Left Ventricular Mass and Mechanics in Mild-to-Moderate Hypertension: Effect of Nebivolol Versus Telmisartan

Katerina Fountoulaki, Vasilis Dimopoulos, John Giannakoulis, Elias Zintzaras, and Filippos Triposkiadis

Background: The aim of this study was to compare the effects of nebivolol and telmisartan on left ventricular mass (LVM) and midwall mechanics in mild-to-moderate hypertension.

Methods: A total of 40 patients with mild-to-moderate hypertension were randomized to receive either nebivolol (2.5 to 5.0 mg/day) or telmisartan (40 to 80 mg/day) to achieve a target diastolic blood pressure of <90 mm Hg. Blood pressure (BP) was measured with sphygmomanometry, and LVM and midwall fractional shortening (mFS) were estimated by two-dimensionally guided M-mode echocardiography at baseline and at 3-month follow-up.

Results: Age, sex distribution, and baseline SBP and DBP and heart rate were similar in the two groups. Both nebivolol and telmisartan reduced systolic (156 ± 7 v 124 ± 8 mm Hg, P < .01, and 153 ± 5 v 120 ± 7 mm Hg, P < .01, respectively) and DBP (99 ± 4 v 80 ± 2 mm Hg, P < .01 and 98 ± 2 v 80 ± 2 mm Hg, P < .01, respectively) and increased mFS (16% ± 2% v 19% ± 2%, P < .01, and 15% ± 2% v 18% ± 2%, P < .01, respectively). The LVM indices decreased significantly with both nebivolol (98 ± 16 v 84 ± 13 g/m², P < .01) and telmisartan (97 ± 13 v 83 ± 8 g/m², P < .01). We found that mFS was inversely related to DBP in the nebivolol but not in the telmisartan group.

Conclusions: In mild-to-moderate hypertension, nebivolol and telmisartan are equally effective in reducing BP and increasing mFS. There may be differences between nebivolol and telmisartan regarding the mechanism of increase in mFS. Am J Hypertens 2005;18:171–177 © 2005 American Journal of Hypertension, Ltd.

Key Words: Hypertension, midwall mechanics, nebivolol, telmisartan.

Essential hypertension is associated with progressive impairment of left ventricular (LV) systolic and diastolic function.1 However, recent data indicate that echocardiographic assessment of LV systolic function varies according to the method used. Standard indices of chamber dynamics such as ejection fraction and endocardial fractional shortening usually overestimate myocardial function, especially when LV wall thickness is increased.2,3 In contrast, fractional shortening at the midwall level, by considering the nonuniform thickening of internal and external myocardial layers, appears to be a physiologically more appropriate marker of LV systolic performance and provides prognostic information in asymptomatic patients at increased risk for target-organ damage.4–9

The reduction of echocardiographically determined LVM index during antihypertensive treatment has been demonstrated to reduce the risk of cardiovascular events,10,11 and recent meta-analyses have shown that antihypertensive medications differ in their ability to reduce LVM.12,13 However, the effect of antihypertensive treatment on LV mechanics assessed at the midwall level has been less well characterized. There is evidence that administration of β-blockers may improve systolic function in eccentric hypertrophy,14 but a paucity of data exist about their effect on pressure-overload hypertrophy. Likewise, there are sparse data regarding the effect of angiotensin II receptor blockers on LV mechanics in essential hypertension.

The present study was designed to assess the effect of two novel drugs: 1) nebivolol, a highly selective β₁ adrenoceptor blocking agent with peripheral vasodilating
properties, and 2) telmisartan, a highly selective antagonist of type 1 angiotensin II receptors. The study examined the effects of these drugs on arterial BP and LV structure and performance in untreated patients with essential hypertension.

Methods
Study Population
A total of 40 patients (13 men and 27 women, mean age 55 ± 6 years) with mild-to-moderate hypertension were enrolled in this open-label trial according to the following criteria: 1) office diastolic BP (DBP) 90 to 114 mm Hg as measured on two visits at a 1-week interval; 2) age <65 years; and 3) no medical treatment for elevated BP. Exclusion criteria were: 1) clinical or laboratory evidence of secondary hypertension, heart failure, ischemic heart disease, valvular heart disease, arrhythmias, peripheral vascular disease, chronic obstructive pulmonary disease, neurologic disorders, diabetes mellitus, renal dysfunction, or notable systemic disease; 2) contraindications to the study drugs; or 3) technically inadequate echocardiographic window.

The study was not sponsored by any pharmaceutical company and was conducted according to the guidelines of the scientific committee of our institution.

Randomization and Follow-Up
Patients were randomized to receive either nebivolol (2.5 to 5 mg/day) or telmisartan (40 to 80 mg/day). Doses were titrated based on weekly visits during the first 2 weeks to achieve a target DBP <90 mm Hg or a DBP reduction by ≥10 mm Hg. If BP remained uncontrolled after 2 weeks of treatment, indapamide was added at a dosage of 2.5 mg/day. If the therapeutic goal was still not achieved, patients were withdrawn from the study.

Baseline and follow-up evaluation at 1 and 3 months of therapy included a complete physical examination, routine blood chemistry, chest x-ray, standard 12-lead electrocardiogram, and transthoracic echocardiogram.

Measurement of BP
Office BP was measured by a standard mercury sphygmomanometer with the patient at the supine position for 10 minutes, using the first and fifth Korotkoff sounds to identify systolic and diastolic values, respectively. The average of six measurements on two separate visits performed 1 week apart was considered as the baseline BP for the analysis. Thereafter, BP was measured at each clinic visit, and the average of three measurements made 10 minutes apart was taken as the BP of the first and the third month.

Echocardiographic Examination
All patients underwent standard two-dimensionally guided M-mode and Doppler echocardiography by an experienced sonographer blinded to patient characteristics, using a commercially available machine (Hewlett-Packard Sonos 2000, Andover, MA) equipped with a 2.5- to 3.5-MHz transducer. Echocardiography was performed in a dimly lit room with the patient in the partial left decubitus position. Images were stored on videotape, coded with a random number, and read by a second blinded observer.

Left ventricular internal diameter and ventricular septal and posterior wall thicknesses were measured from the parasternal long-axis view at or just below the tips of mitral valve leaflets at end-diastole and end-systole according to the recommendations of the American Society of Echocardiography.15 The values of all echocardiographic parameters represent the mean value of measurements obtained in three consecutive cardiac cycles.

Left ventricular mass was calculated according to the method of Devereux et al.16 The LVM was indexed to body surface area and to height at the allometric power of 2.7 to correct for the effects of obesity.17

The LV mechanics were assessed at both the chamber level (as endocardial fractional shortening) and the midwall level (as midwall fractional shortening).

Endocardial fractional shortening (eFS) was calculated by using the standard formula: eFS = LVIDd – LVIDs / LVIDd, where LVIDd and LVIDs are the internal left ventricular dimensions in end-diastole and end-systole, respectively.

Midwall fractional shortening (mFS) was calculated by using a modified ellipsoidal model of LV geometry that took into account the epicardial migration of the LV midwall during systolic myocardial contraction, as previously described in detail.2,4,18,19 Briefly, LV wall is divided into inner and outer shells, which, by definition, have equal thickness in diastole. Assuming that total LV wall and its inner and outer shells have constant volumes throughout the cardiac cycle, at diastole and systole, yields:

\[
(LVIDd + Hd/2)^3 - LVIDd^3 = (LVIDs + Hs/2)^3 - LVIDs^3 (a)
\]

where H is the shell thickness, d is end-diastole, and s is end-systole. Because the two shells are considered to have equal thickness in diastole, \( H_d = (PWT_d + IVS_d) / 2 \), where PWT is the posterior wall thickness and IVS is the ventricular septal thickness. During systole, the inner shell thickens more than the outer shell and there is an epicardial migration of the theoretical midwall ring. A measure of the systolic thickness of the inner shell can be obtained by solving equation (a) for Hs/2. Once Hs/2 is known, mFS can be calculated as:

\[
mFS = [(LVIDd + Hd/2) - LVIDs + Hs/2] / (LVIDd + Hd/2).
\]

Circumferential end-systolic wall stress (cESS) was
used as a measure of myocardial afterload. It is estimated
by using a cylindrical model and systolic BP (SBP)
taken at the end of the echocardiogram, from the following
equation20:
\[
cESS = \text{SBP} \cdot \left(\frac{\text{LVd}^2}{2}\right) \cdot \left(1 + \left\{\frac{\text{LVd}^2}{2} + \frac{\text{PWT}^2}{2}\right\}\right) / \left(\frac{\text{LVd}^2}{2} - \left(\frac{\text{LVd}^2}{2}\right)^2\right).
\]
Observed mFS was also expressed as a percentage of
predicted mFS.6 The latter is calculated from a linear
semi-logarithmic model of regression analysis proposed
by de Simone et al., as follows21:
\[
predicted \text{mFS} = 25.99 - 3.54 \cdot \log (c \text{ESS})
\]
The ratio of observed to predicted mFS was therefore
used as an estimate of myocardial contractility indepen-
dent of afterload conditions and was termed “stress-cor-
corrected mFS.”6

Doppler evaluation of LV diastolic filling was per-
formed from the apical four-chamber view by placing the
pulsed Doppler sample volume at the mitral valve leaflet
tips to measure isovolumic relaxation time (IVRT), peak
early transmitral flow velocity (E), peak late transmitral
flow velocity (A), and deceleration time of E velocity (E
dec), as previously described.22

### Statistical Analysis

The baseline comparisons were performed using the
Kruskal-Wallis test, and individual comparisons were
made using the Mann-Whitney U test with the Bonferonni
correction. The data set from the two drugs was analyzed
using repeated-measures analysis of variance (ANOVA)
for repeated measures. The ANOVA included the follow-
ing sources: drug effect, patients within drug effect, fol-
low-up effect, interaction between follow-up and drug, and
error.23 Subsequent multiple comparisons and confidence
intervals were adjusted using the Bonferonni correction.
The drug effect for each follow-up is presented as a 95%
confidence interval (CI). Comparisons between categorical
variables were made with the \( \chi^2 \) test. The association
between mFS and the parameters heart rate, BP, and LVM
at the end of follow-up was investigated by fitting a linear
regression model. A \( P \) value of < .05 was considered
statistically significant. The analysis was performed using
SPSS, release10 (SPSS Inc., Chicago, IL).

### Results

#### Demographic and Clinical Characteristics

Age, sex distribution, baseline heart rate, body mass index,
and baseline SBP and DBP were not significantly different
between the nebivolol and telmisartan groups (Table 1).
Heart rate decreased significantly in both the nebivolol

#### Table 1. Demographic and clinical characteristics of study subjects at baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nebivolol (N = 20)</th>
<th>Telmisartan (N = 20)</th>
<th>Estimated Difference N-T with 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>54 ± 6.7</td>
<td>56 ± 4.4</td>
<td></td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>6/14</td>
<td>7/13</td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>71.8 ± 7.2</td>
<td>71.7 ± 7.2</td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>29.85 ± 5.15</td>
<td>30.66 ± 4.22</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>155.7 ± 6.8</td>
<td>153.0 ± 4.8</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>98.5 ± 4.1</td>
<td>97.5 ± 2.1</td>
<td></td>
</tr>
</tbody>
</table>

\( P = \) NS for all variables.

#### Table 2. Treatment and follow-up effects on heart rate and blood pressure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nebivolol (N) (N = 20)</th>
<th>Telmisartan (T) (N = 20)</th>
<th>Estimated Difference N-T with 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>71.8 ± 7.2</td>
<td>71.7 ± 7.2</td>
<td>0.12 (−4.61 to 4.84)</td>
</tr>
<tr>
<td>Baseline</td>
<td>63.4 ± 6.4*</td>
<td>67.8 ± 8.5†</td>
<td>−4.4 (−9.39 to −0.50)</td>
</tr>
<tr>
<td>1 month</td>
<td>59.8 ± 6.7</td>
<td>65.0 ± 7.8*</td>
<td>−5.6 (−10.3 to −0.92)</td>
</tr>
<tr>
<td>3 months</td>
<td>155.7 ± 6.8</td>
<td>153.0 ± 4.8</td>
<td>2.5 (−1.33 to 6.36)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg) Baseline</td>
<td>130.9 ± 7.8*</td>
<td>128.2 ± 6.4*</td>
<td>2.7 (−2.01 to 7.36)</td>
</tr>
<tr>
<td>1 month</td>
<td>123.6 ± 8.3*</td>
<td>120.1 ± 6.5*</td>
<td>3.7 (−1.21 to 8.55)</td>
</tr>
<tr>
<td>3 months</td>
<td>98.5 ± 4.1</td>
<td>97.5 ± 2.1</td>
<td>0.96 (−1.18 to 3.10)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg) Baseline</td>
<td>82.8 ± 2.7*</td>
<td>82.9 ± 2.5*</td>
<td>−0.06 (−1.79 to 1.66)</td>
</tr>
<tr>
<td>1 month</td>
<td>79.9 ± 2.3*</td>
<td>79.8 ± 2.2*</td>
<td>0.27 (−1.156 to 1.69)</td>
</tr>
</tbody>
</table>

CI = confidence interval.

* \( P < .01; \) † \( P < .05; \) comparison of the current time point to baseline.
for nebivolol it was 17% (reduction in heart rate in three months was 9%, whereas significantly different in the end time: for telmisartan, the two drugs were increased, whereas cESS decreased significantly in both the nebivolol and telmisartan groups with no significant intergroup differences during follow-up. The increase in mFS was associated with a decrease in DBP (r = -0.33, p < .05) and was not associated with changes in heart rate (r = -0.04, P = NS), SBP (r = 0.11, P = NS) and LVM (r = -0.04, P = NS) in the nebivolol group. No associations between mFS and heart rate (r = -0.01, P = NS), SBP and DBP (r = -0.07 and r = 0.04, respectively, P = NS), and LVM index (r = -0.007, P = NS) were observed in the telmisartan group.

**Transmitral Diastolic Flow**

All parameters of transmitral diastolic flow (E-wave velocity, A-wave velocity, E-wave deceleration time, and isovolumic relaxation time) did not significantly change in the nebivolol and the telmisartan groups, and no signifi-
significant intergroup differences were observed during follow-up (Table 4).

**Discussion**

The findings of the present study indicate that in essential hypertension the following are in effect: 1) abnormalities of LV systolic function assessed at the midwall level are present together with those of LV diastolic filling assessed by Doppler indices of transmirtal diastolic flow; 2) treatment with nebivolol and telmisartan is associated with a significant decrease in SBP and DBP and an increase in mFS; and 3) there may be differences between nebivolol and telmisartan with regard to the mechanism of increase in mFS.

**Left Ventricular Mechanics in Essential Hypertension**

Until recently it was believed that, in essential hypertension, diastolic precedes systolic dysfunction and that systolic myocardial performance in the early stages of the disease is normal or even “supernormal.” However, it has become apparent that use of conventional measures of chamber dynamics, such as ejection fraction and eFS, does not accurately reflect the contractile behavior of myocardial fibers across the LV wall. Furthermore, the above-mentioned standard indices obscure early deficiencies in myocardial performance, failing to reveal changes in systolic function with antihypertensive treatment. Measurement of LV systolic function by mFS has been shown to be more accurate in representing myocardial performance than is eFS.

The definition of a time sequence between systolic and diastolic dysfunction is difficult, given the close relationship of these phenomena from mechanical and energetic points of view. Several studies in essential hypertension have shown that abnormalities of LV filling precede reduced LV systolic performance assessed at the endocardial level. However, recent studies have demonstrated that when LV systolic function is assessed at the midwall level, abnormalities of LV systolic performance parallel those of LV filling. Indeed, in this study, untreated patients with essential hypertension exhibited both reduced midwall fractional shortening and abnormal transmirtal flow velocity pattern.

**Effects of Antihypertensive Treatment**

Both nebivolol and telmisartan effectively reduced SBP and DBP and increased mFS. In contrast, despite the changes in heart rate and loading conditions, there was an apparent stability of the transmirtal flow velocity profile in both groups.

Nebivolol is a new highly selective β1-adrenergic antagonist that causes NO-mediated smooth muscle cell relaxation and vasodilation and that has been shown to control BP over a 24-h period with a single dose. Telmisartan is a blocker of angiotensin II type 1 receptors, with a 24-h antihypertensive efficacy seen across a broad range of patients. In the present study, the reductions in BP produced by treatment with nebivolol (2.5 to 5.0 mg orally every day) and telmisartan (40 to 80 mg orally every day)

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**Table 4.** Treatment and follow-up effects on left ventricular diastolic filling indices

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nebivolol (N = 20)</th>
<th>Telmisartan (T = 20)</th>
<th>Estimated Difference N-T with 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak velocity E wave (cm/sec)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>67.1 ± 15.4</td>
<td>59.8 ± 14.8</td>
<td>6.6 (−3.2–16.4)</td>
</tr>
<tr>
<td>1 month</td>
<td>71.1 ± 15.3</td>
<td>63.5 ± 9.8</td>
<td>13.7 (5.2–22.1)</td>
</tr>
<tr>
<td>3 months</td>
<td>74.0 ± 18.5</td>
<td>65.7 ± 11.1</td>
<td>7.2 (−2.6–17.0)</td>
</tr>
<tr>
<td>Peak velocity A wave (cm/sec)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>74.3 ± 10.5</td>
<td>71.4 ± 12.6</td>
<td>2.5 (−5.1–10.1)</td>
</tr>
<tr>
<td>1 month</td>
<td>67.5 ± 11.6</td>
<td>70.9 ± 11.2</td>
<td>−4.4 (−11.9–3.1)</td>
</tr>
<tr>
<td>3 months</td>
<td>68.0 ± 10.3</td>
<td>70.7 ± 9.2</td>
<td>−1.4 (−10.5–2.3)</td>
</tr>
<tr>
<td>E/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.97 ± 0.2</td>
<td>0.86 ± 0.2</td>
<td>0.1 (−0.06–0.26)</td>
</tr>
<tr>
<td>1 month</td>
<td>1.09 ± 0.2</td>
<td>0.90 ± 0.2</td>
<td>0.31 (−0.17–0.45)</td>
</tr>
<tr>
<td>3 months</td>
<td>1.10 ± 0.2</td>
<td>0.95 ± 0.2</td>
<td>0.15 (−0.003–0.29)</td>
</tr>
<tr>
<td>E-wave deceleration time (msec)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>171.5 ± 22.8</td>
<td>179.0 ± 27.1</td>
<td>−6.4 (−22.7–9.9)</td>
</tr>
<tr>
<td>1 month</td>
<td>175.0 ± 18.8</td>
<td>176.8 ± 18.7</td>
<td>−1.8 (−14.2–10.5)</td>
</tr>
<tr>
<td>3 months</td>
<td>171.5 ± 16.6</td>
<td>171.5 ± 16.6</td>
<td>0.97 (−9.8–11.7)</td>
</tr>
<tr>
<td>Isovolumic relaxation time (msec)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>80.0 ± 8.6</td>
<td>80.5 ± 9.4</td>
<td>−0.53 (−6.5–5.4)</td>
</tr>
<tr>
<td>1 month</td>
<td>81.0 ± 10.2</td>
<td>82.1 ± 6.1</td>
<td>−1.1 (−6.7–4.4)</td>
</tr>
<tr>
<td>3 months</td>
<td>79.5 ± 9.4</td>
<td>83.0 ± 4.7</td>
<td>−3.1 (−8.0–1.7)</td>
</tr>
</tbody>
</table>

CI = confidence interval.
were of similar magnitude. Likewise, both drugs significantly reduced LVM, and no intergroup difference was observed during follow-up. It should be noted that this rapid (within 3 months) LVM regression has been reported by other investigators.9,31

Treatment with both nebivolol and telmisartan was associated with an increase in mFS in the present study. However, the results of regression analysis suggest that the mechanism of increase may be different. Indeed, in the nebivolol group, the improvement in midwall mechanics was associated with a decrease in DBP, a finding that was not observed in the telmisartan group.

In conclusion, abnormalities of midwall mechanics and transmitral diastolic flow are present in untreated patients with mild-to-moderate essential hypertension and normal LV ejection fraction. The disparity between midwall and endocardial mechanics confirms the need to measure mFS to track the beneficial effect of antihypertensive treatment. Nebivolol and telmisartan are equally effective in decreasing SBP and DBP and in increasing mFS. There may be differences between nebivolol and telmisartan regarding the mechanism of increase in mFS.

References


