Change in Systolic Left Ventricular Performance After 3 Years of Antihypertensive Treatment
The Losartan Intervention for Endpoint (LIFE) Study

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Background—We have shown that hypertensive patients with left ventricular (LV) hypertrophy have decreased LV midwall mechanics, but the effect of antihypertensive therapy remains unclear.

Methods and Results—Echocardiograms were recorded at baseline in 679 hypertensive patients and ECG LV hypertrophy and repeated yearly during 3 years of blinded treatment to achieve target blood pressures (BPs) of 140/90 mm Hg. On average, BP was reduced from 174±21 to 147±19 over 95±11 to 82±10 mm Hg and LV mass from 234±56 to 194±50 g. Endocardial fractional shortening (FS) decreased slightly, whereas midwall FS increased from 15.4±2.0% to 16.8±2.1% and stress-corrected midwall FS increased from 97±13 to 105±12% (all P<0.001). Change in midwall FS was related inversely to change in LV mass (LVM), relative wall thickness (RWT), and diastolic BP and directly to change in Doppler stroke volume (SV, all P<0.001). Multivariate analysis showed that change in MWS was independently inversely related to changes in LVM (β=−0.211), RWT (β=−0.334, all P<0.001), and diastolic BP (β=−0.088, P<0.05) and directly related to SV (β=0.192, P<0.001) with control for blinded therapy. Change in stress-corrected midwall shortening was inversely independently associated with changes in LVM (β=−0.153) and RWT (β=−0.562) and directly with changes in SV (β=0.145) and systolic BP (β=0.5221, all P<0.001) with control for blinded therapy.

Conclusions—Antihypertensive therapy reduced LVM and increased LV midwall shortening and contractility with a small decrease in LV chamber function and significant increase in SV. Change in systolic LV performance was independently associated inversely with change in LVM, RWT, and BP and directly with change in SV. (Circulation. 2002;106:227–232.)

Key Words: echocardiography ■ electrocardiography ■ hypertrophy ■ heart failure ■ hypertension

Left ventricular (LV) hypertrophy and LV systolic dysfunction both predict morbidity and mortality, and their relation in hypertensive patients has been extensively studied. LV systolic performance has commonly been assessed as the ratio of observed LV endocardial fractional shortening (FS) to the value predicted by the level of end-systolic stress in healthy individuals. By this analysis, systolic performance appears supranormal in many hypertensive patients, especially in the absence of LV hypertrophy. LV midwall shortening (MWS), in relation to stress, provides a different impression of the integrity of systolic performance; MWS may be impaired in hypertensive patients with normal or supranormal LV ejection fraction. Depressed MWS has been shown to predict adverse outcome in hypertensive patients, especially in the subgroup with LV hypertrophy.

Although it is logical that LV mass (LVM) regression attributable to antihypertensive treatment would improve LV chamber and myocardial systolic function, it has not been well characterized in large series of hypertensive patients, especially not in relation to different geometric patterns of LV adaptation and long-term follow-up. Furthermore, little is known about whether LV systolic performance improvement is independent of blood pressure (BP) reduction and whether this affects only patients with concentric LV geometry (ie, increased relative wall thickness [RWT]).

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Although smaller studies have shown that it is possible to improve systolic LV midwall function, these are somehow conflicting, because one study indicated that LVM regression is important in improving midwall shortening, whereas in another study, improved midwall shortening was more closely related to normalization of RWT than of LVM. Only conflicting, because one study indicated that LVM regression is important in improving midwall shortening, whereas only one controlled moderate-sized study examined the effect of treatment on LV systolic function, but it was restricted to patients with concentric LV hypertrophy and was limited in time. Therefore, this study was undertaken to examine the impact of LVM regression and BP reduction over 3 years of LV endocardial FS and midwall mechanics in a large series of hypertensive patients with ECG LV hypertrophy with known high prevalence of impaired systolic function and whose geometric patterns were assessed by echocardiography.

Methods

Eligible individuals were 963 patients with stage II and III hypertension enrolled in the Losartan Intervention For Endpoint (LIFE) Echocardiography Substudy examined with yearly echocardiograms during 3 years of antihypertensive treatment. Eligible individuals were 963 patients with stage II and III hypertension enrolled in the Losartan Intervention For Endpoint (LIFE) study because of one or more of the following: inability to obtain echocardiography substudy participants were ineligible for the present study because of death (n = 95 and n = 22 and 24, respectively) or Doppler stroke volume.

Echocardiographic Methods

Echocardiographic procedures for this study are previously described. End-diastolic LV dimensions were used to calculate LVM by an anatomically validated formula (r²=0.90 versus necropsy LVM). LV hypertrophy was considered present when LVM >116 g/m² for men and >104 g/m² for women. RWT was calculated as \( \frac{LVM}{LVM + LVMI} \times 100 \). Increased RWT was present when this ratio was >0.430. Normal geometry was present when LVMl and RWT were normal; increased RWT and normal LVMl were classified as concentric LV remodeling, increased LVMl but normal RWT identified eccentric LV hypertrophy, and increases of both variables identified concentric LV hypertrophy.

Left Ventricular Systolic Performance

Endocardial FS (%) was calculated from LV internal dimensions in diastole and systole. To assess LV contractility, we used the relation between MWS and midwall circumferential end-systolic stress (CESS) measured at the level of the LV minor axis. The location in the LV wall at end-systole of the surface between the inner/outer myocardial shell volumes remains constant through the cardiac cycle.

CESS, as the primary measure of myocardial afterload, was estimated at the midwall from M-mode tracings, using a cylindrical model. Previously published equations relating endocardial FS and MWS to CESS in 140 normotensive adults were used to derive predicted FS and MWS. Stress-corrected endocardial FS and MWS were then calculated as the ratios to the predicted value.

Statistics

SPSS software 10.1 (SPSS, Inc) was used for statistical analysis. Results are mean±SD or frequencies expressed as percentages. Differences are expressed by year-3 minus baseline. Differences in continuous variables between 2 groups were assessed by paired Student’s t test; comparison among multiple groups was performed

<table>
<thead>
<tr>
<th>TABLE 1. Descriptive Data of the LIFE Participants at Baseline and During 3 Years of Antihypertensive Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
</tr>
<tr>
<td>End-echo systolic pressure, mm Hg</td>
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<tr>
<td>End-echo diastolic pressure, mm Hg</td>
</tr>
<tr>
<td>Weight, kg</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
</tr>
<tr>
<td>Body surface area, m²</td>
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<tr>
<td>Left ventricular mass, g</td>
</tr>
<tr>
<td>Left ventricular mass/body surface area, g/m²</td>
</tr>
<tr>
<td>Left ventricular mass/height², g/m²</td>
</tr>
<tr>
<td>Relative wall thickness</td>
</tr>
<tr>
<td>Left ventricular fractional shortening, %</td>
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<tr>
<td>Midwall shortening, %</td>
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<tr>
<td>Circumferential end-systolic stress, kdyn/cm²</td>
</tr>
<tr>
<td>Stress-corrected midwall shortening, %</td>
</tr>
<tr>
<td>Doppler stroke volume, mL</td>
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</table>
by ANOVA with the Scheffé post-hoc test. Univariate relations between variables were assessed as partial correlations. Independent correlates of continuous measures of LV systolic performance were identified by multiple linear regression analysis using an enter procedure with assessment of collinearity diagnostics with blinded study treatment as a control variable. A study from the Reading Center showed that calculation of LVM on serial echocardiograms has very high reliability and little regression to the mean. As shown, between-study LVM change of or had 95% or 80% likelihood of being true change; patients were dichotomized to LVM regression at 35 and 17 g, respectively, from their baseline value (data not shown). However, these alternative dichotomizations did not alter any conclusions. Therefore, groups are presented as whether LVM regression occurred or LVM either remained unchanged or increased. Two-tailed \( P < 0.05 \) was considered statistically significant.

**Results**

Descriptive data of the LIFE population and LIFE Echocardiography substudy have been reported elsewhere. A total of 679 patients in the LIFE echocardiographic study had measurements needed to classify LV geometric pattern and derive LV systolic performance parameters for the present study. The patients were 66 years of age at baseline; 41% were women, and mean height was 170 cm. As shown in Table 1, BP was on average reduced from 174/95 to 150/84 mm Hg. There was no change in weight and body mass index.

**Effect of Treatment on LVM and Systolic Performance**

LVM, LVMI, LVM/height, and RWT fell by 17% (Table 1, all \( P < 0.001 \)). Endocardial FS decreased minimally but significantly (\( P < 0.01 \)). However, MWS increased significantly, CESS decreased, and stress-corrected MWS improved by >8% (all \( P < 0.001 \)).

**LV Systolic Performance and Mass Regression**

Endocardial FS decreased both in patients with and without LVM decrease (Figure 1, both \( P < 0.01 \), with a trend toward greater decrease in endocardial FS in patients without LVM regression than with LVM regression (\( P = 0.055 \)). Antihypertensive treatment (Figure 2) resulted in a highly significant increase in MWS in patients with LVM regression, whereas patients without mass regression had a nonsignificant increase in MWS (\( P < 0.001 \)), resulting in a significant between-group difference (\( P < 0.001 \)). CESS did not change in either patient group, nor was there a significant difference between groups in CESS change (data not shown). Final analysis of change in stress-corrected MWS showed that patients with LVM regression had a strong increase in stress-corrected MWS over 36 months of antihypertensive treatment (\( P < 0.001 \)), whereas patients with no change or increase of LVM had a nonsignificant increase in stress-corrected MWS (\( P = 0.058 \), Figure 3).

**Change in LV Systolic Function in Relation to Baseline LV Geometry**

As shown in Table 2 (absolute values), patients with eccentric LV hypertrophy had no change in endocardial FS compared with decreases in patients with either normal (−5.0%), concentric remodeling (−6.2%), or concentric hypertrophy (−6.0%, ANOVA \( P < 0.01 \)). However, stress-corrected endocardial FS fell significantly more in groups with either normal geometry or eccentric hypertrophy than with concentric remodeling or hypertrophy. As also shown in Table 2, patients with concentric remodeling and hypertrophy had significantly larger increases in MWS than patients with normal geometry or eccentric hypertrophy. Furthermore, patients with eccentric geometry had significant reductions in CESS, whereas this measure of myocardial afterload increased in patients with concentric remodeling or hypertro-
phy at baseline. Patients with normal geometry or eccentric LV hypertrophy at baseline had smaller increases in stress-corrected MWS over 3 years of treatment than the groups with either concentric remodeling or hypertrophy. Finally, there was no difference in the change in SV between groups of LV geometric patterns (Table 2).

Patients with normal geometry at baseline had a small decrease in endocardial FS and a decrease in myocardial contractility. Patients with normal geometry and concentric remodeling or hypertrophy had significant decreases in the prevalence of low myocardial contractility, whereas patients with eccentric hypertrophy had a nonsignificant increase in prevalence of low contractility (Figure 4). Whereas patients with normal geometry or LV hypertrophy at baseline had a decreased prevalence, patients with concentric remodeling had a small but significant increased prevalence of low chamber function.

### Univariate and Multivariate Correlates of LV Systolic Performance

In univariate analyses relating changes in LV chamber function, performance, and contractility to LV structural and functional parameters as well as indices of body composition (Table 3), we found that change in endocardial FS correlated directly with changes in SV and RWT and inversely with changes in LVM and diastolic BP. Change in endocardial FS was not related to age, changes in systolic BP, heart rate, left atrial size, blinded study therapy, or pulse pressure/stroke volume ratio as a crude measure of arterial stiffness. Multivariate analysis yielded a model where changes in RWT ($\beta=0.231$) and SV ($\beta=0.187$, all $P<0.001$) were directly associated and change in LVM ($\beta=-0.230$) was inversely independently associated with change in LV endocardial FS ($R=0.311; P<0.001$), whereas body size, left atrial dimension, and diastolic BP did not enter the model. In univariate analyses, change in stress-corrected endocardial FS correlated directly with change in systolic and diastolic BP, LVMI, SV, and pulse pressure/stroke volume ratio and inversely to change in RWT. Change in stress-corrected endocardial FS was not related to age or changes in body composition, septal or posterior wall thicknesses, LVM, LVM/height$^{27}$, left atrial size (Table 3), or blinded study therapy. Regression analysis yielded a model where change in stress-corrected endocardial FS was directly independently associated ($R=0.644$, $P<0.001$) with changes in systolic BP ($\beta=0.532$) and SV ($\beta=0.166$, both $P<0.001$) and inversely with changes in pulse pressure/stroke volume ($\beta=-0.147$, $P<0.01$), LVMI ($\beta=-0.074$, $P<0.05$), and RWT ($\beta=-0.280$, $P<0.001$).

Univariate analyses showed that changes in LV MWS correlated inversely with changes in LVM, RWT, and diastolic BP and directly with changes in SV. However, no relation was found to age or changes in body composition, left atrial size, heart rate, systolic BP, or pulse pressure/stroke volume (Table 3). Multivariate analysis showed that change in MWS was independently inversely related ($R=0.521$) to changes in LVM ($\beta=-0.211$), RWT ($\beta=-0.334$, all $P<0.001$), and diastolic BP ($\beta=-0.088$, $P<0.05$) and directly related to SV ($\beta=0.192$, $P<0.001$) with control for blinded study therapy.

Univariate analyses showed that change in stress-corrected MWS was inversely independently related to change in LVM and RWT and was directly related to changes in SV and systolic BP. However, no relation was found to diastolic BP,
left atrial size, or pulse pressure/stroke volume (Table 3). Additional multiple regression analysis showed that change in stress-corrected MWS was independently inversely related ($R=0.678$) to changes in LVM ($\beta=-0.153$) and RWT ($\beta=-0.562$) and directly related to changes in SV ($\beta=0.145$) and systolic BP ($\beta=0.221$, all $P<0.001$) with control for blinded study therapy.

### Discussion

This study provides the first assessment that is large enough to be conclusive about the impact of BP control, LVM regression, and LV geometric patterns on LV systolic function during 3 years of antihypertensive treatment in a large group of patients with stage II and III hypertension. The ECG entry criteria for LV hypertrophy (Cornell voltage-duration product and Sokolow-Lyon) that patients had to meet on a screening tracing to enroll in the LIFE study identified a population of hypertensive patients with both high prevalence of LV geometric abnormalities and frequent impairment of LV systolic performance.15

During 3 years of antihypertensive treatment, with mean BP reduction and LVM regression of $\approx15\%$ and $17\%$, respectively, myocardial contractility increased significantly despite small decreases in indices of LV chamber performance. These findings indicate that partial normalization of arterial pressure and LV geometry can result in reversal of both the supranormal LV chamber function seen in hypertensive patients8,10 and the low function of the average myocardial fibers at the LV midwall that is even more common in hypertension.3-5

The second important finding is that patients with or without LVM regression both had mild reduction of endocardial FS during antihypertensive treatment. However, only patients with LVM decrease had significant improvement in MWS and stress-corrected MWS. This occurred without significant change in CESS, as expected, if myocardial wall stress was kept relatively constant by LV geometric adaptation to chronic hemodynamic overload.31

The third new finding is that only those with eccentric LV hypertrophy, among groups of patients defined by LV geometry pattern, had an increase in endocardial FS (Table 2). This increase may be a result of reduction of CESS by antihypertensive treatment in patients with eccentric LV hypertrophy. Stress-corrected endocardial FS fell most in patient groups with the highest stress at baseline, whereas the measure of LV chamber contractility actually increased in the group with concentric LV hypertrophy at baseline. MWS, on the other hand, increased in all geometric groups, especially in patients with concentric geometry. A similar pattern was also shown for stress-corrected MWS. When evaluating baseline LV geometry (Figure 4), groups with normal or concentric geometry had significant decreases in the prevalence of low myocardial contractility, whereas patients with eccentric hypertrophy had a small, nonsignificant increase in prevalence. Only patients with concentric remodeling had increased prevalence of depressed FS.

The fourth new finding is that increase during antihypertensive treatment of SV, derived from measurements completely separate from measurements used to assess LV geometry and function, was an independent correlate of change in all measures of LV systolic function, even taking the blinded study therapy with losartan or atenolol into account. A possible explanation for these associations is that alterations in LV preload, acting by the Frank-Starling mechanism, exert parallel effects on LV contractility and pump performance.

### Table 3. Univariate Correlates of Left Ventricular Chamber Function, Performance, and Contractility

<table>
<thead>
<tr>
<th></th>
<th>$\Delta$ Endocardial Fractional Shortening, $r$</th>
<th>$\Delta$ Stress-Corrected Endocardial Shortening, $r$</th>
<th>$\Delta$ Midwall Fractional Shortening, $r$</th>
<th>$\Delta$ Stress-Corrected Midwall Shortening, $r$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.042</td>
<td>-0.003</td>
<td>0.051</td>
<td>0.08</td>
</tr>
<tr>
<td>Height</td>
<td>0.074*</td>
<td>0.017</td>
<td>0.046</td>
<td>0.016</td>
</tr>
<tr>
<td>$\Delta$ Weight</td>
<td>0.032</td>
<td>-0.002</td>
<td>0.007</td>
<td>-0.023</td>
</tr>
<tr>
<td>$\Delta$ Body mass index</td>
<td>0.015</td>
<td>-0.011</td>
<td>0.013</td>
<td>-0.014</td>
</tr>
<tr>
<td>$\Delta$ Body surface area</td>
<td>0.041</td>
<td>0.002</td>
<td>0.003</td>
<td>-0.029</td>
</tr>
<tr>
<td>$\Delta$ Systolic blood pressure</td>
<td>-0.040</td>
<td>0.394†</td>
<td>-0.068</td>
<td>0.159†</td>
</tr>
<tr>
<td>$\Delta$ Diastolic blood pressure</td>
<td>-0.089*</td>
<td>0.138†</td>
<td>-0.148†</td>
<td>-0.003</td>
</tr>
<tr>
<td>$\Delta$ Interventricular septal thickness</td>
<td>0.026</td>
<td>0.007</td>
<td>-0.480†</td>
<td>-0.300†</td>
</tr>
<tr>
<td>$\Delta$ Posterior wall thickness</td>
<td>0.069</td>
<td>0.004</td>
<td>-0.429†</td>
<td>-0.278†</td>
</tr>
<tr>
<td>$\Delta$ LV internal dimension</td>
<td>-0.245†</td>
<td>0.157†</td>
<td>0.168†</td>
<td>0.314†</td>
</tr>
<tr>
<td>$\Delta$ LV mass</td>
<td>-0.158†</td>
<td>0.062</td>
<td>-0.309†</td>
<td>-0.092*</td>
</tr>
<tr>
<td>$\Delta$ LV mass/body surface area</td>
<td>-0.151†</td>
<td>0.084*</td>
<td>-0.299†</td>
<td>-0.067</td>
</tr>
<tr>
<td>$\Delta$ LV mass/height$^{22}$</td>
<td>-0.146†</td>
<td>0.054</td>
<td>-0.283†</td>
<td>-0.087*</td>
</tr>
<tr>
<td>$\Delta$ Relative wall thickness</td>
<td>0.161†</td>
<td>-0.084*</td>
<td>-0.426†</td>
<td>-0.378†</td>
</tr>
<tr>
<td>$\Delta$ Left atrial dimension</td>
<td>-0.026</td>
<td>0.008</td>
<td>0.008</td>
<td>0.046</td>
</tr>
<tr>
<td>$\Delta$ Doppler stroke volume</td>
<td>0.140‡</td>
<td>0.191‡</td>
<td>0.225‡</td>
<td>0.247‡</td>
</tr>
<tr>
<td>$\Delta$ Pulse pressure/stroke volume</td>
<td>-0.001</td>
<td>0.217‡</td>
<td>-0.019</td>
<td>0.073</td>
</tr>
</tbody>
</table>

*PS<0.05; †PS<0.01; ‡PS<0.01.
Clinical Significance of the Study
The present study improves our understanding of the relationships between LV systolic mechanics and LV hypertrophy during antihypertensive treatment. Depressed systolic LV midwall function in patients with hypertensive LV hypertrophy may play a key role in the development of heart failure and ultimately in hypertensive pulmonary edema, which might be the cause of increased mortality found in these patients. The present findings also suggest that treatment of LV hypertrophy improves depressed LV systolic midwall contractility and may therefore contribute to additional reduction of morbidity and mortality associated with LV hypertrophy.

Conclusion
Antihypertensive control reduces LVM and improves systolic performance in all groups of LV geometry. Control of SV potentiates the improvement of LV systolic performance in all groups of LV geometry. Control of SV and ultimately in hypertensive pulmonary edema, which might be the cause of increased mortality found in these patients. We present findings also suggest that treatment of LV hypertrophy improves depressed LV systolic midwall contractility and may therefore contribute to additional reduction of morbidity and mortality associated with LV hypertrophy.

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Merck & Co, Inc (West Point, Pa) and Kaarson’s Foundation (Copenhagen, Denmark) supported this study. We thank Mary Parancas for her valuable work in reading echocardiograms management and Anne-Grethe Thorn for her valuable help in preparing the manuscript. Furthermore, we would like to thank the LIFE echocardiography study investigators.15–18

References
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