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

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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. (Hypertension. 2009;53:205-209.)

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

Studies performed in the past few years have shown that sympathetic nerve traffic increase is associated with cardiac alterations, eg, left ventricular hypertrophy or heart failure.1–5 No information is available, 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 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.)

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Methods

Population

Our study was performed in middle-age male patients with cardiac sinus rhythm and no evidence of secondary hypertension, who were recruited in the study if there was an office BP>140 mm Hg systolic or 90 mm Hg diastolic, based on the average of 3 sphygmomanometric values taken with the patient in the sitting position, and a 24-hour mean BP >125 mm Hg systolic or 80 mm Hg diastolic, ie, the cutoff values for ambulatory BP normality or elevation indicated by international guidelines.15 Ambulatory BP was obtained by an oscillometric device (SpaceLabs 90207, SpaceLabs), with the readings set at 15-minute and 20-minute intervals during the daytime (7 AM to 11 PM) and nighttime (11 PM to 7 AM), respectively.16 The device was applied in the morning, and the subjects were allowed to return home with the instruction to attend to their usual activities and to come back to the hospital the following day for the device removal. Recruitment also requested absence of conditions affecting sympathetic activity,ie, (1) overweight (body mass index...
incrementally infused in an antecubital vein at doses of 0.5 and 1.0
isovolumic relaxation time [IVRT]
function; and (7) history of regular exercise habit or involvement in
(4) use of antihypertensive or metabolic drugs; (5) symptoms or
bolic diseases, including metabolic syndrome and diabetes mellitus;
body surface area.23 Left ventricular systolic function was assessed
mass index was calculated by Devereux’s formula and normalized to
side. Data were then further averaged to obtain MSNA- or heart
separately for the 2-step infusions of phenylephrine and nitroprus-
the ratio between MSNA or heart rate changes was analyzed
previously.1–4,17–19 Integrated nerve activity was monitored by a loud
speaker, displayed on a storage oscilloscope (model 511A, Tektro-
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.21–19 Heart rate was monitored beat-to-beat during the experimental session by a cardiochotometer triggered 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 investigator 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. Compared 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 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.21,22 Briefly, phenylephrine was incrementally infused in an antecubital vein at doses of 0.5 and 1.0 μg kg−1 per minute, 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 100 heartbeats), 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, i.e., 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.21,17–19 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 measure-
ments were performed. Conventional thoracic 2D and Doppler echocardiography were performed with commercially available 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 intraserver 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 intraserver 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.

>26 kg/m²); (2) electrocardiographic and/or echocardiographic evi-
dence of left ventricular hypertrophy; (3) history of smoking, excessive alcohol consumption, and major cardiovascular or meta-

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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 hypertensives 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).

**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
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 sympathoinhibition 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. Evidence is available, however, that, in hypertension, the sympathetic drive is increased not only at the level of the skeletal muscle but also in the cerebral, coronary, and renal circulation,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.6–10 The therapeutic implication is that the impairment in left ventricular diastolic function may require the use of drugs that combine the antihypertensive efficacy with sympathomodering properties.37

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**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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