Midwall Mechanics Are Improved After Regression of Hypertensive Left Ventricular Hypertrophy and Normalization of Chamber Geometry

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Background—It is still unclear whether substantial regression of hypertensive left ventricular hypertrophy (LVH) and normalization of chamber geometry are associated with improved left ventricular (LV) myocardial function.

Methods and Results—Midwall mechanics were evaluated in 152 patients undergoing 1 year of effective antihypertensive treatment. Two-dimensionally directed M-mode echocardiography was performed as follows: (1) after a 4-week placebo “run-in” period, (2) after 1 year of treatment with 20 mg/d lisinopril (alone or associated with 12.5 to 25 mg/d hydrochlorothiazide), and (3) after a final 1-month placebo period to allow blood pressure (24-hour average ambulatory monitoring) to return to pretreatment levels. Treatment-induced reductions in blood pressure (from 149±16/95±11 to 131±12/83±10 mm Hg, P<0.05) and circumferential end-systolic wall stress (from 84±22 to 72±19 g/cm², P<0.05) were associated with a marked reduction in LV mass index (from 159±30 to 133±26 g/m², P<0.05). LVH regression was accompanied by an increase in midwall fractional shortening (from 19.7±2.7% to 20.9±2.7%, P<0.05) and by a decrease in relative wall thickness (from 48.2±7.7% to 44.1±6.7%, P<0.05). The improvement in midwall function associated with afterload reduction and substantial LVH regression persisted after antihypertensive therapy withdrawal and restoration of the hypertensive state. Despite a significant increase in end-systolic wall stress, further LV chamber remodeling did not occur. The preservation of relative wall thickness was associated with a persistent improvement in midwall systolic function.

Conclusions—Regression of concentric LVH is associated with an improvement of midwall systolic function, which is more dependent on the normalization of LV geometry than on the reduction in LV systolic stress. (Circulation. 2001; 103:678-683.)

Key Words: echocardiography ■ hemodynamics ■ hypertrophy ■ myocardial contraction ■ systole

Left ventricular hypertrophy (LVH) represents a structural adaptation of the heart to chronic pressure overload, which contributes to wall stress normalization.1-2 However, hypertensive LVH is accompanied by a number of adverse consequences for the heart, including a reduction in systolic and diastolic function,3-5 reduced coronary reserve,6-7 an increased incidence of arrhythmias,8,9 and a reduced ability of cardiac volume receptors to reflexly modulate systemic vascular resistance and renin production.10 It has also been shown that at any given blood pressure (BP) level, the presence of electrocardiographic LVH is associated with an increased cardiovascular risk11,12 and that this is also the case for echocardiographic LVH, both in the general population13,14 and in hypertensive individuals.15-17

Although it may seem logical that an antihypertensive treatment that causes a regression of LVH should be followed by a reduction of its consequences, this has not been conclusively proven. This is because the studies that have supported the hypothesis that LVH regression by antihypertensive treatment leads to a reduction in cardiovascular morbidity and mortality have inevitably made use of an uncontrolled design.17-21 Furthermore, the reports that LVH regression is accompanied by an improvement of the cardiac functions that are disturbed by LVH (increased coronary reserve,22 reduced arrhythmias,8 increased myocardial contractility,21 increased sensitivity of the cardiopulmonary reflex,10 etc) have been based on studies that had at least one of the following limitations: (1) small sample size, (2) open nature, and (3) assessment of the relationship between cardiac functions and LVH regression during antihypertensive treatment (ie, when the improvement could be due to the reduced pressure overload or the drug effects per se).
In the present study, the effects of LVH regression caused by long-term antihypertensive treatment on left ventricular (LV) systolic function were studied without the above limitations. Thus, our study included (1) a large number of patients in whom 12 months of antihypertensive treatment caused a substantial regression of echocardiographic LVH and (2) a further month of placebo washout from treatment to avoid the confounding, direct cardiac effect of antihypertensive drugs and to permit LV afterload to return to pretreatment levels. LV systolic function was studied by midwall shortening because this may better characterize myocardial contractility and predict, when depressed, patients’ prognosis. Because the regression of echocardiographic LVH correlated more closely with changes in ambulatory LVH than in clinic BP, the former was also used to assess the efficacy of antihypertensive therapy and the return to pretreatment levels during the final placebo washout period.

Methods

Patient Population

The study was performed on patients enrolled in the SAMPLE study (Study on Ambulatory Monitoring of Blood Pressure and Lisinopril Evaluation), a multicenter trial involving 11 hypertension clinics located in Italy. Briefly, patients with essential hypertension of age range from 20 to 65 years, (2) diastolic BP between 95 and 115 mm Hg after a 4-week period without antihypertensive drugs (previously treated patients) or a 3-week observation period (previously untreated patients), and (3) echocardiographic LVH and (see below). Exclusion criteria were as follows: (1) history and/or signs of cardiovascular complications (eg, heart failure, myocardial infarction, stroke, and/or angina pectoris) or major target-organ damage (eg, serum creatinine >1.5 mg/dL), (2) major cardiovascular or noncardiovascular disease besides hypertension, (3) pregnancy or lactation, (4) contraindications to the antihypertensive study drug(s), (5) conditions that would prevent the collection of technically adequate echocardiograms (eg, obesity or pulmonary emphysema), and (6) atrial fibrillation or other major arrhythmias. Patients were also excluded if previous antihypertensive treatment consisted of >2 drugs to reduce the risk of subsequent withdrawal because of inadequate BP control (see below). All patients gave informed consent to the study, and the protocol was approved by the Ethical Committees of the centers involved.

Blood Pressure

In all patients, supine BP was measured by a mercury sphygmomanometer using the first and fifth Korotkoff sounds to identify systolic and diastolic values, respectively. The average of 2 measurements was used as the clinic BP. In each individual, all measurements were performed in the morning, in the same arm, and by a single doctor just before starting the 24-hour ambulatory BP monitoring, which was performed using an oscillometric automatic device (Spacelab 90202 or 90207). During treatment and placebo, both measurements were made after administration of the tablet(s) (see below). Automatic BP readings were obtained at 15-minute intervals during the day (6 AM to midnight) and at 20-minute intervals during the night (midnight to 6 AM). In all patients, ambulatory BP and heart rate were averaged to obtain 24-hour means.

Study Protocol

The study was designed to evaluate whether LVH regression induced by antihypertensive treatment was related more closely to treatment-induced changes in ambulatory BP compared with the clinic or home BP. An additional purpose, however, was to investigate the changes in midwall function associated with LVH regression when the direct cardiac effect of antihypertensive agents and of the BP reduction per se were removed. To this aim, recruited patients were given 20 mg of lisinopril daily. After 1 month, nonresponders to lisinopril (ie, patients in whom clinic diastolic BP was not reduced to <90 mm Hg or by ≥10 mm Hg) were given additional treatment with 12.5 mg of hydrochlorothiazide, which was increased to 25 mg daily after 1 more month if a satisfactory response was not obtained. Effective treatment was continued to complete an overall treatment period of 12 months, after which antihypertensive treatment was substituted with placebo for 1 additional month to allow BP to vanish, while preserving all or most of the LVH regression seen at the end of the active treatment period. Clinic BP was measured before treatment, after 1, 2, 3, 6, and 12 months of treatment, and at the end of the final placebo period. Ambulatory BP and echocardiographic measurements were obtained

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<table>
<thead>
<tr>
<th>Hemodynamic and Echocardiographic Variables at Baseline, During Antihypertensive Treatment, and After the Placebo Period</th>
<th>Baseline</th>
<th>Treatment (3 mo)</th>
<th>Treatment (12 mo)</th>
<th>Final Placebo Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinic SBP/DBP, mm Hg</td>
<td>165±15/105±5</td>
<td>141±13/87±7</td>
<td>139±12/87±7</td>
<td>158±14/103±8†</td>
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<tr>
<td>24-h SBP/DBP, mm Hg</td>
<td>149±16/95±11</td>
<td>130±12/81±8*</td>
<td>131±12/83±10*</td>
<td>145±14/92±9†</td>
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<tr>
<td>24-h HR, beats/min</td>
<td>73±10</td>
<td>74±9</td>
<td>74±9</td>
<td>75±9</td>
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<tr>
<td>LVMI, g/m²</td>
<td>157±32</td>
<td>143±20*</td>
<td>133±26</td>
<td>141±28†</td>
</tr>
<tr>
<td>EDD, mm</td>
<td>50.6±4.6</td>
<td>50.2±4.2</td>
<td>50.1±3.9*</td>
<td>50.9±4.4†</td>
</tr>
<tr>
<td>ESd, mm</td>
<td>30.4±4.8</td>
<td>30.0±4.6</td>
<td>29.8±4.3*</td>
<td>30.4±4.6†</td>
</tr>
<tr>
<td>Endocardial FS, %</td>
<td>40.1±6.2</td>
<td>40.4±6.4</td>
<td>40.6±5.9</td>
<td>40.6±6.2</td>
</tr>
<tr>
<td>Midwall FS, %</td>
<td>19.8±2.7</td>
<td>20.4±2.6*</td>
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<td>20.6±2.9*</td>
</tr>
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<td>CWS, g/cm²</td>
<td>83.5±22.2</td>
<td>71.3±19.8*</td>
<td>72.0±19.3*</td>
<td>83.7±24.7†</td>
</tr>
<tr>
<td>Posterior wall thickness, mm</td>
<td>11.4±1.6</td>
<td>10.8±0.15*</td>
<td>10.3±1.5</td>
<td>10.6±1.6</td>
</tr>
<tr>
<td>Septal wall thickness, mm</td>
<td>12.8±1.7</td>
<td>12.0±0.16*</td>
<td>11.6±1.5'</td>
<td>11.7±0.16*</td>
</tr>
<tr>
<td>RWT, %</td>
<td>48.2±7.7</td>
<td>45.7±6.9*</td>
<td>44.0±6.6*</td>
<td>44.1±7.2*</td>
</tr>
</tbody>
</table>

Values are mean±SD. SBP indicates systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; LVMI, left ventricular mass index; EDD, end-diastolic diameter; ESd, end-systolic diameter; FS, fractional shortening; CWS, circumferential wall stress; and RWT, relative wall thickness. *P<0.05 vs baseline; †P<0.05 vs treatment at 12 months.
before treatment, after 3 and 12 months of treatment, and at the end of the final placebo period.

**Echocardiographic Data**

**LV Mass and Wall Thickness**

Echocardiographic data were collected in the morning by the same physician in each center with the patient in a supine left lateral decubitus position. Two-dimensionally targeted M-mode echocardiography was performed after the longitudinal parasternal view had been checked to avoid angulation of the ultrasonic beam and consequent changes in the LV shape. Tracings were recorded on light-sensitive paper at a speed of 50 mm/s. LV internal dimensions, posterior wall thickness, and interventricular septum thickness were analyzed by a single reader according to the standards of the American Society of Echocardiography. LV mass was calculated according to the Penn convention and was indexed to body surface area. Relative wall thickness was computed as the sum of posterior wall thickness and interventricular septum thickness divided by LV end-diastolic dimension.

LV was considered to be present (and the patient was then recruited) if LV mass index (LVMI) exceeded 110 g/m² in women or 131 g/m² in men. All echocardiographic tracings, however, were examined by 4 expert readers from 2 previously established centers to remove echocardiographic tracings of poor quality by uniform criteria and to recalculate the data blindly. The LVMI provided by the control analysis (which was, on average, 2.9% less than that reported by peripheral centers) was used for calculations. The intraobserver and interobserver coefficients of variation of the “central” measurements were, respectively, 0.5% and 0.8% for LV end-diastolic diameter, 3.2% and 3.9% for LV internal dimensions, and 3.4% and 3.9% for posterior wall thickness.

**LV Chamber Function and Myocardial Function**

Fractional shortening at the endocardium was calculated as the difference between the end-diastolic and end-systolic circumference divided by the end-diastolic circumference and then multiplied by 100. Myocardial function was assessed as midwall fractional shortening and calculated using a 2-shell cylindrical model, a method that allows a better characterization of systolic myocardial function than endocardial fractional shortening, especially when relative wall thickness is high. To assess LV chamber and myocardial function, endocardial and midwall fractional shortening were related to circumferential end-systolic wall stress (σw), which was calculated as follows: 

\[ \sigma_w = \frac{P \times 2\pi \times (1 + \frac{b^2}{r^2})}{b^2 - a^2}, \]

where P indicates end-systolic pressure, which is derived as one-third of the sum of systolic pressure plus twice the diastolic pressure. a is the endocardial radius, b is the epicardial radius, and r is the midwall radius.

**Statistics**

Data from individual patients were expressed as mean±SD. Comparisons between continuous variables were performed by repeated-measure ANOVA followed by a 2-tailed paired Student’s t test with Bonferroni correction. The number of patients presenting with LVH at the different times of the study were compared by χ² test. P<0.05 was considered statistically significant.

**Results**

**Changes in Blood Pressure and Cardiac Structure**

The BP and echocardiographic values before treatment, during treatment, and after the final placebo period are shown in the Table. Of the 184 patients who completed the 12-month treatment, 46% were treated only with lisinopril, whereas the others required lisinopril plus hydrochlorothiazide. The study population was composed of 152 patients in whom technically suitable echocardiographic data were available before treatment, at the end of treatment, and after the final placebo period. Treatment markedly reduced 24-hour average BP at month 3, with no further change at month 12, and a return toward pretreatment values after the final placebo period. The 24-hour average heart rate and body surface area did not change during the study. At entry, LVMI was much above the cutoff values, without chamber dilatation, thus indicating concentric LVH. LVMI showed a reduction after 3 months of treatment and more so after 12 months of treatment, with a 46% decrease in the number of patients who had LVH according to the entry criteria (82 of 152 patients). The difference was statistically significant by χ². LVH regression was due to a reduction of both the posterior wall and the septal thicknesses; only a minor decrease in LV internal dimensions occurred during treatment, which thus caused a decrease in relative wall thickness (ie, a tendency for chamber geometry to normalize). During the final placebo period, only one-third of the treatment-induced LVH regression was reversed, mainly due to a slight increase in LV dimensions.

Both entry BP and LVMI showed a normal distribution. This was also the case for the changes in BP and LVMI induced by the 12-month treatment (data not shown).
LV Systolic Chamber Function and Myocardial Function

The Table and Figure also show that the 12 months of treatment decreased circumferential end-systolic stress, which returned toward pretreatment values after the placebo period. Endocardial fractional shortening did not change at 3 and 12 months of treatment; this caused an increase in circumferential shortening at the midwall. The improvement in midwall fractional shortening persisted after the final placebo period, at a time when BP, systolic stress, and LV mass had all increased. Relative wall thickness was reduced by treatment and did not change after placebo, suggesting that the improvement in LV chamber geometry was preserved, despite the increase in LV afterload and in LV mass.

With respect to baseline, treatment-induced changes in midwall fractional shortening were linearly correlated with changes in LV end-systolic stress ($r=0.603, P<0.01$), peak systolic stress ($r=0.563, P<0.01$), relative wall thickness ($r=0.451, P<0.01$), LV end-diastolic dimension ($r=0.272, P<0.01$), and LV mass ($r=0.168, P<0.05$). Stepwise regression analysis was performed to assess the relationships between changes in midwall fractional shortening (dependent variable) and changes in LV mass, LV end-diastolic dimension, LV end-systolic stress, and relative wall thickness (independent variables). In addition to the expected correlation with changes in end-systolic stress, changes in midwall fractional shortening were correlated with changes in relative wall thickness but not with changes in the LV end-diastolic dimension, which failed to enter the stepwise regression model. Similar results were obtained when comparing data at baseline and at the end of the final placebo period (ie, after treatment-induced changes in LV mass and geometry, but at comparable BP values). Changes in LV end-diastolic dimensions entered the multiple regression analysis model ($P=0.048$) only when comparing data at the end of the 12-month treatment period and at the end of the final placebo period.

Discussion

In our 152 hypertensive patients with LVH, the 12-month administration of an ACE inhibitor (plus, when needed, a diuretic) was accompanied by a clear-cut reduction in BP, which was associated with a reduced prevalence of LVH (~46%), LV geometric remodeling, and a reduction in the initially elevated LVMI (~14%). The main finding of the study, however, is that while leaving systolic chamber function relatively unaffected, the 12-month treatment was accompanied by a significant improvement in LV midwall shortening, which was entirely maintained after the 1-month placebo period that followed the treatment, during which (1) one third of the regression of LVH was reversed, (2) any direct cardiac effect of antihypertensive treatment was washed out, and (3) BP was restored almost to the elevated pretreatment values. This indicates that myocardial systolic function is improved by LVH regression and normalization of chamber geometry, independent of the drugs used to cause it or on the favorable consequences of a reduced LV afterload on the myocardium. To our knowledge, this is the first unequivocal evidence of this phenomenon obtained in a large human database.

Several other findings of our study deserve to be discussed. First, the improvement of midwall shortening was related to the treatment-induced improvement of relative wall thickness (ie, the tendency of LV chamber geometry to become less concentric). This is in line with previous observations by Aurigemma et al,25 who showed that in a substantial portion of older patients with a pronounced relative wall thickness, myocardial function was depressed despite normal ejection fraction and LVMI. Thus, myocardial function and LV geometry seem to have a preferential relationship, which implies that the latter should always be assessed when investigating systolic function and its variations in patients with LVH regression. Second, in our patients, there was a discrepancy between the modifications in the midwall and the endocardial indices of LV systolic function that followed LVH regression, because while the former improved, the latter remained unchanged. This expands on previous studies that have shown a similar discrepancy in patients in whom LVH was due to aortic stenosis,25 hypertensive heart disease,24,35 or hypertrophic cardiomyopathy36 and that have additionally reported that in the presence of increased relative wall thickness, chamber indices of systolic function such as endocardial shortening or ejection fraction may be normal or even supranormal at a time when there is reduced myocardial shortening. Studying midwall mechanics, therefore, seems to be of fundamental importance to properly characterize LV systolic function in the presence of LVH and after this structural abnormality has been reduced or reversed by treatment. Unfortunately, thus far, studies addressing changes in LV systolic function after LVH regression by antihypertensive treatment have mainly used endocardial indices and, thus, have often been unable to observe any consistent improvement.37–41

The observed absolute increase in midwall shortening with regression of LVH was ~1.1 points, ie, a percentage variation of ~5.5%. This must be viewed in the light of the data from De Simone and coworkers,26 who found that a 2-point difference in midwall shortening (15% versus 17%) was associated with a marked increase in the relative risk of cardiac morbidity or death in hypertensive patients, particularly in the presence of LVH (ie, in patients comparable to our patients). Thus, it is likely that the observed change in midwall shortening has biological importance.

Our study has 3 limitations. (1) Because our population consisted of hypertensive patients with concentric LVH, caution should be exercised in extending our conclusions to patients in whom antihypertensive treatment causes a regression of LV chamber dilation and eccentric LVH. (2) In our study, systolic function was only measured in the resting state, which does not allow for conclusions about the improvement of myocardial performance during exercise or a sudden increase in LV afterload after LVH regression. The few studies that are available on this issue have thus far concluded that preserved cardiac output, ejection fraction, and exercise tolerance occur after a treatment-induced reduction of (an initially elevated) LV
mass. However, an abnormal response to exercise was recently described in asymptomatic, hypertensive patients with midwall myocardial dysfunction. Thus, this sensitive marker of LV systolic performance might also be useful in the detection of subtle alterations in myocardial reserve in the presence of \( V \) and after changes of \( V \) mass. (3) De Simone at al showed that midwall shortening may be increased when preload is increased. Although in our study we did not directly measure preload, it is likely that its contribution to the observed changes in midwall shortening was only minor because \( V \) end-diastolic diameter (ie, an indirect measure of preload) showed only a small reduction after 12 months of treatment \( \text{vis a vis} \) a much greater change in \( V \) midwall shortening. Furthermore, although at multivariate analysis the change in \( V \) end-diastolic diameter and midwall shortening between treatment and final placebo showed a correlation of borderline significance, on average the latter remained stable in the face of an increase in the former. Finally, compared with baseline, midwall shortening was increased after the final placebo period, despite similar \( V \) end-diastolic diameters.

In conclusion, our study shows that a regression of concentric \( V \) by antihypertensive treatment is accompanied by an improved \( V \) systolic function, which can be visualized at the midwall level and is presumably due to the normalization of \( V \) chamber geometry. This offers new evidence in favor of the beneficial effect of \( V \) regression in hypertension, supporting the conclusion that \( V \) regression should be regarded as an important intermediate goal of antihypertensive treatment (ie, a goal that could prevent the deterioration of cardiac function and the appearance of cardiac complications).

References

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