Diastolic Dysfunction and Baroreflex Sensitivity in Hypertension

Maria Vittoria Pitzalis, Andrea Passantino, Francesco Massari, Cinzia Forleo, Cataldo Balducci, Giuseppe Santoro, Filippo Mastropasqua, Gianfranco Antonelli, Paolo Rizzon

Abstract—The determinants of diastolic dysfunction in patients with systemic hypertension are not completely known. To evaluate the possible role of age, arterial blood pressure, and baroreflex heart rate response impairment in causing diastolic dysfunction, we studied 61 patients (42 male; mean±SD age, 43.9±12 years) with newly recognized and therefore previously untreated systemic hypertension. Diastolic dysfunction was evaluated by means of Doppler echocardiography (and diagnosed as such when the early to atrial peak velocity ratio corrected to heart rate was <1), arterial blood pressure by 24-hour ambulatory monitoring, and baroreflex heart rate response by means of the spectral technique (α index) during paced (0.27 Hz) and spontaneous breathing (in a supine position and during tilt). Nineteen patients had diastolic dysfunction, the most powerful predictor of which was age (r=−0.63, P<0.001). The patients with diastolic dysfunction had significantly lower values for spectral baroreflex gain in the high-frequency band than those without (5.2±3 versus 8.4±5 ms/mm Hg during paced breathing, P<0.05; 7.4±4 versus 13.3±7 ms/mm Hg in a supine position, P<0.05; 4.3±4 versus 5.2±2 ms/mm Hg during tilt, P<NS). Ambulatory blood pressure values were not significantly different in the patients with (137±14 and 89±9 mm Hg) and without (144±11 and 82±24 mm Hg) diastolic dysfunction. In conclusion, age and impaired baroreflex heart rate response (but not pressure overload) are determinants of left ventricular diastolic dysfunction in patients with newly recognized and untreated systemic hypertension. (Hypertension. 1999;33:1141-1145.)

Key Words: hypertension, systemic ▪ ventricular function, left ▪ baroreflex ▪ blood pressure monitoring, ambulatory

The cause and time of occurrence of cardiac impairment in patients with essential hypertension are not precisely known. It has been shown that diastolic dysfunction is the earliest cardiac abnormality in this patient population1 and may precede ventricular hypertrophy.2 Age and pressure load are considered possible determinants,3 whereas the role of the autonomic nervous system is still debated. Animal studies have suggested that a high sympathetic tone may favor the development of hypertrophy,4 but the role of the autonomic nervous system in the genesis of cardiac abnormalities is unclear. Some studies have reported increased sympathetic activity in hypertensive patients with cardiac hypertrophy,5 but this has not been confirmed by other authors.6 Furthermore, no data are yet available concerning the role of depressed baroreflex sensitivity in determining cardiac impairment in these patients. It is possible that it is too late for any autonomic nervous system abnormalities to be detected once hypertrophy becomes evident, and therefore the early phase of essential hypertension could offer important information on the role of autonomic nervous system activity in determining the presence of cardiac involvement.

The purpose of this study was to evaluate the role of pressure load and baroreflex heart rate response in determining the appearance of diastolic ventricular dysfunction in patients with previously unrecognized and untreated mild to moderate essential hypertension.

Methods

Study Population

The study involved 61 consecutive patients referred to our outpatient clinic for previously untreated mild to moderate hypertension. Only the patients whose diastolic blood pressure was >90 mm Hg at 3 different examinations were included in the study. All of the patients were asymptomatic and underwent a full medical examination, 12-lead ECG, routine laboratory tests, and a treadmill stress test to rule out neurological disease, secondary hypertension, and coronary artery disease. Obese (body mass index >30 kg/m²) and diabetic patients were also excluded. The control group consisted of 15 nonhospitalized healthy volunteers (10 male; mean±SD age, 42±9 years).

Echocardiographic Examination

M-mode 2-dimensional echocardiography and cardiac Doppler recordings were obtained by means of a phased-array echo-Doppler system (HP-Sonos 500) equipped with a 2.5-Hz transducer. We examined the patients in the left lateral recumbent position, using standard parasternal, short axis, and apical views. The recordings were analyzed offline by 2 independent observers. M-mode record-
ings were obtained, and left ventricular diastolic diameter and septal and posterior wall thickness were measured. Left ventricular mass index (LVMI) was obtained by dividing the left ventricular mass by body surface area. Left ventricular hypertrophy (LVH) was defined as LVMI >139 g/m² in men and >109 g/m² in women. Pulsed Doppler recordings were made from the standard apical 4-chamber view. Mitral inflow velocity was recorded with the sample volume at the mitral annulus level; the average of ≥3 cardiac cycles was taken. The following measurements were made: peak velocity of early left ventricular filling (E), peak velocity of late ventricular filling (A), and the ratio between early and late flow velocity peaks (E/A). The E/A ratio was then normalized by dividing it by the heart rate (E/Ac). An E/Ac of <1 was considered the cutoff point for identifying patients with diastolic dysfunction.

**Ambulatory Blood Pressure Monitoring**

Ambulatory blood pressure (ABP) was monitored with a fully automatic portable recorder (SpaceLabs 90209) equipped with an occlusion cuff to determine systolic blood pressure (SBP) and diastolic blood pressure (DBP) every 15 minutes during daytime (6 AM to 10 PM) and every 30 minutes during nighttime (10 PM to 6 AM). The cuffs were positioned on the nondominant arm. The patients were instructed to perform their usual activities. Mean 24-hour SBP and DBP were calculated.

**Baroreflex Sensitivity Assessment**

The evaluations were made in the morning in a quiet and light-attenuated room, with an ambient temperature of ~24°C. Before evaluation, the patients lay supine for 30 minutes to allow their cardiovascular mechanisms to reach steady state.

Cardiac baroreceptor sensitivity was assessed by means of power spectral analysis with the patients in a supine position during spontaneous and metronomically-paced breathing at 0.27 Hz and after a head-up tilt test at 70° for 5 minutes. During each session, the signals of the R-R interval (model 78354C, Hewlett Packard), respiration (CR) (bottom), and noninvasive blood pressure (Finapres model 2300, Ohmeda) were continuously and simultaneously recorded as previously described. Univariate and bivariate spectral analyses of time series were made with the autoregressive approach. The spectral baroreflex gain is calculated as the square root of the ratio between the high-frequency band (from 0.15 to 0.40 Hz; -HF) and the ratio between early and late flow velocity peaks (E/A).

**Statistical Analysis**

The data are expressed as mean±SD values. Linear univariate correlations were analyzed by means of Pearson’s product moment; the multivariate correlations were analyzed by means of multiple correlation. The between-group differences in α-HF were evaluated by means of multifactorial ANOVA for repeated measures, with age used as a covariate. A value of P<0.05 was considered statistically significant.

**Results**

**Analysis of Overall Population of Hypertensive Patients**

The clinical characteristics of the studied population are shown in Table 1. Nineteen (31%) of the patients had diastolic dysfunction, and 16 (26%) had LVH (including 6 with diastolic dysfunction). ABP monitoring resulted in mean 24-hour SBP and DBP of 142±13 and 88±15 mm Hg, respectively. In regard to spectral baroreflex gain, the α-HF values in the hypertensive patients as a whole were significantly less than those in the control subjects during spontaneou

### Table 1. Clinical Characteristics of Hypertensive Patients With (E/Ac <1) and Without (E/Ac >1) Diastolic Dysfunction

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall Population</th>
<th>E/Ac &lt;1</th>
<th>E/Ac &gt;1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>43.9±12</td>
<td>53±7</td>
<td>40±12</td>
</tr>
<tr>
<td>Gender, M/F</td>
<td>42/19</td>
<td>8/11</td>
<td>11/31</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>154±16</td>
<td>149±14</td>
<td>155±21</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>99±8</td>
<td>99±7</td>
<td>100±8</td>
</tr>
<tr>
<td>24-h SBP, mm Hg</td>
<td>142±13</td>
<td>137±14</td>
<td>144±11</td>
</tr>
<tr>
<td>24-h DBP, mm Hg</td>
<td>88±15</td>
<td>89±9</td>
<td>82±24</td>
</tr>
<tr>
<td>LVMI, g/m²</td>
<td>103±30</td>
<td>112±38</td>
<td>99±27</td>
</tr>
<tr>
<td>LVMI (Male)</td>
<td>107±24</td>
<td>122±20</td>
<td>102±24</td>
</tr>
<tr>
<td>LVMI (Female)</td>
<td>94±39</td>
<td>100±50</td>
<td>89±31</td>
</tr>
<tr>
<td>E/Ac</td>
<td>1.2±0.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean±SD.

neous respiration (11.4±7 versus 17.3±8 ms/mm Hg) and during controlled breathing (7.4±5 versus 10.6±5 ms/mm Hg) and tilt (4.8±3 versus 8±3 ms/mm Hg). Univariate analysis showed that the presence of diastolic ventricular dysfunction significantly correlated with age (r=-0.65, P<0.0001), LVMI (r=-0.34, P=0.01), and α-HF during controlled breathing (r=0.31, P=0.014) (Figure 1) but did not correlate with the values of ABP. LVMI significantly correlated with age (r=0.31, P=0.02), mean 24-hour SBP (r=0.28, P=0.039), and α-HF during controlled breathing (r=-0.32, P=0.02). At multivariate analysis, age was the only independent variable (r=-0.63, P<0.001).

![Figure 1. Univariate correlations between E/Ac and age (top); E/Ac and LVMI (middle); and E/Ac and α-HF during controlled respiration (CR) (bottom).](image-url)
Patients With and Without Left Ventricular Diastolic Dysfunction

The clinical characteristics of the hypertensive patients with and without diastolic dysfunction are given in Table 1. When considered separately with age as covariate, the subgroups had a similar mean R-R interval (Table 2). In contrast, the $\alpha$-HF values were lower in the patients with diastolic dysfunction than in normal subjects and hypertensive patients without diastolic dysfunction during spontaneous respiration ($P<0.05$) and controlled breathing ($P<0.05$); during tilt, the patients with and without diastolic dysfunction had similar $\alpha$-HF values (Table 2 and Figure 2A). The $\alpha$-HF values of the control subjects were always significantly higher than those of the hypertensive patients with and without diastolic dysfunction.

Patients With and Without LVH

The clinical characteristics of the hypertensive patients with and without LVH are given in Table 3. The 2 subgroups had similar mean R-R and $\alpha$-HF values (Table 2 and Figure 2B). The $\alpha$-HF values of the control subjects were always significantly higher than those of the hypertensive patients with LVH; in the patients without LVH, $\alpha$-HF was significantly lower than in control subjects at baseline and was nonsignificantly lower during controlled breathing and tilt.

Changes in $\alpha$-HF During Controlled Breathing and Tilt

The values of $\alpha$-HF decreased during controlled breathing and tilt in all 3 groups; however, the reduction in the hypertensive patients with diastolic dysfunction was much less than that in the patients without dysfunction and in normal subjects (Figure 2A). Moreover, the tilt values of patients with and without diastolic dysfunction, which were statistically different at baseline and during controlled breathing, became almost similar (Figure 2A). When this change was evaluated in hypertensive patients with and without LVH, it was found to be similar in the 2 groups (Figure 2B).

Discussion

The main result of the present study is the finding that older age and less baroreflex heart rate response characterize the patients with previously unknown and untreated systemic hypertension and left ventricular diastolic dysfunction (who represented 31% of the 61 consecutive patients in our study population).

The role of each of the parameters considered in this study as a possible determinant of left ventricular diastolic dysfunction is separately discussed below.

Age

Although $\alpha$-HF and LVMI were also associated with diastolic dysfunction at univariate analysis, multivariate analysis showed that age was the only independent parameter predictive of the occurrence of diastolic impairment. The importance of age found in our study is in agreement with previously published data.\(^2\)\(^{11}\)

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**TABLE 2.** Values of R-R Interval, SBP, DBP, and $\alpha$ Index in Patients With and Without Diastolic Dysfunction and With and Without LVH

<table>
<thead>
<tr>
<th>Variable</th>
<th>E/Ac &lt;1</th>
<th>E/Ac &gt;1</th>
<th>With LVH</th>
<th>Without LVH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spontaneous respiration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-R interval, ms</td>
<td>861±113</td>
<td>816±117</td>
<td>868±86</td>
<td>806±116</td>
</tr>
<tr>
<td>$\alpha$-HF, ms/mm Hg</td>
<td>7.3±4*</td>
<td>13.3±7</td>
<td>11.5±8</td>
<td>11.3±6</td>
</tr>
<tr>
<td><strong>Controlled respiration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-R interval, ms</td>
<td>860±116</td>
<td>786±169</td>
<td>859±71</td>
<td></td>
</tr>
<tr>
<td>$\alpha$-HF, ms/mm Hg</td>
<td>5.2±3*</td>
<td>8.4±5</td>
<td>5.7±2</td>
<td>7.6±5</td>
</tr>
<tr>
<td><strong>Tilt</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-R interval, ms</td>
<td>773±112</td>
<td>736±102</td>
<td>783±64</td>
<td>732±101</td>
</tr>
<tr>
<td>$\alpha$-HF, ms/mm Hg</td>
<td>4.3±4</td>
<td>5.0±2</td>
<td>3.7±1</td>
<td>5.3±3</td>
</tr>
</tbody>
</table>

Values are mean±SD.

*P<0.05, E/Ac <1 vs E/Ac >1.

**TABLE 3.** Clinical Characteristics of Hypertensive Patients With and Without Cardiac Hypertrophy

<table>
<thead>
<tr>
<th>Variable</th>
<th>With LVH</th>
<th>Without LVH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>47±11</td>
<td>43±13</td>
</tr>
<tr>
<td>Gender, M/F</td>
<td>10/6</td>
<td>32/13</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>157±13</td>
<td>152±17</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>103±7</td>
<td>98±8</td>
</tr>
<tr>
<td>24-h SBP, mm Hg</td>
<td>149±11</td>
<td>140±12</td>
</tr>
<tr>
<td>24-h DBP, mm Hg</td>
<td>94±8</td>
<td>85±16</td>
</tr>
<tr>
<td>E/Ac</td>
<td>1.1±0.3</td>
<td>1.3±0.3</td>
</tr>
</tbody>
</table>

Values are mean±SD.

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**Figure 2.** A, Trends of $\alpha$-HF values (and SE) in hypertensive patients with (☐) and without (◇) diastolic dysfunction and in controls (○) during spontaneous respiration (SR), controlled respiration (CR), and tilt. B, Trends of $\alpha$-HF values (and SE) in hypertensive patients with (●) and without (▲) LVH and in controls (○) during SR, CR, and tilt. *P<0.05; †P<0.01.
Systolic Blood Pressure
Pressure load did not seem to be a determinant of left ventricular diastolic dysfunction because, when evaluated by means of ABP, it did not correlate with diastolic impairment at either univariate or multivariate analysis. This finding is in contrast with previously published results showing a significant correlation between ABP indices and diastolic dysfunction; however, these studies analyzed normal subjects and hypertensive patients as a continuum, and this may have given rise to a spurious correlation since hypertensive patients can be expected to have lower values of E/Ac and higher values of ABP than normal subjects. On the other hand, pressure load was associated with the occurrence of LVH. LVMI also correlated with the presence of diastolic dysfunction, a finding that is in contrast with those of previous studies showing no correlation between the 2 parameters. However, the same authors stressed the fact that the major limit of cross-sectional studies is that patients with abnormal left ventricular filling may have an increased LVMI even if it remains within the normal range.

Baroreflex Sensitivity
α-HF has been widely demonstrated to be a reliable measure of baroreflex sensitivity. Although multivariate analysis did not identify it as an independent parameter in predicting the occurrence of left ventricular diastolic dysfunction, it was significantly different in our hypertensive patients with and without diastolic dysfunction. The absence of any significant role at multivariate analysis may be due to the fact that the weight of age in the analysis is so strong that it cancels that of other factors. Moreover, age is itself capable of modifying reflex cardiac activity, since it has been shown that baroreflex sensitivity tends to decrease with aging. Furthermore, from a mathematical point of view, it is also possible that the small changes in the values of E/Ac at different ages (although hardly significant in clinical terms) may play a greater role than the greater changes in baroreflex sensitivity. We therefore decided to dichotomize our population into patients with and without diastolic dysfunction using age as covariate and found that there was a difference in their α-HF values. This may have been due to our selected population (patients with previously unknown and untreated essential hypertension), which allowed us to evaluate the role of autonomic nervous system activity in a very early disease phase. An impaired sympathovagal balance during the early phases of hypertension has been revealed by various methods; however, these generally placed greater emphasis on increased sympathetic tone, and only a few evaluated the presence of impaired tonic and reflex vagal activity.

Our study suggests that hypertensive patients show an impaired baroreflex heart rate response and that this is particularly evident in those with functional and anatomic involvement. Greater impairment in the reflex control of circulation is also suggested by another interesting finding of this study: the different trend of α-HF changes in the 3 groups. It is worth noting that patients without dysfunction still have a partial reflex control of circulation, which is completely lost in those with diastolic dysfunction; when a reduction in α-HF occurs during tilt, the patients with dysfunction are not capable of further reducing their baroreflex sensitivity.

The cross-sectional nature of the present study does not allow us to explore further the reason for this correlation or to identify a causal link between the cardiac abnormality and autonomic nervous system activity imbalance. It may be that the 2 abnormalities are coincidental, but different mechanisms are possible. A reduced baroreflex heart rate response and depressed E/Ac ratio may coexist only at a more advanced disease stage; however, our patients with diastolic dysfunction did not have significantly higher blood pressure values than the other hypertensive patients (Table 2). Impaired diastolic filling may increase the firing of the cardiopulmonary receptors that have a tonic inhibitory effect on arterial baroreflex responsiveness through the sympathetic afference; this reduced restraint from the heart might occur at the same time as an increased positive feedback mechanism. In addition, a reduction in the inhibitory effects on sympathetic drive exerted by cardiopulmonary receptors with vagal afferent, as well as resetting of arterial baroreceptors, might also favor the progression of sympathetic activation characterizing the early hypertensive state. Finally, the possibilities described are not mutually exclusive.

Limitation of the Study
Although it only measures diastolic ventricular filling, we used E/Ac as an indirect measure of diastolic dysfunction since it is a generally accepted method; other methods of analyzing diastolic dysfunction, such as radioisotopic or contrastographic ventriculography, are more accurate but also more difficult to obtain.

Conclusions
Diastolic dysfunction is related to age and abnormal baroreflex sensitivity; ABP does not influence diastolic dysfunction. Further prospective studies are needed to assess the causal nature of the relationship between baroreflex bradycardia abnormalities and functional and structural abnormalities in hypertensive patients.

Acknowledgments
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