Change in Diastolic Left Ventricular Filling After One Year of Antihypertensive Treatment
The Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) Study

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Background—It is well established that hypertensive patients with left ventricular (LV) hypertrophy have impaired diastolic filling. However, the impact of antihypertensive treatment and LV mass reduction on LV diastolic filling remains unclear.

Methods and Results—Echocardiograms were recorded in 728 hypertensive patients with ECG-verified LV hypertrophy (Cornell voltage-duration or Sokolow-Lyon) at baseline and after 1 year of blinded treatment with either losartan or atenolol-based regimen. Systolic and diastolic blood pressures (BP) were reduced on average 23/11 mm Hg; isovolumic relaxation time and E/A ratio became more normal, and LV inflow deceleration time prolonged (all \( P < 0.001 \)). Directionally opposite changes in isovolumic relaxation time (IVRT) and deceleration time indicate improvement in active LV relaxation and passive chamber stiffness during early diastole. Prevalences of normal LV filling increased, abnormal relaxation and pseudonormalization decreased, and restrictive filling pattern remained unchanged (\( P < 0.05 \)). Patients with reduction in LV mass had smaller left atrial diameter, shortened IVRT, increased E/A ratio, and prolonged LV inflow deceleration time (all \( P < 0.001 \)). Patients without LV mass reduction had no change in diastolic filling parameters (\( P \approx \text{NS} \)). IVRT shortening was independently associated with reduction in LV mass. Increase in E/A ratio was independently associated with reduction in diastolic BP, and increase in the deceleration time was independently associated with reduced end-systolic relative wall thickness.

Conclusions—Antihypertensive therapy resulting in LV mass or relative wall thickness regression is associated with significant improvement of diastolic filling parameters related to active relaxation and passive chamber stiffness compared with patients without regression, independent of BP reduction; however, abnormalities of diastolic LV filling remain common. (Circulation. 2002;105:1071-1076.)

Key Words: diastole ▪ ventricles ▪ hypertension ▪ blood pressure

Hypertensive patients have a 2- to 3-fold higher risk of development of congestive heart failure than normoten sive adults.1 Furthermore, patients with congestive heart failure and normal left ventricular (LV) ejection fraction have a 4-fold increase in mortality rate.2 There is evidence that hypertensive LV hypertrophy plays an important role in the development of heart failure.3 We have shown that diastolic filling parameters are strongly related to LV hypertrophy and relative wall thickness (RWT) in hypertensive patients.4 This might be a result of remodeling, muscle hypertrophy, and alterations of collagen structure.5 Several animal and small human studies examining regression of LV hypertrophy and diastolic dysfunction in hypertensive patients showed that treatment-induced regression of LV hypertrophy did not decrease myocardial collagen levels or reduce the abnormal LV diastolic stiffness and hence improve LV diastolic filling.6-11 However, other small studies show improvement of diastolic filling parameters along with systolic and diastolic blood pressure (BP) and/or LV mass reduction.12-14 Furthermore, studies in patients with diastolic dysfunction without concomitant LV hypertrophy have either shown no improvement15 or improvement after multiyear antihypertensive treatment.16 This might be a result of simultaneous changes in active LV relaxation and passive LV chamber stiffness.17

To our knowledge, there are no large studies examining the effect of antihypertensive treatment on LV diastolic function.
in hypertensive patients. The aim of this study was to investigate changes in LV diastolic filling and their relation to regression of LV hypertrophy due to systematic antihypertensive treatment.

As part of the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) trial,18 >10% of study participants enrolled in a substudy in which echocardiograms are performed at study baseline and yearly thereafter.4,19,20 This report uses the baseline and follow-up year-1 echocardiograms from this substudy to determine the effect of antihypertensive treatment on LV diastolic filling in hypertensive patients.

Methods

Patients gave informed consent, and the Committees of Ethical Science accepted this study. All patients had a screening ECG with LV hypertrophy by either sex-adjusted Cornell voltage duration \( \geq 2440 \text{ mV} \cdot \text{ms} \) or Sokolow-Lyon voltage criteria \( > 38 \text{ mV} \); exclusion criteria have been previously described.18

Subjects

Eligible individuals were 960 hypertensive patients; 876 had echocardiograms at baseline and at year-1, as 84 follow-up studies were not performed because of death (n=10) or disability or failure to cooperate (n=74). A total of 148 participants in the echocardiography substudy were ineligible for the present study because of inability to obtain baseline and/or year-1 measurements of LV mass (n=19) or transmitral Doppler flow profiles (n=129). Compared with ineligible patients, the present study patients were younger at enrollment (mean 66.2±6.7 versus 68.4±7.7 years, \( P<0.01 \)) but did not differ in sex distribution, body mass index, systolic or diastolic BP, LV mass, RWT, isovolumic relaxation time (IVRT), E/A ratio, or mitral valve deceleration time.

Echocardiographic Methods

Echocardiographic procedures for this study are previously described.4,19,20 End-diastolic LV dimensions were used to calculate LV mass by an anatomically validated formula \( r = 0.90 \) versus necropsy LV mass.21 RWT at end-diastole was calculated as end-diastolic posterior wall thickness/LV internal radius22; RWT at end-systole was also calculated by a similar formula because this contributes to the LV geometric component of passive ventricular stiffness that is superimposed on the active process of myocardial relaxation in early diastole. LV hypertrophy was considered present when LV mass indexed for body surface area was \( > 116 \text{ g/m}^2 \) for men and \( > 104 \text{ g/m}^2 \) for women.23 Increased diastolic RWT was present when this ratio was \( > 0.430,24 \) LV geometry definitions19 and methods of pulsed Doppler recordings4 have previously been described.

Statistics

Statistical software (SPSS Version 9.0, SPSS, Inc) was used for statistical analysis. Results are mean±SD when appropriate, and frequencies are expressed as percentages. Differences in continuous variables between two groups were assessed by Student’s t test for parametric data and by \( \chi^2 \) analysis for categorical data; comparison among multiple groups was performed by ANOVA with the Scheffé post hoc test.

A study from the Reading Center showed that LV mass on serial echocardiograms has high reliability and little regression to the mean.25 Between-study LV mass change of \( \geq 35 \text{ g} \) or \( \geq 17 \text{ g} \) had \( \geq 95\% \) or \( \geq 80\% \) likelihood of being true change. Explanatory analyses dichotomized patients at LV mass reduction partitions of \( \geq 35 \text{ and } 17 \text{ g} \), respectively, from baseline values. However, this did not alter any conclusions (data not shown). Therefore, patients were dichotomized to whether LV mass decreased or, alternatively, either remained unchanged or increased. Independent correlates of continuous measures of LV transmitral flow patterns were identified by multiple linear regression analysis with an enter procedure with assessment of collinearity diagnostics. A value of \( P<0.05 \) (2-tailed) was considered statistically significant.

Results

Patient Characteristics

Descriptive data of the whole LIFE population18 and LV diastolic function at baseline in the LIFE echocardiography substudy have been reported elsewhere.4 Of the total 960 patients, 728 patients had paired imaging and Doppler measurements at baseline, and year-1 follow-up was needed for inclusion in the present study. Mean age was 67±7 years, and 41% were women.

Changes in Left Atrial and Ventricular Structure and Diastolic Function

As shown in Table 1, mean end-echo BPs were reduced by 23/11 mm Hg (\( P<0.001 \)). Mean LV mass was reduced by \( \approx 12\% \). The reduction of LV mass was due to reduction of interventricular septal, posterior wall, and end-diastolic RWT by \( \approx 10\% \). Furthermore, we found an \( \approx 9\% \) reduction in end-systolic RWT and an \( \approx 3\% \) reduction in left atrial size. However, LV internal diameter in diastole increased by <1%, as did mean body mass index. IVRT shortened and the E/A ratio increased; deceleration time increased by \( \approx 7\% \) and atrial filling fraction decreased by \( \approx 10\% \).

Change in Left Ventricular Filling Patterns

At baseline, abnormal relaxation was by far the most common abnormal transmitral flow pattern, whereas 15% had normal mitral valve flow profile, 11% had pseudonormal flow profile, and only 5% had restrictive flow pattern (Figure 1). After 1 year of treatment, the prevalence of normal flow pattern increased to \( \approx 26\% \) and abnormal relaxation decreased to 57%. The prevalence of pseudonormal pattern decreased to \( \approx 5\% \), whereas the restrictive pattern prevalence changed little (\( P<0.05 \)).

LV Hypertrophy Regression and Diastolic Filling

Comparing patients with LV mass decrease and those with no decrease or an increase in LV mass, patients with LV mass decrease had the same reduction in systolic and diastolic BP (Table 1) as well as in mean BP (Figure 2) and a slight increase in body mass index (\( P<0.05 \)), compared with patients without LV mass reduction.

Patients with LV mass regression had significant reduction in left atrial diameter, shortened IVRT, increased E/A ratio, prolonged mitral valve deceleration time, and decreased atrial filling fraction. Patients without change or with increase in LV mass, after 1 year of antihypertensive treatment, had no change in left atrial size, IVRT, E/A ratio, or mitral valve deceleration time but had decreased mean atrial filling fraction from baseline values (Table 1). In an analysis of the changes between baseline and year-1 values, patients with LV mass reduction, compared with patients without LV mass reduction, had significantly greater reduction in left atrial size and in IVRT but similar changes in E/A ratio, mitral valve deceleration time, and atrial filling fraction (Table 1).
Patients with reduction of end-diastolic RWT (n=561) had significantly reduced left atrial size (3.92±0.53 to 3.79±0.56 cm), shortened IVRT (117±24 to 104±22 ms), increased E/A ratio (0.84±0.31 to 0.93±0.34), prolonged mitral valve deceleration time (219±65 to 234±69 ms), and decreased atrial filling fraction (0.42±0.10 to 0.38±0.12, all P<0.001) from baseline values after 1 year of antihypertensive treatment. Patients without change or with increase in end-diastolic RWT after 1 year of antihypertensive treatment (n=167) had no change in IVRT (112±27 to 108±20 ms), E/A ratio (0.89±0.42 to 0.90±28), deceleration time (215±67 to 220±51 ms), and atrial filling fraction (0.42±0.10 to 0.40±0.11, all P=NS) but had reduced left atrial size (4.00±0.63 to 3.89±0.56, P<0.05) from baseline values.

Correlates of Changes in Diastolic Filling Parameters

Univariate analyses (Table 2) showed that shortened IVRT was related to younger age and reductions in LV mass and end-diastolic and end-systolic RWT and left atrial dimension. Multivariate analyses yielded a model (R=0.257, P<0.001) in which younger age (β=0.74, P=0.05) and reductions in LV mass (β=0.123), left atrial diameter (β=0.120), and end-diastolic RWT (β=0.112, all P<0.01) were independently associated with IVRT reduction. In an alternative
model \((R=0.251)\), reduction in LV mass \((\beta=0.147)\), reduction in left atrial diameter \((\beta=0.121, \text{all } P=0.001)\), and reduction in end-systolic RWT \((\beta=0.072, P=0.059)\) tended to be independently associated with IVRT shortening. Because IVRT is closely negatively related to the rate of early diastolic LV relaxation before the onset of LV inflow, IVRT summates the effects of LV geometry and altered myocardial properties on inflow.

Univariate analysis (Table 2) showed that increase in E/A ratio correlated with reduction in BP, prolonged IVRT, and increase in LV internal diameter in diastole and end-diastolic RWT but not end-systolic RWT. Multivariate analysis yielded a model \((R=0.204)\) in which increased E/A ratio was independently associated with reduced diastolic arterial BP \((\beta=-0.137)\), prolonged IVRT \((\beta=-0.110, \text{all } P<0.01)\), and reduction in end-diastolic RWT \((\beta=-0.082, P<0.05)\).

Univariate analysis (Table 2) showed that prolonged deceleration time correlated with smaller end-systolic RWT, smaller left atrial dimension, and smaller E/A ratio. Multivariate analyses \((R=0.171)\) showed that prolongation of mitral valve deceleration time was independently associated with reduced end-systolic RWT \((\beta=0.082)\), E/A ratio \((\beta=0.078, \text{both } P<0.05)\), and left atrial dimension \((\beta=0.112, P<0.01)\).

Final univariate analysis (Table 2) showed that reduction in atrial filling fraction correlated with reduced diastolic BP, end-diastolic RWT, and E/A ratio, shortened deceleration time and time-velocity integral, and increased LV internal dimension. Reduced atrial filling fraction was independently associated with both decreased diastolic BP \((\beta=0.116)\) and increased LV internal dimension \((\beta=0.102, \text{both } P<0.01)\) in multivariate analysis \((R=0.160, P<0.001)\).

**Discussion**

This study provides the first assessment of the relation of changes in LV geometry to changes in diastolic LV function during antihypertensive treatment in a large series of hypertensive patients with ECG-verified LV hypertrophy. This study shows four new observations.

Antihypertensive treatment resulting in \(\approx 10\%\) reduction in LV mass results in a \(3\%\) reduction in left atrial diameter, \(9\%\) shortened IVRT, and \(10\%\) decrease in atrial filling fraction, and \(9\%\) and \(7\%\) increases in E/A ratio and mitral valve deceleration time, respectively. The apparent paradoxical prolongation of the mitral valve deceleration time with shortening of IVRT may be due to improved active relaxation and reduction of passive chamber stiffness associated with reduction of end-systolic RWT\(^{26}\) as well as probable normalization of connective tissue.\(^{17,27}\)

Our results support the finding by Yalcin and coworkers\(^{28}\) that 6 months antihypertensive treatment with perindopril led to reduction in LV mass and left atrial volume and increased E/A ratio. However, our study contrasts with a study by Cuspidi et al\(^{7}\) in a smaller population \((n=39)\) in which 6 months of antihypertensive treatment had no significant effect on LV diastolic filling parameters.

Reduction of LV mass and RWT by \(\approx 10\%\) are associated with an increase in the proportion of the patients with normal mitral valve flow pattern by 73\%, reduction of abnormal relaxation by 17\%, and of the pseudonormal pattern by 60\%, with almost no change in restrictive pattern. The antihypertensive treatment normalized LV filling parameters in 20\% of patients, whereas 10\% had LV filling abnormalities and 69\% remained unchanged.

Another major observation is that patients with reduction in LV mass, as opposed to no change or an increase in LV mass, had shortening of IVRT, reductions in left atrial dimension and atrial filling fraction, and increase in E/A ratio and mitral valve deceleration time, whereas no change in diastolic filling parameters was seen in patients without LV mass reduction. In parallel, patients with reduction of end-di-
astolic RWT, compared with patients without RWT reduc-
tion, had shortening of IVRT, reduction of in left atrial
dimension and atrial filling fraction, and increase in E/A ratio
and mitral valve deceleration time.

Finally, shortening of IVRT is independently associated
with LV mass reduction. Increase in E/A ratio is independ-
ently associated with reduction in diastolic BP, and finally,
increase in mitral valve deceleration time is independently
associated with decreased in mitral valve deceleration time.
This corresponds well with what is found in dogs. 
Patients with aortic stenosis and aortic valve replacement, and	hropertensive patients without LV hypertrophy who had RWT
regression. Decrease in hemodynamic overload and remodel-
ing of the myocardium have been associated with a de-
crease in muscle mass but a “relative” increase in fibrous
tissue, which regresses less rapidly than myocardial tissue,
necessitating 7 years for normalization of myocardial stiff-
ness in one study.

Clinical Implications
Regression of hypertensive LV hypertrophy and of concentric
LV geometry is associated with partial normalization of
several LV diastolic filling parameters, including the IVRT,
E/A-ratio and atrial filling fraction. In multivariate analyses,
the associations were independent of the reduction in BP,
indicating direct effects of normalization of LV geometry on
diastolic filling parameters. The complexity of factors influ-
encing LV diastolic filling is highlighted by the fact that the
deceleration time of early diastolic filling passive inflow
increased at the same time as the as the IVRT decreased.
This implies that the deceleration time at enrollment in the LIFE
echocardiography study was effected in opposite directions,
being lengthened by impaired relaxation and shortened by
increased LV stiffness due to increased relative wall thick-
ness and probable alterations in myocardial connective tissue.
A strong relation between invasively-measured early diastolic
chamber stiffness and shortened deceleration time was re-
ported in an experimental study by Little et al. 
and in a human study by Garcia et al.
Treatment improved relaxation predominated in shortening the IVRT while reducing cham-
ber stiffness predominated by prolonging the deceleration
time of early diastolic transmural flow. The improvement of
diastolic dysfunction parameters may contribute to the ability
of BP reduction to prevent congestive heart failure and highlights the role of antihypertensive therapy in primary
prevention of congestive heart failure in hypertensive patients
with LV hypertrophy.

Limitations of the Study
Data are analyzed in patients with ECG-verified LV hyper-
trophy, of whom 70% had echocardiographically verified LV
hypertrophy. Hence, our data may be representative of
patients with LV mass in the hypertrophied or high normal
range. No attempts were made to measure LV filling pres-
sures, although it is likely that in outpatients volunteering
for a long-term treatment trial, they are in a relatively narrow
range of normal to mildly elevated levels. To simplify the
protocol, no measurements of pulmonary venous flow were
made, making it possible that the group with normal diastolic
dysfunction may contain patients who should be classified as
“pseudonormal” and visa versa. The antihypertensive treat-
ment regime is at the moment blinded and will remain so until
the LIFE study ends. Furthermore, because of the known
effect of β-blockers to reduce heart rate, the LIFE Steering
Committee has decided that change in heart rate during
treatment cannot be reported until the study is unblinded.
Therefore it was not possible to report findings in relation to
treatment with either atenolol or losartan. However, 
β-blockade has been shown to increase the deceleration time
of early diastolic transmural flow in patients with dilated
cardiomyopathy.
Therefore, where appropriate, data were
controlled for heart rate (data not shown), and this did not
alter any conclusions.

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