SUMMARY We previously used the Doppler transmitral flow velocity ratio A/E (A = late ventricular filling peak velocity; E = early ventricular filling peak velocity) and the age-adjusted ratio A/E/Age to detect left ventricular filling abnormalities in untreated mild hypertension. This study is a double-blind assessment of the effect of combined α- and β-blockade (labetalol) and β-blockade alone (atenolol) on left ventricular filling in mild hypertension. Twenty-seven patients blindly randomized to labetalol (12 patients) and atenolol (15 patients) treatment completed the echocardiographic and Doppler studies. Clinical and echo-Doppler data obtained at baseline and 6 weeks after initiation of therapy showed no difference between the two groups for age (49 ± 10 vs 46 ± 10 years), mean blood pressure (before therapy, 118 ± 9 vs 117 ± 8 mm Hg; after therapy, 108 ± 12 vs 108 ± 10 mm Hg), left ventricular dimensions, wall thickness, systolic function, and mean late filling velocity A. There was no significant change in left ventricular mass and mass index with labetalol (left ventricular mass, 211 ±36 vs 216 ±38; mass index, 110 ±17 vs 112 ±16) or atenolol (245 ±41 vs 271 ±65; 120 ± 18 vs 130 ± 35). The mean velocity E, A/E, and A/E/Age ratios significantly improved with labetalol (p<0.05) but did not change significantly with atenolol. The improvement in A/E and A/E/Age ratios was primarily due to an increase in early filling velocity E. There was a significant correlation between improvement in velocity E and reduction in systolic blood pressure (r = 0.57, p< 0.05) and mean blood pressure with labetalol (r = 0.63, p< 0.05). In conclusion, short-term combined α- and β-adrenergic blockade improves diastolic filling in mild hypertension.

KEY WORDS Doppler echocardiography • ventricular filling • α- and β-adrenergic receptor inhibition

Effect of antihypertensive pharmacological therapy on diastolic dysfunction largely remains to be determined, however.

We therefore designed an echocardiographic and Doppler study to assess the effects of treatment with combined α- and β-adrenergic blockade and β-adrenergic blockade alone on left ventricular diastolic filling abnormalities in mild hypertension.

Subjects and Methods

Twenty-nine patients with mild hypertension as defined by supine diastolic blood pressure of 90 to 104 mm Hg were randomized in a double-blind manner to one of two drug treatment groups. Sex and race were included in the randomization process. Prior to initiation of drug therapy, all patients were either newly diagnosed (8 subjects) or had all antihypertensive medications discontinued for at least 4 weeks (21 subjects). Patients with clinical coronary, valvular, or congenital heart disease, diabetes, or renal disease were excluded from the study.

Blood pressure was measured in the right arm of the
patients in the supine position after 10 to 15 minutes of rest in a quiet room, at weekly intervals for 3 to 4 weeks prior to active drug therapy. Fourteen patients were randomized to Group A (mean age, 49 ± 10 years; mean blood pressure, 118 ± 9 mm Hg) and 15 to Group B (mean age, 46 ± 10 years; mean blood pressure, 117 ± 8 mm Hg). Group A had 7 men and 7 women, and Group B had 8 men and 7 women. The racial distribution was 7 blacks and 7 whites in Group A and 5 blacks and 10 whites in Group B. Five subjects in Group A and three in Group B were not taking any antihypertensive therapy prior to entering the study.

Each subject underwent echocardiographic and Doppler studies prior to and 6 weeks after initiation of therapy. All echocardiographic studies were coded so that group identity could not be revealed.

Echocardiographic Studies
Each subject underwent standard M-mode, two-dimensional, and Doppler examinations with a mechanical sector scanner (3-MHz transducer, Diasonics DRF 400, Milpitas, CA, USA). Left ventricular internal dimensions were measured according to the leading edge method of the American Society of Echocardiography.13 Diastolic dimensions were taken at the onset of the QRS complex; systolic dimensions were measured at the nadir of systolic excursion of the ventricular septum, from three to five cardiac cycles. Left ventricular systolic function was evaluated by determining the percentage of fractional shortening of the minor axis diameter of the left ventricle, end-systolic wall stress,16 end-systolic wall stress index,17 and ejection fraction. Left ventricular mass was derived from internal diameter and wall thickness by the cube method.14

Doppler Studies
Pulsed Doppler examination of transmitral flow was recorded from the apical four-chamber view as previously described from our laboratory.12 The sample volume was placed in the left ventricular inflow tract between the mitral annulus and the tips of the mitral leaflets. This position was adjusted to maintain the sample volume at an angle as nearly parallel to transmitral flow as possible by using the audible signal and the spectral display. When the maximum transmitral velocity E was detected, the velocity profile was recorded at 50 mm/sec paper speed. The early filling phase peak instantaneous velocity E and the late filling phase peak instantaneous velocity A were then measured from three to five consecutive cardiac cycles displaying the highest measurable velocity profiles. An average of each respective peak velocity was calculated, and the ratio of peak velocities A/E derived and adjusted for age (A/E/Age).12

Echocardiographic and Doppler records were analyzed blindly by an investigator who had no knowledge of the group identity of the patients. After all clinical, echocardiographic, and Doppler data were obtained, the treatment code was broken to reveal group identity.

Control Group
Patients were age- and sex-matched with 17 normotensive control subjects (mean age, 45 ± 11 years; 8 men and 9 women).

Reproducibility Study
The reproducibility of echocardiographic measurements was similar to that in our previously reported values.18

Transmitral flow velocities were reproduced in 10 patients with untreated mild hypertension to evaluate day-to-day variability, and intraobserver and interobserver variability. The day-to-day variability was as follows: velocity A, 1%; velocity E, 3%; A/E ratio, 4%; A/E/Age, 5%. The respective intraobserver variability was 2%, 7%, 3%, and 2%, while the respective interobserver variability was 1%, 0.3%, 3%, and 0.9%.

Drug Titration
Group A patients received labetalol, starting with 100 mg twice daily. The daily dose was increased weekly in increments of 200 mg until adequate blood pressure control was obtained or a maximum daily dose of 800 mg was reached. The average labetalol daily dose was 667 mg for the group. Group B received atenolol with an initial daily dose of 50 mg. Similarly, the daily dose was increased every 2 weeks until adequate blood pressure control was obtained or a maximum dose of 100 mg was reached. The average atenolol daily dose for the group was 93 mg.

The study protocol was conducted according to the guidelines for human experimentation as outlined by the institutional review board of Allegheny-Singer Research Institute.

Statistical Analysis
The data are presented as means ± standard deviation. Student’s t test for paired and unpaired data was performed where appropriate. Correlation coefficients were derived by the least-squares method. A p value of less than or equal to 0.05 was considered to be significant.

Results
Baseline Data
Twenty-seven of the 29 patients who entered the study completed the echocardiographic and Doppler evaluations. Two were dropped from the study because of an inadequate ultrasonic window. Twelve of the 14 patients in the labetalol group and all 15 in the atenolol group had adequate echocardiographic and Doppler records for analysis. Clinical, echocardiographic, and Doppler data obtained at the baseline showed no difference between the groups for age (49 ± 10 vs 46 ± 10 years), blood pressure, left ventricular internal diameter and wall thickness, ejection fraction, fractional shortening, wall stress transmitral flow velocity A and velocity E, and A/E and A/E/Age ratios (Table 1). The groups differed significantly in left ventricular mass, with the mass being higher in the atenolol group.
Table 1. Comparison of Baseline and Posttreatment Data: Clinical, Echocardiographic, and Doppler Values

<table>
<thead>
<tr>
<th>Values</th>
<th>Labetalol treatment</th>
<th>Atenolol treatment</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean BP (mm Hg)</td>
<td>Pre</td>
<td>Post</td>
<td></td>
</tr>
<tr>
<td></td>
<td>118 ± 9</td>
<td>108 ± 12</td>
<td>0.01</td>
</tr>
<tr>
<td>Diastolic LVD (cm)</td>
<td>4.90 ± 0.40</td>
<td>5.00 ± 0.44</td>
<td>NS</td>
</tr>
<tr>
<td>Ventricular septum (cm)</td>
<td>0.98 ± 0.13</td>
<td>1.00 ± 0.14</td>
<td>NS</td>
</tr>
<tr>
<td>Posterior wall (cm)</td>
<td>0.95 ± 0.13</td>
<td>0.95 ± 0.11</td>
<td>NS</td>
</tr>
<tr>
<td>LV mass (g)*</td>
<td>211 ± 36</td>
<td>216 ± 38</td>
<td></td>
</tr>
<tr>
<td>LV mass index (g/m²)*</td>
<td>110 ± 17</td>
<td>112 ± 16</td>
<td>NS</td>
</tr>
<tr>
<td>End-systolic stress (× 10³ dyn/cm²)</td>
<td>78 ± 25</td>
<td>66 ± 16</td>
<td>NS</td>
</tr>
<tr>
<td>End-systolic stress index (mm Hg)</td>
<td>205 ± 43</td>
<td>188 ± 36</td>
<td></td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>66 ± 6</td>
<td>67 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>Fractional shortening (%)</td>
<td>37 ± 4</td>
<td>38 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>Velocity A (cm/sec)†</td>
<td>60 ± 15</td>
<td>57 ± 12</td>
<td>NS</td>
</tr>
<tr>
<td>Velocity E (cm/sec)†</td>
<td>60 ± 13</td>
<td>71 ± 11</td>
<td>0.05</td>
</tr>
<tr>
<td>A/E ratio†</td>
<td>1.03 ± 0.23</td>
<td>0.81 ± 0.21</td>
<td>0.01</td>
</tr>
<tr>
<td>A/E/Age ratio†</td>
<td>0.022 ± 0.005</td>
<td>0.018 ± 0.004</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Values are means ± SD. BP = blood pressure; LVD = left ventricular dimension; LV = left ventricular; Posterior wall = left ventricular posterior free wall; Pre = before treatment; Post = 6 weeks after institution of treatment.

*There was a significant between-group difference in LV mass at baseline and after treatment (p < 0.05). This difference was no longer present when LV mass was normalized to body surface area (LV mass index). The mean left ventricular mass index in the control group was 106 ± 21 g/m² in men and 98 ± 17 g/m² in women.

Data from Treatment Groups

After a mean of 6 weeks of treatment, both labetalol and atenolol treatment had lowered blood pressure to the same degree (see Table 1). Similarly, no significant difference occurred between baseline and treatment values within each group or between the two groups for left ventricular internal diameter, except for an increased diastolic dimension in the atenolol group (5.10 ± 0.60–5.40 ± 0.70 cm; p < 0.05), wall thickness, ejection fraction, fractional shortening, wall stress, or transmitral flow velocity A. The left ventricular mass did not change significantly within each group after treatment (see Table 1). The labetalol-treated patients showed a statistically significant increase in velocity E and decrease in A/E and A/E/Age ratios (see Table 1; Figure 1). In contrast, these changes did not reach statistical significance in the atenolol group (see Table 1 and Figure 1), although the in-

Figure 1. Comparison between baseline and treatment A/E ratios in labetalol- and atenolol-treated patients (A = Doppler transmitral flow peak velocity during late left ventricular diastolic filling; E = Doppler transmitral flow peak velocity during early left ventricular diastolic filling.)
crease in velocity E approached the level of significance \((p = 0.07)\).

The improvement in \(A/E\) and \(A/E/Age\) ratios after treatment with labetalol came primarily from an increase in early filling velocity \(E\) (see Table 1). Significant positive correlation was noted between the improvement in velocity \(E\) and the reduction in mean blood pressure \((r = 0.63, p < 0.05)\) and with the reduction in systolic blood pressure \((r = 0.57, p < 0.05)\). A positive correlation was also found between the drop in systolic and mean blood pressures and \(A/E\) ratio in the labetalol group \((r = 0.55\) and 0.53, respectively). This correlation approached but did not reach statistical significance.

**Discussion**

This double-blind study compared the effect of combined \(\alpha-\) and \(\beta\)-adrenergic blockade (labetalol) to that of \(\beta\)-adrenergic blockade alone (atenolol) on left ventricular diastolic filling in mild hypertension, using transmitral flow velocities measured by Doppler echocardiography. Patients treated with labetalol showed a significant increase in mean early diastolic filling velocity \(E\) and a decrease in \(A/E\) and \(A/E/Age\) ratios (see Table 1 and Figure 1). The improvement in the ratios was primarily due to the increase in early filling velocity \(E\). Furthermore, there was a significant correlation between the increase in velocity \(E\) and the reduction in systolic and mean blood pressures in the labetalol group.

In contrast, the atenolol group showed a similar reduction in blood pressure, but improvement in diastolic filling values failed to reach statistical significance. There were seven patients with normal baseline left ventricular mass index and eight with increased left ventricular mass index (LV mass index \(> 125 \text{ g/m}^2\) for men, \(> 110 \text{ g/m}^2\) for women). Both groups showed no significant change in systolic function, wall thickness, ventricular mass, or wall stress as determined by echocardiographic methods. Left ventricular end-diastolic dimension significantly increased in the atenolol group \((p < 0.05)\), reflecting the effect of \(\beta\)-blockade.

**Left Ventricular Hypertrophy**

Due to differences in methods and patient populations, studies of regression of left ventricular hypertrophy have shown variable results with pharmacological antihypertensive therapy. \(^{20}\) Sympatholytic agents (methyldopa, reserpine), converting enzyme inhibitors (captopril, enalapril), and calcium channel blockers have shown significant regression of ventricular hypertrophy. The results in patients treated with diuretics alone and those treated with \(\beta\)-blockers are variable. \(^{20}\)

On the other hand, combined \(\alpha-\) and \(\beta\)-blockade (labetalol) has been shown to reduce left ventricular mass, while vasodilators (hydralazine, trimazosin) used alone have failed to induce regression of hypertrophy despite adequate blood pressure reduction. \(^{20}\) The lack of reduction in left ventricular mass in labetalol-treated patients in the present study was most likely due to the fact that the majority of patients had normal left ventricular mass and mass index (only two men and two women had increased mass). The short duration of treatment may also have played a role.

Looking at the raw data, we see in the labetalol group that 1 patient showed a tendency toward decreased left ventricular mass, while 8 showed no change and 3 tended to show an increase. In contrast, in the atenolol group, where the mean left ventricular diastolic dimension increased significantly, 10 patients showed a tendency toward increased left ventricular mass, 4 showed no change, and 2 tended to decrease. The latter changes did not reach statistical significance, however, and this variable response to \(\beta\)-blockade is consistent with previous reports. \(^{20}\)

**Left Ventricular Diastolic Function**

Evidence shows that left ventricular dysfunction may be an early and more sensitive marker of hypertensive heart disease than ventricular hypertrophy. \(^{1, 3, 9, 11, 12}\) The effects of treatment on diastolic dysfunction in hypertension largely remain to be determined, however. Treatment with diuretics, \(\beta\)-blockers, calcium channel blockers, and vasodilators has yielded variable results. \(^{8, 10, 13, 21}\) Differences in methods, patient selection, and stage and duration of treatment may have contributed to this variability.

In the present study, short-term treatment with combined \(\alpha-\) and \(\beta\)-blockade (labetalol) effected an improvement in diastolic filling. Improvement with \(\beta\)-blockade (atenolol) alone, on the other hand, did not reach statistical significance regardless of whether patients had normal or increased left ventricular mass. It is possible, however, that a longer treatment period with atenolol might have resulted in significant improvement in diastolic filling values. On the other hand, the so-called double-edged effects of \(\alpha\)-blockade in reducing atrial filling pressure through increased venous capacitance and maintaining systolic function through a reduction in total peripheral resistance may potentially improve ventricular relaxation, as noted in the present study.

**Clinical Importance**

Diastolic dysfunction leading to heart failure has been reported in hypertensive hypertrophic cardiomyopathy with normal or supernormal systolic function. \(^{10}\) Whether diastolic dysfunction will play an independent role in the stratification of risk in hypertension, as has ventricular hypertrophy, remains to be determined in long-term population studies.

The improvement in diastolic filling with short-term treatment with labetalol, in the absence of significant structural change, and the fact that a significant correlation was found between improvement in diastolic filling and reduction in mean blood pressure may reflect, at least in part, the combined role of \(\alpha-\) and \(\beta\)-adrenergic receptors on diastolic function. Of note, the heart rate was similar in both groups at baseline (labetalol, 76; atenolol, 77 beats/min) and with treatment (68 and 67 beats/min, respectively).
In summary, left ventricular filling abnormalities in mild hypertension are reversible with combined α- and β-adrenergic blockade. In view of the trend toward improvement in diastolic filling indexes with β-blockade alone, it is possible also that long-term treatment with atenolol may reverse diastolic dysfunction in mild hypertension. It would appear, however, that the addition of α-blockade enhances ventricular relaxation through maintaining cardiac output at lower filling pressures. Although this study was not designed to investigate the mechanism of this improvement, one may speculate that sympathetic inhibition is a major determining factor. The existence of a myocardial α-adrenergic receptor has been reported. When stimulated, these receptors produce trophic changes. It is tempting to speculate that inhibition of the same receptors could lead to improvement in ventricular compliance and filling. Other mechanisms, together with the hemodynamic changes discussed above, may certainly play a role, since improvement in diastolic function does not appear to be drug-specific.

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