Gender Differences in Left Ventricular Structure and Function During Antihypertensive Treatment
The Losartan Intervention for Endpoint Reduction in Hypertension Study

Eva Gerdtsev, Peter M. Okin, Giovanni de Simone, Dana Cramariuc, Kristian Wachtell, Kurt Boman, Richard B. Devereux

Abstract—In hypertensive patients with left ventricular hypertrophy, antihypertensive treatment induces changes in left ventricular structure and function. However, less is known about gender differences in this response. Baseline and annual echocardiograms until the end of study or a primary end point occurred were assessed in 863 hypertensive patients with electrocardiographic left ventricular hypertrophy aged 55 to 80 years (mean: 66 years) during 4.8 years of randomized losartan- or atenolol-based treatment in the Losartan Intervention for Endpoint Reduction in Hypertension Echocardiography substudy. Left ventricular hypertrophy was diagnosed as left ventricular mass divided by height\(^2\) \(\times\) 46.7 g/m\(^2\) and 49.2 g/m\(^2\) in women and men, respectively, and systolic function as ejection fraction and stress-corrected midwall fractional shortening. Women included more patients with obesity, isolated systolic hypertension, and mitral regurgitation (all \(P<0.01\)). Ejection fraction, stress-corrected midwall shortening, and prevalence of left ventricular hypertrophy were higher in women at baseline and at the end of study (all \(P<0.01\)). In particular, more women had residual eccentric hypertrophy (47% versus 32%; \(P<0.01\)) in spite of similar in-treatment reduction in mean blood pressure. In logistic regression, left ventricular hypertrophy at study end was more common in women (odds ratio: 1.61; 95% CI: 1.16 to 2.26; \(P<0.01\)) independent of other significant covariates. In linear regression analyses, female gender also predicted 2% higher mean in-treatment ejection fraction and 2% higher mean stress-corrected midwall shortening (both \(\beta=0.07\); \(P<0.01\)). Hypertensive women in this study retained higher left ventricular ejection fraction and stress-corrected midwall shortening in spite of less hypertrophy regression during long-term antihypertensive treatment. (Hypertension. 2008;51:1109-1114.)

Key Words: gender ■ hypertension ■ systolic function ■ left ventricular hypertrophy ■ hypertrophy regression

It is well documented that aggressive antihypertensive treatment reduces left ventricular (LV) mass and improves myocardial function in a majority of hypertensive patients with LV hypertrophy. Less LV hypertrophy reduction has been described in subgroups of patients, including patients with obesity, diabetes, or renal disease.\(^1\)\(^-\)\(^5\) Several studies have reported gender differences in LV adaptation to chronic pressure overload in hypertension: women exhibit a greater prevalence of concentric LV geometry, as well as better indices of LV systolic chamber and myocardial function evaluated by echocardiography.\(^6\)\(^-\)\(^8\) Little is known about the impact of gender on changes in LV structure and systolic function during long-term antihypertensive treatment.

Accordingly, the present analysis was undertaken to assess gender differences in LV structure and systolic function during 4.8 years of losartan- or atenolol-based antihypertensive therapy in hypertensive patients with electrocardiographic LV hypertrophy recruited in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) echocardiography substudy.

Methods

Patient Population

The present analysis was carried out in the LIFE echocardiography substudy, which enrolled 960 of the 9193 participants in the parent trial for annual echocardiographic follow-up.\(^9\)\(^-\)\(^10\) This analysis was not prespecified as part of the LIFE protocol but added to the data analysis plan before completion of the LIFE Study in 2001; therefore, neither selection of patients nor treatment randomization were related to gender.

Patient characteristics and outcome results from the main LIFE Study have been reported.\(^10\)\(^-\)\(^11\) The LIFE Study was a double-blind, randomized trial in 55- to 80-year--old hypertensive patients (baseline blood pressure: 160 to 200/95 to 115 mm Hg) with electrocardiographic LV hypertrophy (according to Cornell voltage-duration or Sokolow-Lyon voltage criteria) and compared treatment based on losartan or atenolol over an average of 4.8 years. Of the 960 patients enrolled in the LIFE echocardiographic substudy, 863 patients had...
LV measurements at enrollment and on ≥1 follow-up echocardiogram and, thus, were eligible for the present analysis (Table 1). Patients were classified as having isolated systolic hypertension if systolic blood pressure was ≥140 mm Hg and diastolic blood pressure was <90 mm Hg at baseline clinic visits. Pulse pressure was calculated as the difference between sitting clinic systolic and diastolic blood pressures and mean blood pressure as sitting diastolic blood pressure plus one-third pulse pressure. Diabetes mellitus was diagnosed by the 1985 World Health Organization criteria or use of hypoglycemic medication. Albuminuria was diagnosed as a albumin:creatinine ratio >3.5 mg/mmol on a spot morning urine sample. Obesity was defined as body mass index >30.0 kg/m². All of the patients gave written informed consent to participate in the LIFE echocardiography substudy, which was approved by regional ethics committees in all of the participating countries. The study was performed in accordance with the Helsinki Declaration.

Doppler Echocardiography

Organization, patient recruitment, protocol, and echocardiographic methods used in the LIFE echocardiography substudy have been published previously. All of the echocardiograms were sent to the Cornell Echocardiography Reading Center for blinded, expert interpretation. Measurements of LV dimensions and wall thicknesses were made on 2D parasternal long-axis views according to American Society of Echocardiography standards. LV mass was calculated using an autopsy-validated formula and indexed for height².¹⁷ Intraobserver reliability of the reading center was assessed previously in a separate study. LV hypertrophy was identified by prognostically validated gender-specific partition values of LV mass/height².¹⁷,¹⁸ Previous myocardial infarction, % 4 7† Prevalence of overweight and isolated systolic hypertension were greater among women than among men, whereas previous myocardial infarction and stroke were less frequent (Tables 1 and 2). During treatment, blood pressure reduction was comparable in both genders, but women had higher end-study systolic blood pressure and pulse pressure (146±16 and 65±16 mm Hg versus 143±12 and 61±15 mm Hg; both *P<0.001), whereas end-study mean blood pressure did not differ between genders (103±9 versus 102±10 mm Hg, respectively).

Changes in LV Geometry

At baseline and end study, LV mass/height² was minimally higher in women than men (by 0.6 and 1.3 g/m²; respectively; Table 2). In a general linear model taking study and gender into account and expressed as the percentage of observed MWS related to MWS predicted from end-systolic stress using equations derived from normal subjects. Gender-specific partition values derived from normal subjects were used for detection of low EF and scMWS. Mitral and aortic regurgitation were assessed by color Doppler using a previously described 4-category grading system. Supine blood pressure measured by arm-cuff sphygmomanometer at the end of the echocardiogram was used for calculation of hemodynamic variables. Heart rate was measured from the echocardiographic recordings.

Statistical Analyses

Data management and analysis were performed using SPSS 13.0 (SPSS) software. Data are presented as means±SDs for continuous variables and as percentages for categorical variables. Between-gender comparisons were made by χ² statistic, unpaired Student t test, and ANOVA, as appropriate. Changes of LV mass, geometry, and systolic function were calculated from the difference between baseline values and values on the final study echocardiogram or the last echocardiogram before occurrence of a primary composite end point in each individual patient. In-trtreatment changes in blood pressure and body mass index were calculated in the same way. Univariate correlates of end-study LV mass/height², EF, and scMWS were identified by Pearson’s correlation coefficients. Predictors and covariates of having LV hypertrophy at the end of the study were assessed by binary logistic models. Results are presented as odd ratios (ORs; 95% CIs) and level of significance. Covariates of end-study EF and scMWS were assessed by multiple linear regression analyses using an enter procedure with assessment of collinearity diagnostics. Results are presented as multiple R² of the model and β-coefficients of significant covariates within the model. Two-tailed *P<0.05 was considered significant both in univariate and multivariate analyses.

Results

Prevalences of overweight and isolated systolic hypertension were greater among women than among men, whereas previous myocardial infarction and stroke were less frequent (Tables 1 and 2). During treatment, blood pressure reduction was comparable in both genders, but women had higher end-study systolic blood pressure and pulse pressure (146±16 and 65±16 mm Hg versus 143±12 and 61±15 mm Hg; both *P<0.001), whereas end-study mean blood pressure did not differ between genders (103±9 versus 102±10 mm Hg, respectively).

Changes in LV Geometry

At baseline and end study, LV mass/height² was minimally higher in women than men (by 0.6 and 1.3 g/m²; respectively; Table 2). In a general linear model taking study and gender into account, the increase in LV end diastolic diameter during treatment was significantly larger in women, and reduction in LV mass/height² was significantly less (both *P<0.05), whereas similar reductions were found in LV interventricular and posterior wall thicknesses during the study (Table 2). Women had higher prevalence of LV hypertrophy both at baseline and at study end (Figure). In particular, more women had residual eccentric LV hypertrophy (47% versus 32%; *P<0.01; Figure). Using multivariable binary logistic regression analysis, female gender (OR: 2.01; 95% CI: 1.44 to 2.81), age (OR: 1.40 per SD higher; 95% CI: 1.18 to 1.67), and body mass index (OR: 1.53 per SD higher; 95% CI: 1.28 to 1.83); baseline EF (OR: 1.47 per SD lower EF; 95% CI: 1.23 to 1.72; all *P<0.001); and presence of
aortic regurgitation (OR: 1.58; 95% CI: 1.01 to 2.48; P=0.047) or LV hypertrophy on the baseline echocardiogram (OR: 6.68; 95% CI: 4.08 to 10.95; P<0.001) were all identified as baseline predictors of LV hypertrophy at the end of study, whereas no significant association was found with race, concomitant diabetes, baseline systolic blood pressure or pulse pressure, albuminuria, mitral regurgitation, or with history of previous myocardial infarction. In a similar model, using end-study variables, female gender was associated with end-study LV hypertrophy (OR: 1.83; 95% CI: 1.34 to 2.51; P<0.001), independent of significant associations with higher end-study pulse pressure (OR: 1.48 per SD higher pulse pressure; 95% CI: 1.26 to 1.73), body mass index (OR: 1.95 per SD higher body mass index; 95% CI: 1.64 to 2.32), lower EF (OR: 1.59 per SD lower EF; 95% CI: 1.35 to 1.89; all P<0.001), and end-study mitral regurgitation (OR: 1.50; 95% CI: 1.09 to 2.07; P=0.013) or aortic regurgitation (OR: 1.97; 95% CI: 1.33 to 2.91; P=0.001) without independent associations with end-study albuminuria, new-onset diabetes mellitus, or randomized study treatment.

Combining significant variables from the 2 models, women had a 61% higher prevalence of in-treatment LV hypertrophy, independent of other significant covariates (Table 3). Running the same model in the subgroup of patients without any mitral or aortic regurgitation at baseline (n=646) gave similar results: again, female gender was an independent predictor of end-study LV hypertrophy (OR: 1.60; 95% CI: 1.08 to 2.38; P=0.02). In this model, neither new-onset mitral nor aortic regurgitation was an independent covariate of end-study LV hypertrophy. Furthermore, in an additional model including age, gender, randomized study treatment, in-treatment changes in pulse pressure, body mass index, LV ejection fraction, and new-onset mitral and aortic regurgitation among the covariates, female gender remained an independent predictor of end-study LV hypertrophy (OR: 1.82; 95% CI: 1.37 to 2.42; P<0.001) with additional significant associations with age and new-onset aortic regurgitation. In a supplemental regression model with end-study LV hypertrophy defined as LV mass/body surface area >104 and 116 g/m² in women and men, respectively, as a dependent variable, female gender remained an independent predictor of end-study LV hypertrophy (OR: 1.64; 95% CI: 1.15 to 2.32; P=0.006). However, when a common partition value of 51 g/m²², derived from an early study, was used for both genders, the prevalence of LVH was substantially reduced, and the association between female gender and end-study LV hypertrophy became insignificant (OR: 1.25; 95% CI: 0.90 to 1.78; P=0.220). In analysis that added interaction terms of gender with age and with end-study pulse pressure and body mass index, the interaction terms with age and pulse pressure did not enter the model, whereas that with body mass index did (P=0.013). Still, female gender remained an independent predictor of

<table>
<thead>
<tr>
<th>Variable</th>
<th>Women (n=355)</th>
<th>Men (n=508)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>Baseline</td>
<td>End of Study</td>
</tr>
<tr>
<td>LV end-diastolic diameter, cm</td>
<td>5.06±0.48</td>
<td>5.22±0.47</td>
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<tr>
<td>LV end-systolic diameter, cm</td>
<td>3.32±0.53</td>
<td>3.53±0.53</td>
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<tr>
<td>Interventricular septal thickness, cm</td>
<td>1.12±0.14</td>
<td>0.95±0.14</td>
</tr>
<tr>
<td>Posterior wall thickness, cm</td>
<td>1.04±0.12</td>
<td>0.85±0.14</td>
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<tr>
<td>EF, %</td>
<td>63±8</td>
<td>60±8</td>
</tr>
<tr>
<td>Low EF, %</td>
<td>14</td>
<td>19</td>
</tr>
<tr>
<td>MWS, %</td>
<td>15.8±2.0</td>
<td>17.0±2.3</td>
</tr>
<tr>
<td>Circumferential end-systolic stress, dyne/cm²</td>
<td>176±41</td>
<td>187±45</td>
</tr>
<tr>
<td>Stress-corrected MWS, %</td>
<td>99±12</td>
<td>107±14</td>
</tr>
<tr>
<td>Low stress-corrected MWS, %</td>
<td>22</td>
<td>9</td>
</tr>
<tr>
<td>LV mass/height², g/m²²</td>
<td>56.5±13.0</td>
<td>47.4±12.6</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.41±0.06</td>
<td>0.33±0.05</td>
</tr>
<tr>
<td>LV hypertrophy, %</td>
<td>80</td>
<td>50</td>
</tr>
<tr>
<td>Mitral regurgitation, %</td>
<td>30</td>
<td>42</td>
</tr>
<tr>
<td>Grade 1 mitral regurgitation, %</td>
<td>26.7</td>
<td>34.2</td>
</tr>
<tr>
<td>Grade 2 mitral regurgitation, %</td>
<td>3.4</td>
<td>6.8</td>
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<tr>
<td>Grade 3 mitral regurgitation, %</td>
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<td>0.6</td>
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<tr>
<td>Grade 4 mitral regurgitation, %</td>
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<tr>
<td>Aortic regurgitation, %</td>
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<td>18</td>
</tr>
<tr>
<td>Grade 1 aortic regurgitation, %</td>
<td>9.9</td>
<td>12.4</td>
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<tr>
<td>Grade 2 aortic regurgitation, %</td>
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<td>4.5</td>
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<tr>
<td>Grade 4 aortic regurgitation, %</td>
<td>0</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*P<0.01; †P<0.05 vs women.
end-study LV hypertrophy (OR: 1.88; 95% CI: 1.27 to 2.78; \( P<0.01 \)) in the subgroup of patients with baseline body mass index <30 kg/m\(^2\) (n=682).

### In-Treatment Systolic Function

During treatment, EF decreased comparably in both genders, whereas sMWS increased significantly more in women when study treatment allocation was taken into account in a general linear model (Table 2). In univariate correlations, greater end-of-study EF was associated with higher end-study pulse pressure, relative wall thickness, and end-systolic stress (all \( P<0.01 \)), whereas higher end-of-study sMWS was correlated with younger age, higher end-study pulse pressure, and lower end-study relative wall thickness (all \( P<0.05 \)). At study end, women with end-study LV hypertrophy had, compared with their female counterparts without end-study LV hypertrophy, lower mean levels of end-study ejection fraction (59% versus 62%), MWS (16% versus 18%), and stress-corrected MWS (103% versus 110%, all \( P<0.001 \)), but in each case these values were higher than in men with end-study hypertrophy (55%, 15% [both \( P<0.001 \)], and 101%; \( P=0.09 \)).

Using gender-specific cut points, low end-study EF (<55% in women and <51% in men) was associated with male gender, end-study LV hypertrophy, and history of myocardial infarction (all \( P<0.01 \)). Low end-study MWS (<90% in women and <87% in men) was associated with history of diabetes, new-onset diabetes, end-study LV hypertrophy, and albuminuria (all \( P<0.05 \)). Adjusting for significant univariate covariates in multiple linear regression analyses, female gender independently predicted higher end-study EF and sMWS (Table 4).

### Discussion

Several studies have reported gender differences in LV adaptation to chronic pressure overload in hypertension, including women more often having concentric LV geometry, asymmetrical LV hypertrophy, and higher indices of LV systolic chamber and myocardial function evaluated by echocardiography.\(^6\)\(^-\)\(^8\) The present study adds to previous knowledge by demonstrating that, despite aggressive antihypertensive therapy, hypertensive women with electrocardiographic LV hypertrophy, compared with their male counterparts, more commonly have residual LV hypertrophy but, nevertheless, maintain higher LV EF and sMWS.

### Treatment-Induced Change in LV Geometry

The first finding, that hypertensive women had 61% more residual LV hypertrophy during treatment, was unexpected. However, several factors associated with LV hypertrophy were more common among women than men in our study population, in particular, higher prevalences of obesity and isolated systolic hypertension.\(^26\)\(^,\)\(^27\) To account for the unequal distribution of obesity between women and men in the present study popula-
tion, in-treatment change in LV mass was assessed using LV mass/height$^{27}$. Although women had only slightly higher mean LV mass/height$^{27}$ than men both at baseline and at end of study, using gender-specific cutoffs in normal limits for LV mass/height$^{27}$ resulted in appreciably more LV hypertrophy in women, whereas the difference became nonsignificant when a higher common normal limit for LV mass/height$^{27}$ was used. Still, as demonstrated by our data analysis, nonobese women in our study population had significantly more residual LV hypertrophy. Similar findings have been reported previously in elderly patients undergoing balloon dilatation of the aortic valve for isolated aortic stenosis.$^{28}$

We have previously demonstrated similar effects of isolated systolic and combined hypertension on baseline LV geometry and function in the LIFE echocardiography study.$^{29}$ However, in a community-based elderly Italian study population, isolated systolic hypertension was associated with higher prevalences of both LV hypertrophy and carotid atherosclerosis.$^{30}$ In the same study, cardiovascular target-organ damage was independently associated with pulse pressure but not with systolic blood pressure.$^{30}$ The present study adds to this knowledge by demonstrating that, in older hypertensive patients with electrocardiographic signs of LV hypertrophy, higher end-study pulse pressure was associated with more residual LV hypertrophy. Still, in multivariate analysis, women had more end-study LV hypertrophy independent of end-study body mass index and pulse pressure. Of note, hypertensive patients were recruited in the LIFE Study based on electrocardiographic diagnosis of LV hypertrophy by Sokolow-Lyon criterion or Cornell product. Although gender-specific criteria for Cornell product were used, a similar cutoff for Sokolow-Lyon criterion was used in both genders, possible leading to inclusion of women with more advanced anatomic LV hypertrophy.

End-Study LV Systolic Function

As a consequence of treatment-induced changes in LV geometry, including a slight increase in LV end-diastolic diameter, EF decreased significantly in both genders during the study in spite of blood pressure reduction and increase in myocardial contractility. However, EF is a poor marker of contractility and more accurately represents the coupling between ventricle and vasculature.

Our second finding, that women retained higher EF and scMWS during long-term antihypertensive treatment, adds to previous reports of higher systolic function in normotensive and hypertensive women.$^{7,8}$ However, at study end, women with residual LV hypertrophy had significantly lower EF and scMWS than their female counterparts with normal LV mass. Our finding that women had higher end-study scMWS compared with men also when LV size was taken into account is in accordance with results published recently from our echocardiography laboratory demonstrating that, among 1720 patients with asymptomatic mild-to-moderate aortic stenosis, women have higher scMWS at any given LV internal diameter, in particular, in eccentric LV geometry, as well as results from the community-based Olmsted County Study.$^{31,32}$

Although a higher prevalence of LV systolic dysfunction was reported in men than in women in the Hypertension Genetic Epidemiology Network cohort,$^{7}$ the present analysis, using gender-specific partition values, found comparable prevalences of low end-study EF and scMWS in women and men. A similar prevalence of LV dysfunction in both genders was also reported in a population sample of 274 healthy Italian hypertensive subjects by Celentano et al.$^{8}$ However, compared with previous reports, low end-study scMWS was less frequent, whereas low end-study EF was more common in the present study population, possibly as a consequence of effective antihypertensive treatment used in the LIFE Study, as well as differences in population characteristics, including higher prevalences of LV hypertrophy and lower prevalences of diabetes, obesity, and history of previous myocardial infarction, all important covariates of LV systolic dysfunction in hypertension.$^{7,26}$ In spite of the known association of obesity with LV systolic dysfunction, obesity was not identified as an independent covariate of end-study LV systolic function in the present study population. Still, as demonstrated by the multivariate analyses, female gender significantly impacted continuous measures of end-study LV systolic function independent of significant associations with history of diabetes or previous myocardial infarction.

Perspectives

The present findings add to previous documentation from echocardiographic studies in patients with chronic pressure overload by demonstrating that hypertensive women with electrocardiographic LV hypertrophy, compared with their male counterparts, more commonly remain with residual LV hypertrophy but maintain higher LV EF and scMWS despite having more residual LV hypertrophy during aggressive antihypertensive therapy. It is well known that hypertensive women with LV hypertrophy have an increased risk for the development of clinical heart failure in spite of preserved EF, possibly associated with more pronounced vascular-ventricular stiffening with aging.$^{33}$ The present study did not have statistical power to evaluate the impact of residual LV hypertrophy in women on the development of heart failure. An association between the reduction in electrocardiographic signs of LV hypertrophy during systematic antihypertensive treatment and reduced incidence of hospitalization for heart failure was published recently from the main LIFE Study.$^{33}$ However, the implications of our findings for the development of heart failure in hypertensive women with preserved EF should be addressed in future research.

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speakers’ bureau, and is a consultant/member of an advisory board for Merck. G.D.S. and D.C. have nothing to disclose.

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