th>HTD (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>45.2±1.7</td>
<td>46.3±2.4</td>
<td>47.7±2.9</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.0±0.6</td>
<td>24.2±0.8</td>
<td>24.8±0.9</td>
</tr>
<tr>
<td>Clinic SBP, mm Hg</td>
<td>120.2±2.7</td>
<td>158.8±2.8</td>
<td>160.5±2.9</td>
</tr>
<tr>
<td>Clinic DBP, mm Hg</td>
<td>78.5±1.9</td>
<td>96.7±2.2</td>
<td>97.8±2.5</td>
</tr>
<tr>
<td>24-h SBP, mm Hg</td>
<td>116.7±2.2</td>
<td>138.1±2.4</td>
<td>142.9±2.6</td>
</tr>
<tr>
<td>24-h DBP, mm Hg</td>
<td>72.9±1.6</td>
<td>86.3±2.2</td>
<td>87.4±2.2</td>
</tr>
<tr>
<td>Finger HR, bpm</td>
<td>118.0±2.5</td>
<td>156.4±2.7</td>
<td>158.2±2.4</td>
</tr>
<tr>
<td>Finger DBP, mm Hg</td>
<td>76.8±2.2</td>
<td>95.2±2.4</td>
<td>96.0±2.4</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>68.5±2.0</td>
<td>70.5±2.3</td>
<td>71.5±2.2</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>65.7±0.9</td>
<td>67.5±1.1</td>
<td>66.2±1.3</td>
</tr>
<tr>
<td>FS, %</td>
<td>38.5±2.8</td>
<td>38.6±2.8</td>
<td>38.0±2.7</td>
</tr>
<tr>
<td>LVMI, g/m²</td>
<td>47.2±0.7</td>
<td>47.7±0.8</td>
<td>47.5±0.9</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>86.3±4.8</td>
<td>110.0±4.5</td>
<td>115.3±4.6</td>
</tr>
<tr>
<td>E/A ratio, au</td>
<td>1.14±0.2</td>
<td>1.15±0.2</td>
<td>0.64±0.02</td>
</tr>
<tr>
<td>Dec time, ms</td>
<td>193.4±3.0</td>
<td>205.1±4.1</td>
<td>249.7±4.7</td>
</tr>
<tr>
<td>IVRT, ms</td>
<td>93.8±2.3</td>
<td>97.0±2.2</td>
<td>136.2±32.8</td>
</tr>
<tr>
<td>E/E' ratio, au</td>
<td>6.51±0.8</td>
<td>7.09±0.9</td>
<td>7.4±1.5</td>
</tr>
<tr>
<td>Plasma NE, pg/mL</td>
<td>201.1±26</td>
<td>276.6±39</td>
<td>279±38</td>
</tr>
<tr>
<td>MSNA, bs/min</td>
<td>29.7±0.8</td>
<td>41.8±0.8</td>
<td>52.9±1.4</td>
</tr>
<tr>
<td>MSNA, bs/100 hb</td>
<td>41.7±1.0</td>
<td>55.1±1.2</td>
<td>71.2±1.6</td>
</tr>
</tbody>
</table>

NT indicates normotensive subjects; HT, hypertensive subjects without left ventricular diastolic dysfunction; HTD, hypertensive subjects with left ventricular diastolic dysfunction; BMI, body mass index; SBP, systolic BP; DBP, diastolic BP; HR, heart rate; LVEF, left ventricular ejection fraction; FS, fractional shortening; bs, bursts; LVEDD, left ventricular end-diastolic diameter; LVMI, left ventricular mass index; IVRT, isovolumic relaxation time; NE, norepinephrine; hb, heart beats; au, arbitrary units. Data are shown as means±SEMs.

*P<0.05 vs NT; †P<0.01 vs NT; ‡P<0.05 vs HT.
our data do not allow us to determine whether the greater sympathetic activation seen in patients with diastolic dysfunction is the cause or rather the consequence of the cardiac alteration. Data collected in experimental animal models may, although indirectly, suggest that the former hypothesis is a likely one, because pharmacological-induced sympathetic inhibition may prevent the development or delay the progression of the diastolic dysfunction.28–30 Future studies are, thus, needed to clarify this issue.

Several other results of our study deserve to be discussed. First, confirming several previous studies,2,26,27,31 in uncomplicated hypertension, baroreflex control of heart rate was impaired, but baroreflex control of MSNA was not. Our data add to this evidence that a clear-cut impairment in MSNA baroreflex (together with a greater alteration in the baroreflex heart rate reflex) is present when the functional diastolic abnormality is detected. This allows us to speculate that the enhanced sympathetic activation seen in hypertensive patients with diastolic dysfunction depends on a reduced reflex restraint of baroreceptors on sympathetic tone, as the inverse relationship between resting MSNA values and baroreflex function suggests. It is possible that the baroreflex alterations may include a component originating from volume receptors located in the left ventricle,32 the activity of which may be impaired by the diastolic dysfunction. Second, in contrast to MSNA values, plasma norepinephrine and heart rate did not show any significant difference in the various hypertensive states regardless of the presence or absence of cardiac hypertrophy and diastolic dysfunction. This represents a further example that these 2 indirect indices of adrenergic cardiovascular drive display a limited sensitivity in reflecting different increases in sympathetic tone.2,18,19,33–35 Third, our data do not clarify whether the excessive sympathetic activation occurring in hypertension complicated by a diastolic dysfunction is limited to the muscle vascular district or is generalized to the whole cardiovascular system.3,12,36 suggesting that what is seen in the skeletal muscle reflects, at least qualitatively, what occurs elsewhere.

**Perspectives**

The results of the present study have clinical and therapeutic implications. The clinical implication is that the particularly elevated levels of sympathetic activity observed when hypertension is associated with left ventricular diastolic dysfunction may account, at least in part, for the increased cardiovascular risk documented in this condition in observational studies.5–10 The therapeutic implication is that the impairment in left ventricular diastolic function may require the use of drugs that combine the antihypertensive efficacy with sympathomodulating properties.37

![Graph](http://hyper.ahajournals.org/)

**Figure 2.** Left, Absolute changes in MSNA and heart rate (HR) during graded increases and reductions in mean blood pressure (MAP) induced by vasoactive drugs in the 3 groups of subjects of Figure 1. Right, Baroreceptor-MSNA and HR sensitivities, expressed as average ratios between changes in MSNA (Δ MSNA) or HR (Δ HR) over changes in mean arterial pressure (MAP) in the 3 groups of subjects of Figure 1. Data are shown as means±SEMs. For symbols and explanations, see Figure 1. *P<0.05 and **P<0.01 refer to the statistical significance between groups.
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**Disclosures**
None.

**References**
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