Abstract—Although in cross-sectional studies left ventricular mass (LVM), which exceeds that predicted by workload (inappropriate LVM [LVM_{inapp}]), but not absolute LVM or LVM index (LVMI), is inversely related to LV ejection fraction (EF), whether on-treatment decreases in LVM_{inapp} (%observed/predicted LVM) account for increases in EF beyond LVM or LVMI is unclear. Echocardiography was performed in 168 mild-to-moderate hypertensives treated for 4 months. Although in patients with an LVMI >51 g/m^2.7 (n=112; change in LVMI, -13.7±14.0 g/m^2.7; P<0.0001) but not in patients with an LVMI ≤51 g/m^2.7 (n=56; change in LVMI, 1.3±9.3 g/m^2.7) LVMI decreased with treatment, treatment failed to increase EF in either group (1.2±10.8% and 2.7±10.7%, respectively). In contrast, in patients with inappropriate LV hypertrophy (LVM_{inapp} >150%; n=33) LVM_{inapp} decreased (-32±27%; P<0.0001) and EF increased (5.0±10.3%; P<0.05) after treatment, whereas in patients with an LVMI ≤150% (n=135), neither LVM_{inapp} (-0.5±23%) nor EF (0.9±10.3%) changed with therapy. With adjustments for circumferential LV wall stress and other confounders, whereas on-treatment decreases in LVMI or LVMI were weakly related to an attenuated EF (partial r=0.17; P>0.05), on-treatment decreases in LVM_{inapp} were strongly related to increases in EF even after further adjustments for LVMI or LVMI (partial r = -0.63 [CI, -0.71 to −0.52]; P<0.0001). In conclusion, decreases in LVM_{inapp} are strongly related to on-treatment increases in EF beyond changes in LVM and LVMI. LV hypertrophy can, therefore, be viewed as a compensatory change that preserves EF, but when in excess of that predicted by stroke work, it can be viewed as a pathophysiological process accounting for a reduced EF. (Hypertension. 2012;60:00-00.) ● Online Data Supplement

Key Words: left ventricular systolic function ■ left ventricular hypertrophy ■ pump function

Left ventricular (LV) hypertrophy (LVH) is a predictor of heart failure and the development of a reduced ejection fraction (EF) independent of myocardial infarction. LV mass (LVM) may, therefore, determine the progression to heart failure with a reduced rather than a preserved EF. However, in keeping with the classic tenet that LVH is a compensatory response to LV load, an increased LVM or on-treatment decreases in LVMI have been associated with an unchanged EF. Moreover, LVH may even be associated with an enhanced EF for that predicted by wall stress, and on-treatment decreases in LVM have been related to reductions rather than increases in indices of systolic LV chamber function. There is, therefore, considerable uncertainty as to whether LVH contributes to decreases in systolic chamber function.

One possibility that may explain discrepancies in the ability to show consistent relations between LVM or LVMI (LVM) and a reduced systolic LV chamber function is that absolute LVM and LVMI may incorporate a component of LVH considered compensatory in nature, whereas there may also be a component of LVH that contributes to decompensation. In this regard, LVH in excess of that predicted by workload (ie, stroke work = blood pressure [BP] × stroke volume), termed “inappropriate LVM” (LVM_{inapp}), is inversely associated with systolic LV chamber function. However, these relationships have largely been demonstrated in cross-sectional studies and are at odds with on-treatment decreases in systolic LV chamber function associated with LVH regression. Inverse LVM_{inapp}—LV systolic chamber function relations may, therefore, reflect compensatory increases in LVM as a consequence of systolic dysfunction or associated confounding effects. Although one previous study has reported that on-treatment regression but not persistence of LVM_{inapp} is associated with an improved EF, whether

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increases in EF in the participants showing regression of LVM\textsubscript{inappr} in that study were independent of or stronger than changes in LVM or LVMI is uncertain. To further explore the possibility that increases in LVM beyond workload and absolute LVM may contribute toward a decreased systolic LV chamber function, in the present study we, therefore, aimed to evaluate whether treatment-induced decreases in LVM\textsubscript{inappr} in mild-to-moderate hypertension are associated with increases in EF independent of and more strongly than LVM or LVMI.

**Methods**

**Study Group**

The present study was conducted according to the principles outlined in the Helsinki Declaration. The University of the Witwatersrand Committee for Research on Human Subjects approved the protocol (approval No. M940106). Participants gave informed, written consent. The study design has been described previously.\textsuperscript{26,27} Hypertensives of black African descent 18 to 70 years of age, free of clinically significant cardiovascular and noncardiovascular disease, were enrolled. Hypertension was diagnosed after a 2-week placebo run-in period, if daytime ambulatory diastolic BP was 90 to 114 mm Hg.

Eligible patients were randomly assigned to receive nifedipine gastrointestinal system at 30.0 mg/d, verapamil slow release at 240.0 mg/d, hydrochlorothiazide at 12.5 mg/d, or enalapril at 10.0 mg/d, and patients were followed up at monthly intervals for 4 months.\textsuperscript{26} At each monthly visit, up titration of therapy or the addition of therapy occurred as described.\textsuperscript{26} If target BP was not achieved (daytime diastolic BP <90 mm Hg), at 1 month, the daily dose of therapy was increased (nifedipine gastrointestinal system, 60 mg; verapamil slow release, 360 mg; hydrochlorothiazide, 25 mg; and enalapril, 20 mg), and at 2 months in patients receiving nifedipine gastrointestinal system (enalapril, 10 mg/d; carvedilol, 25 mg/d) or verapamil slow release were added or the dose of nifedipine gastrointestinal system was increased to 90 mg/d. In patients receiving verapamil slow release at 2 months, the dose could be increased to 480 mg/d. In those receiving hydrochlorothiazide 25,000 mg/d, reserpine 0.125 mg/d could be added, and in those receiving enalapril 200 mg/d, hydrochlorothiazide 12.5 mg/d could be added.

Of the 409 patients randomized, 233 were eligible for inclusion in the substudy because echocardiograms were of sufficient quality. Of the latter patients, 23 were withdrawn before 4 months, and 42 did not have all measurements. Thus, data in 168 participants were available for analysis. High-quality echocardiograms could not be obtained in 176 participants because of the high participant rate of obese females with a generalized fat distribution, including the thoracic region.

**Blood Pressure**

High-quality conventional BP measurements were obtained by trained nurse technicians according to guidelines\textsuperscript{28,29} using a standard mercury sphygmomanometer, as described previously.\textsuperscript{26-27} Ambulatory 24-hour, day, and night BP were determined using SpaceLabs monitors (model 90207), as described previously.\textsuperscript{26,27}

**Echocardiography**

M-mode, 2D pulse and color Doppler echocardiography was performed as described previously,\textsuperscript{26,27} and M-mode variables were analyzed according to the American Society of Echocardiography convention.\textsuperscript{30} All of the participants were assessed for mitral valve abnormalities as determined using 2D and color Doppler imaging. All of the measurements were recorded and analyzed offline by experienced investigators who were unaware of the clinical data of the participants. LV mass (LVM) was determined using a standard formula\textsuperscript{13} and indexed (LVMI) to height\textsuperscript{2-7}. LV mean wall thickness was calculated as the mean of septal+posterior wall thickness and LV relative wall thickness as (septal+ posterior wall thickness)/LV end diastolic diameter. An LVMI \textgreater;51 g/m\textsuperscript{2.7} was considered to be increased.\textsuperscript{32} LV EF (biplane Simpson) and midwall fractional shortening (FS\textsubscript{mid}) were calculated to determine LV chamber and myocardial systolic function, respectively, using standard formulas (see the online-only Data Supplement for FS\textsubscript{mid} calculation).

The calculation of FS\textsubscript{mid} using a modified ellipsoidal model as described previously\textsuperscript{33} accounts for epicardial migration of the midwall during systole. Stroke volume was evaluated from the difference between LV end diastolic and systolic volumes determined using both the Teichholz\textsuperscript{34} and the z-derived\textsuperscript{35} methods. Circumferential LV systolic wall stress was calculated as described previously (see the online-only Data Supplement for calculation).\textsuperscript{33}

The extent of LVM\textsubscript{inappr} was determined from predicted LVM as described by others,\textsuperscript{36} where predicted LVM was calculated as 55.37+\textsuperscript{30}(0.64×height\textsuperscript{2-7})+(0.64×(systolic BP×stroke volume×0.014))−(18.07×sex), where male sex is 1 and female sex is 2 and where stroke volume was calculated from LV volumes assessed from the z-derived method.\textsuperscript{35} Inappropriate LVM was expressed either as actual−predicted LVM in grams or percentage of actual LVM/predicted LVM. An LVM\textsubscript{inappr} >150% was considered to be increased. This threshold was identified from the upper 95% CI for LVM\textsubscript{inappr} determined in 140 of 678 participants from a community-based study without clinically significant disease and normal blood parameters who were normotensive, nondiabetic, and had a body mass index <30 kg/m\textsuperscript{2}. In these participants the upper 95% CI for LVMI was 51.8 g/m\textsuperscript{2-7}.

**Data Analysis**

Database management and statistical analyses were performed with SAS software, version 9.1 (SAS Institute Inc., Cary, NC). Continuous data are reported as mean±SD. Unadjusted means and proportions were compared by the large-sample z test and the \(\chi^2\) statistic, respectively. Changes in variables over the 4-month treatment period and a comparison of these changes between groups with versus without increases in LVM\textsubscript{inappr} or LVM were determined using a 2-way ANOVA with a Tukey post test. A comparison of changes in adjusted EF between groups with and without increases in LVM\textsubscript{inappr} or LVMI was determined using multivariate regression analysis. Independent relations between baseline or change in LVM, LVMI, or LVM\textsubscript{inappr} and baseline or change in EF were assessed from multivariate linear regression analysis with appropriate adjustors. Adjustors included age, sex, circumferential LV systolic wall stress, diabetes mellitus, pulse rate, previous treatment for hypertension, regular smoking, regular alcohol intake, and body weight, because in bivariate or multivariate models these parameters were associated with EF, LVMI, or OLM\textsubscript{inappr}. The use of carve- dilol was also included as an adjustor, because a modestly higher proportion of participants with an increased LVM\textsubscript{inappr} were receiving this agent. Z statistics were used to compare correlation coefficients.

**Results**

**Participant Characteristics**

A high proportion of participants were obese (Table 1). A total of 19.6% had inappropriate increases in LVM, and 66.7% had LVH (LVMI \textgreater;51 g/m\textsuperscript{2-7}). As compared with the 176 nonparticipants, the 168 participants who had all of the data available for analysis were younger and less obese (Table 1). Otherwise, participants with data available had similar characteristics as compared with nonparticipants, including similar conventional and ambulatory BP values (Table 1).

**Suitability of the LVM\textsubscript{inappr} Calculation**

In contrast to strong positive correlations between LVM (or LVMI) and stroke work \((r=0.56–0.60; P<0.0001)\), LVM\textsubscript{inappr} was unrelated to stroke work \((r=0.001; P=0.99)\).
Clinical and Demographic Factors at Baseline Independently Associated With LVM_{inapp}r

On bivariate analysis age, female sex, regular alcohol intake, body mass index, and body weight were positively associated with LVM_{inapp}r at baseline ($P<0.05$ to $<0.0001$). In a multivariate model, sex ($P<0.05$), body mass index ($P<0.0001$), and body weight ($P<0.0001$; separate model from body mass index) were independently and positively related to LVM_{inapp}r.

Relationships Between LV Systolic Function and LVM_{inapp}r, LVM, or LVMI at Baseline

Strong relationships between baseline LVM_{inapp}r and both baseline EF and FSmid independent of confounders and either LVM or LVMI were noted (Table S1, available in the online-only Data Supplement). In contrast, neither baseline LVM nor LVMI was independently related to either baseline EF or FSmid (Table S1).

Treatment Effects in the Whole Group

Four months of antihypertensive therapy in all of the participants resulted in decreases in conventional and ambulatory BP, LV wall stress, stroke work, LVM, LVMI, and LVM_{inapp}r (Table 2) and a modest increase in EF but no changes in FSmid or LV relative wall thickness (Table 2).

Treatment Effects on BP, Wall Stress, and Stroke Work in Patients With or Without an Increased LVM_{inapp}r or LVMI

At the end of the 4-month treatment period, participants with an increased LVM_{inapp}r or LVMI were receiving similar drug classes as compared with participants with an appropriate LVM or normal LVMI except for a modestly greater use of carvedilol in the group with an increased LVM_{inapp}r (Table S2). Antihypertensive treatment of participants with an increased LVM_{inapp}r resulted in decreases in conventional or 24-hour BP and circumferential LV systolic wall stress and stroke work, which were not statistically different from those noted in participants with an appropriate LVM (Table 3). However, as compared with participants with a normal LVMI, antihypertensive treatment of participants with an increased LVMI resulted in greater decreases in systolic BP and stroke work (Table 3).

Treatment Effects on LV Structure in Patients With or Without an Increased LVM_{inapp}r or LVMI

Treatment of participants with an increased LVM_{inapp}r or LVMI resulted in decreases in all of the LV structural parameters (Table 4). In participants with an appropriate LVMI, treatment also decreased LVM but not other LV structural parameters (Table 4). The decrease in LV structural parameters with treatment was greater in patients with an increased LVM_{inapp}r as compared with those with an appropriate LVMI (Table 4). In participants with a normal LVMI, treatment did not alter LV structure, and treatment-induced decreases in LVM, LVMI, LV mean wall thickness, and LV end diastolic diameter were greater in participants with an increased LVMI than in those without (Table 4).

Treatment Effects on LV Systolic Function in Patients With or Without an Increased LVM_{inapp}r or LVMI

As compared with patients with an appropriate LVM, where unadjusted and multivariate-adjusted EF failed to improve with antihypertensive therapy, in patients with an increased LVM_{inapp}r unadjusted and multivariate-adjusted EF increased with antihypertensive therapy (Table 5). In contrast, no significant unadjusted or multivariate-adjusted changes in EF were noted in patients with either an increased or a normal LVMI (Table 5). No significant treatment effects on FSmid were noted (Table 5).
Table 3. Changes in Conventional and Ambulatory BP, Circumferential Left Ventricular Systolic Wall Stress, and Stroke Work With Antihypertensive Treatment in Mild-to-Moderate Hypertensives (n=168) With or Without LVM_{inapp}, or LVM at Baseline

<table>
<thead>
<tr>
<th>Hemodynamic and LV Variables</th>
<th>0 mo</th>
<th>4 mo</th>
<th>Change in</th>
<th>% Change</th>
<th>0 mo</th>
<th>4 mo</th>
<th>Change in</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline LVM_{inapp}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conventional systolic BP, mm Hg</td>
<td>172±20</td>
<td>154±27</td>
<td>−18±26</td>
<td>−10.1±15.1</td>
<td>171±20</td>
<td>146±19*</td>
<td>−25±25</td>
<td>−14.1±13.9</td>
</tr>
<tr>
<td>Conventional diastolic BP, mm Hg</td>
<td>102±8</td>
<td>95±12*</td>
<td>−7±14</td>
<td>−6.1±14.0</td>
<td>103±9</td>
<td>91±11*</td>
<td>−12±13</td>
<td>−10.9±12.6</td>
</tr>
<tr>
<td>24-h systolic BP, mm Hg</td>
<td>152±14</td>
<td>133±20*</td>
<td>−19±16</td>
<td>−12.4±10.1</td>
<td>150±15</td>
<td>128±13*</td>
<td>−23±15</td>
<td>−14.5±8.8</td>
</tr>
<tr>
<td>24-h diastolic BP, mm Hg</td>
<td>97±7</td>
<td>85±11*</td>
<td>−12±9</td>
<td>−12.7±9.0</td>
<td>96±7</td>
<td>82±8*</td>
<td>−14±9</td>
<td>−14.2±8.7</td>
</tr>
<tr>
<td>LV systolic wall stress, g/cm²</td>
<td>132±40</td>
<td>115±35*</td>
<td>−17±45</td>
<td>−12.6±22.5</td>
<td>135±33</td>
<td>115±35*</td>
<td>−21±39</td>
<td>−15.0±24.4</td>
</tr>
<tr>
<td>Stroke work, g-m</td>
<td>153±53</td>
<td>135±52*</td>
<td>−18±56</td>
<td>−11.1±34.4</td>
<td>149±47</td>
<td>121±35*</td>
<td>−29±50</td>
<td>−17.2±25.6</td>
</tr>
<tr>
<td>Baseline LVM</td>
<td>&gt;51 g/m²^2 (n=112)</td>
<td>≤51 g/m²^2 (n=56)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Conventional systolic BP, mm Hg</td>
<td>176±19</td>
<td>148±23*</td>
<td>−27±25*</td>
<td>−14.9±13.4†</td>
<td>163±18</td>
<td>145±18*</td>
<td>−18±26</td>
<td>−10.1±15.3</td>
</tr>
<tr>
<td>Conventional diastolic BP, mm Hg</td>
<td>103±8</td>
<td>92±12*</td>
<td>−12±14</td>
<td>−10.7±13.1</td>
<td>101±8</td>
<td>92±10*</td>
<td>−9±12</td>
<td>−8.4±12.8</td>
</tr>
<tr>
<td>24-h systolic BP, mm Hg</td>
<td>153±15</td>
<td>130±16*</td>
<td>−23±15</td>
<td>−14.8±9.1</td>
<td>145±13</td>
<td>126±10*</td>
<td>−19±14</td>
<td>−12.6±9.0</td>
</tr>
<tr>
<td>24-h diastolic BP, mm Hg</td>
<td>97±7</td>
<td>83±9*</td>
<td>−14±9</td>
<td>−14.3±8.4</td>
<td>95±7</td>
<td>82±10*</td>
<td>−13±10</td>
<td>−13.2±9.5</td>
</tr>
<tr>
<td>LV systolic wall stress, g/cm²</td>
<td>135±33</td>
<td>114±31*</td>
<td>−21±40</td>
<td>−14.6±25.1</td>
<td>134±36</td>
<td>115±32*</td>
<td>−19±40</td>
<td>−14.7±24.5</td>
</tr>
<tr>
<td>Stroke work, g-m</td>
<td>162±48</td>
<td>128±43*</td>
<td>−34±53†</td>
<td>−20.1±25.6§</td>
<td>126±38</td>
<td>115±30*</td>
<td>−11±42</td>
<td>−8.2±28.0</td>
</tr>
</tbody>
</table>

LVM_{inapp} indicates inappropriate left ventricular mass; LVM, left ventricular mass index; LV, left ventricular; BP, blood pressure.

*P<0.0001 vs 0 mo.
†P<0.05 values in groups without an increased LVM_{inapp} or LVM (interative effects).
‡P<0.005 vs values in groups without an increased LVM_{inapp} or LVM (interactive effects).
§P<0.0001 vs values in groups without an increased LVM_{inapp} or LVM (interactive effects).

Relationship Between On-Treatment Change in LVM, LVM_{inapp}, and LV EF

With or without adjustments for potential confounders, on-treatment decreases and percentage decreases in LVM_{inapp} were strongly associated with an increase and percentage increase in EF (Table 6). The strength of the multivariate-adjusted relationships was unchanged with further adjustments for baseline EF included in the model (Table 6). In contrast, decreases and percentage decreases in LVM and LVM_{inapp} were modestly associated with a decrease and percentage decrease in EF (Table 6). The positive relationships between LVM or LVM{inapp} and EF were abolished with further adjustments for baseline EF (Table 6). The inverse relationships between change in or percentage change in LVM_{inapp} and change in or percentage change in EF were far stronger than the relationships between change in or percentage change in EF and LVM_{inapp}.

Table 4. Changes in LV Structure With Antihypertensive Treatment in Mild-to-Moderate Hypertensives (n=168) With or Without LVM_{inapp}, or LVM at Baseline

<table>
<thead>
<tr>
<th>LV Variables</th>
<th>0 mo</th>
<th>4 mo</th>
<th>Change in</th>
<th>% Change</th>
<th>0 mo</th>
<th>4 mo</th>
<th>Change in</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline LVM_{inapp}</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>LVM, g</td>
<td>287±70</td>
<td>217±62†</td>
<td>−70±51</td>
<td>−25.0±14.9§</td>
<td>190±46</td>
<td>170±40*</td>
<td>−20±43</td>
<td>−8.2±21.5</td>
</tr>
<tr>
<td>LVM indexed for height^{2.7}, g/m²^{2.7}</td>
<td>80.19</td>
<td>60.15†</td>
<td>−29.15</td>
<td>−25.0±14.9</td>
<td>55±14</td>
<td>50±12</td>
<td>−5±12</td>
<td>−8.2±21.5</td>
</tr>
<tr>
<td>LV mean wall thickness, cm</td>
<td>1.41±0.15</td>
<td>1.21±0.14†</td>
<td>−0.19±0.14</td>
<td>−14.7±9.3</td>
<td>1.12±0.16</td>
<td>1.07±0.14</td>
<td>−0.05±0.17</td>
<td>−3.5±15.0</td>
</tr>
<tr>
<td>LV relative wall thickness</td>
<td>0.58±0.13</td>
<td>0.51±0.09*</td>
<td>−0.07±0.12†</td>
<td>−12.8±18.9§</td>
<td>0.48±0.11</td>
<td>0.48±0.10</td>
<td>−0.004±0.12</td>
<td>−2.0±25.4</td>
</tr>
<tr>
<td>LV end diastolic diameter, cm</td>
<td>4.92±0.64</td>
<td>4.56±0.64†</td>
<td>−0.36±0.62†</td>
<td>−6.6±12.5§</td>
<td>4.58±0.51</td>
<td>4.44±0.50</td>
<td>−0.14±0.54</td>
<td>−2.6±11.3</td>
</tr>
<tr>
<td>Actual LVM/predicted LVM (LVM_{inapp}, %)</td>
<td>169±22</td>
<td>137±30†</td>
<td>−32±27</td>
<td>−20.1±15.0</td>
<td>112±20</td>
<td>112±22</td>
<td>−0.5±23</td>
<td>−0.3±18.5</td>
</tr>
<tr>
<td>Actual LVM-predicted LVM, g</td>
<td>117±47</td>
<td>58±53†</td>
<td>−59±38</td>
<td>−55.0±32.8§</td>
<td>19±35</td>
<td>18±33</td>
<td>−1±35</td>
<td>−6.4±120.1</td>
</tr>
<tr>
<td>Baseline LVM</td>
<td>&gt;51 g/m²^{2.7} (n=112)</td>
<td>≤51 g/m²^{2.7} (n=56)</td>
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</tr>
</tbody>
</table>

LVM_{inapp} indicates inappropriate left ventricular mass; LVM, left ventricular mass index; LV, left ventricular.

*P<0.001 vs 0 mo.
†P<0.05 values in groups without an increased LVM_{inapp} or LVM (interactive effects).
‡P<0.005 vs values in groups without an increased LVM_{inapp} or LVM (interactive effects).
§P<0.0001 vs values in groups without an increased LVM_{inapp} or LVM (interactive effects).
The main finding of the present study is that, in the treatment of mild-to-moderate hypertension over a 4-month period, in contrast to a modest treatment-induced attenuation in EF accompanying decreases in LVM and LVMI, on-treatment decreases in LVMinappr were strongly and independently related to improvements in EF. Importantly, relationships between on-treatment changes in LVMinappr and EF were unaltered by adjustments for LVMI and were noted to be far stronger than relationships between on-treatment changes in LVM or LVMI and EF.

Although one previous study has demonstrated that on-treatment regression but not persistence of LVMinappr is associated with an improved EF, whether changes in EF associated with decreases in LVMinappr are independent of or stronger than changes in LVM or LVMI is uncertain. To the best of our knowledge, the present study provides the first prospective, intervention data to show that regression of LVH as indexed by LVMinappr is associated with improvements in EF beyond that of LVM or LVMI. The present study therefore supports the notion that LVH in excess of that associated with decrease in LV systolic chamber function.

Previous studies showing inverse relationships between LVMinappr and indices of systolic chamber function have

### Table 5. Changes in LV Systolic Function With Antihypertensive Treatment in Mild-to-Moderate Hypertensives (n=168) With or Without LVMinappr, or LVMI at Baseline

<table>
<thead>
<tr>
<th>LV Systolic Function</th>
<th>0 mo</th>
<th>4 mo</th>
<th>Change in % Change</th>
<th>0 mo</th>
<th>4 mo</th>
<th>Change in % Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline LVMinappr</td>
<td>Inappropriate LVM (LVMinappr &gt;150%) (n=33)</td>
<td>Appropriate LVM (LVMinappr ≤150%) (n=135)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>57.8±8.6</td>
<td>62.0±9.8*</td>
<td>4.95±10.30†</td>
<td>11.1±19.7†</td>
<td>64.5±8.6</td>
<td>65.5±9.2</td>
</tr>
<tr>
<td>Adjusted LV ejection fraction, %‡</td>
<td>58.0±8.0</td>
<td>61.8±8.6*</td>
<td>4.99±9.87†</td>
<td>11.8±19.0†</td>
<td>64.5±7.0</td>
<td>65.7±8.1</td>
</tr>
<tr>
<td>LV midwall fractional shortening, %</td>
<td>17.5±5.4</td>
<td>17.2±5.0</td>
<td>-0.26±6.78</td>
<td>-2.4±36.0</td>
<td>20.1±5.2</td>
<td>20.1±4.6</td>
</tr>
<tr>
<td>Baseline LVMI</td>
<td>&gt;51 g/m².7 (n=112)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>63.4±9.3</td>
<td>64.7±9.5</td>
<td>1.21±10.80</td>
<td>2.2±16.4</td>
<td>62.8±8.8</td>
<td>65.5±9.0</td>
</tr>
<tr>
<td>Adjusted LV ejection fraction, %‡</td>
<td>63.5±7.4</td>
<td>64.5±8.5</td>
<td>0.63±9.10</td>
<td>1.9±14.9</td>
<td>62.7±8.8</td>
<td>65.8±8.9</td>
</tr>
<tr>
<td>LV midwall fractional shortening, %</td>
<td>20.0±5.3</td>
<td>19.5±5.4</td>
<td>-0.51±6.63</td>
<td>-2.2±37.8</td>
<td>18.8±4.7</td>
<td>19.6±5.1</td>
</tr>
</tbody>
</table>

LVMinappr indicates inappropriate left ventricular mass; LVMI, left ventricular mass index; LV, left ventricular.

*P<0.05 vs 0 mo.
†P<0.05 vs values in groups without an increased LVMinappr (interactive effect).
‡Adjustments are for age, sex, circumferential LV systolic wall stress, diabetes mellitus, pulse rate, previous treatment for hypertension, regular smoking, regular alcohol intake, body weight, body height (when assessing relations with LVM), and carvedilol therapy.

### Table 6. Relationships Between On-Treatment Changes in Indices of LVM and LVEF With LVM Expressed as an LVMinappr, Absolute LVM, or LVMI Indexed to Height².⁷ (LVM) in Mild-to-Moderate Hypertensives (n=168)

<table>
<thead>
<tr>
<th>Adjustments</th>
<th>None</th>
<th>Confounders†</th>
<th>Confounders + EF‡</th>
<th>Confounders + ΔLVM or % ΔLVM†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in ejection fraction vs</td>
<td>Pearson r (CI)</td>
<td>P Value</td>
<td>Pearson r (CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>ΔLVMinappr</td>
<td>-0.29* (-0.42 to -0.14)</td>
<td>&lt;0.0001</td>
<td>-0.38* (-0.50 to -0.23)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ΔLVM</td>
<td>0.08 (-0.07 to 0.23)</td>
<td>0.30</td>
<td>0.17 (0.01 to 0.31)</td>
<td>0.04</td>
</tr>
<tr>
<td>ΔLVMI</td>
<td>0.07 (-0.08 to 0.22)</td>
<td>0.34</td>
<td>0.17 (0.01 to 0.32)</td>
<td>0.04</td>
</tr>
<tr>
<td>% Change in ejection fraction vs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔLVMinappr</td>
<td>-0.24* (-0.38 to -0.09)</td>
<td>&lt;0.005</td>
<td>-0.31* (-0.44 to -0.16)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ΔLVM</td>
<td>0.14 (-0.02 to 0.28)</td>
<td>0.08</td>
<td>0.18 (0.03 to 0.33)</td>
<td>0.02</td>
</tr>
<tr>
<td>ΔLVMI</td>
<td>0.14 (-0.02 to 0.28)</td>
<td>0.08</td>
<td>0.18 (0.03 to 0.33)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

LVM indicates left ventricular mass; LVEF, left ventricular ejection fraction; LVMinappr, inappropriate left ventricular mass; LVMI, left ventricular mass index; LV, left ventricular; EF, baseline ejection fraction; Δ LVM, change in LVM. A negative relationship represents an increase in EF with a decrease in LVM.

*P<0.001 vs correlation coefficients for LVM and LVMI.
†Adjustments are for age, sex, circumferential LV systolic wall stress, diabetes mellitus, pulse rate, previous treatment for hypertension, regular smoking, regular alcohol intake, body weight, body height (when assessing relations with LVM), and carvedilol therapy.
largely been reported in cross-sectional studies conducted in select clinical samples, and none have demonstrated these effects beyond LVM or LVMI. Such relationships may, therefore, reflect a compensatory increase in LVM in response to a depressed LV systolic function to residual confounding effects, or to an effect that depends on absolute LVM. With respect to whether the relationships shown in the present study may also be attributed to a decrease in LVM in response to a reduction in LV systolic function, there is little preclinical or clinical evidence to our knowledge to indicate that antihypertensive therapy is able to increase LV systolic chamber function independent of load over a short duration of therapy (4 months). In contrast, there is substantial evidence to show that antihypertensive therapy in part regresses LVH over this time period. It is, therefore, likely that, in the present study, antihypertensive therapy regressed LVMinapp, and the reduced LVMinapp or associated myocardial changes consequently enhanced EF.

Previous studies have demonstrated that regression of LVH after treatment with antihypertensive therapy is associated with either no change rather than improved indices of systolic LV chamber function. Similarly, in the present study we show that decreases in LVM or LVMI are associated with a modest attenuation rather than an increase in EF with antihypertensive therapy. Together with the often enhanced EF observed relative to that predicted from LV wall stress in LVH, such data have previously cast doubt on inverse relationships between LVH and EF being attributed to LVH, accounting for a decreased LV systolic chamber function. However, as in the present study, on-treatment decreases in LVMinapp were strongly and independently associated with the opposite effect on EF (an increase); the present study provides evidence to support the notion that LVH or factors related to LVH may be responsible for decreases in systolic LV chamber function but that LVMinapp and not absolute LVM or LVMI accounts for this effect.

Although not a primary outcome of the present study, it is important to consider the potential mechanisms for the on-treatment LVMinapp-EF relations observed. In this regard, EF is in part determined by myocardial systolic function, which is indexed by FSmid. Despite our ability to show strong inverse relations between FSmid and LVMinapp independent of LVM or LVMI at baseline, after 4 months of antihypertensive therapy, no significant relationships between change in FSmid and change in LVMinapp were noted. These data suggest that on-treatment changes in FSmid over a short treatment period are too small to show relations with decreases in LVMinapp unless larger study samples are used. Indeed, previous studies have demonstrated that LVH regression after 3 months of antihypertensive treatment was associated with only a 0.6% increase in FSmid and required 152 patients to show a trend for significance.

The exact mechanisms at a myocardial level that may account for the improved LV systolic function associated with regression of an increased LVMinapp are also unclear. This may reflect the regeneration of cardiomyocytes damaged by LVH-associated apoptosis and necrosis. However, the short duration over which LV systolic chamber function increased suggests an alternative mechanism, such as an improved cardiomyocyte function. In this regard, LVMinapp may be accompanied by an imbalance in myocardial oxygen supply:demand ratios, a change that promotes cardiomyocyte dysfunction. With a decrease in LVMinapp, the balance between myocardial oxygen supply and demand may be restored and function improved.

Caution should be exercised when interpreting the results of the present study. In this regard, the present findings do not challenge the prognostic value of LVM or LVMI in contrast to LVMinapp. Indeed, although not improving EF, antihypertensive therapy nevertheless also decreased LVM in participants with appropriate LVM, and this is likely to be of prognostic importance. However, the present study does indicate that future prospective studies specifically assessing the impact of regression of increases in LVMinapp independent of absolute LVM or LVMI on the development of heart failure with a reduced EF are required.

A limitation of the present study is that it was conducted in one ethnic group with a high prevalence of mild-to-moderate hypertension, treatment-induced decreases in LVMinapp as compared with those participants with an appropriate LVMI may reflect a type II statistical error. However, this is likely to have biased against the results of the present study and, hence, resulted in an underestimation of the size effect on EF that antihypertensive therapy could achieve in participants with an increased LVMinapp.

In conclusion, in the present study we show that, with adjustments for LV wall stress and other confounders, in mild-to-moderate hypertension, treatment-induced decreases in LV in excess of that predicted by LV workload (LVMinapp) were strongly related to improvements in on-treatment EF independent of absolute LVM or LVMI. These data, therefore, support the notion that LVH, as indexed by LVM or LVMI, incorporates a component of LVH that can be viewed as a compensatory change that preserves EF, but when this exceeds that predicted by LV workload, this excess in LV growth or associated changes may account for decreases in EF. Future prospective studies specifically assessing the impact of regression of increases in LVMinapp independent of absolute LVM or LVMI on the development of heart failure with a reduced EF are required.
Perspectives

Currently there is considerable uncertainty as to whether LVH contributes to decreases in systolic chamber function. Although, LVM predicts the development of a reduced EF\(^8\), an increased LVM\(^11-13\) or on-treatment decreases in LVM\(^14\) have been associated with an unchanged EF. Furthermore, LVH may be associated with an enhanced EF for that predicted by wall stress,\(^15\) and on-treatment decreases in LVM have been related to reductions in indices of systolic chamber function.\(^16\) A possible explanation for these discrepancies is that LVM incorporates a component of LVH that is compensatory in nature, as well as a component that contributes to decompensation. Indeed, in cross-sectional studies,\(^18-24\) LVM in excess of that predicted by workload (LVM\(_{\text{inapp}}\))\(^17\) is inversely associated with systolic chamber function. In the present study, we provide the first longitudinal intervention data showing that regression of LVH as indexed by LVM\(_{\text{inapp}}\), but not LVM or LVMl, is associated with improvements in EF independent of load, LVM, and LVMl. Hence, although LVH is a compensatory change that preserves EF, when LVH is in excess of that predicted by stroke work, it is a pathophysiological process that accounts for reduced EF.

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Disclosures

None.

References


Novelty and Significance

**What Is New?**
- These are the first prospective, intervention data showing that regression of LVH as indexed by an increase in LVM beyond that predicted by stroke work but not LVM or LVMI is associated with improvements in EF independent of load, LVM, and LVMI.

**What Is Relevant?**
- In hypertensives who have an increase in LVM beyond that predicted by stroke work, therapy that regresses LVH will increase systolic chamber function (EF) independent of absolute LVM.

**Summary**
LVH can be viewed as a compensatory change that preserves EF, but LVH in excess of that predicted by stroke work is a pathophysiological process accounting for a reduced EF.
Relationship Between On-Treatment Decreases in Inappropriate Versus Absolute or Indexed Left Ventricular Mass and Increases in Ejection Fraction in Hypertension
Angela J. Woodiwiss, Carlos D. Libhaber, Elena Libhaber, Pinhas Sareli and Gavin R. Norton

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Angela J Woodiwiss, Carlos D Libhaber, Elena Libhaber, Pinhas Sareli, Gavin R Norton.

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Running title: Inappropriate LVH.

Conflict of interest: None
AJW, CDL, PS and GRN, contributed equally to this work

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Methods

Midwall fractional shortening (FSmid) was calculated using a previously described formula as \[\frac{(LVIDed + 0.5 Hed)-(LVIDes + 0.5 Hes)}{(LVIDed + 0.5 Hed)},\]
where LVID is left ventricular internal diameter, H is wall thickness, ed is end diastole and es is end systole. As previously described, circumferential systolic wall stress of the left ventricle was calculated as:

\[
\frac{SBP \cdot (0.5 \text{LVIDs})^2 \left[1 + \frac{(0.5 \text{LVIDs} + \text{PWTs})^2}{(0.5 \text{LVIDs} + 0.5 \text{PWTs})^2}\right]}{(0.5 \text{LVIDs} + \text{PWTs})^2 - (0.5 \text{LVIDs})^2}
\]

where SBP is systolic blood pressure, LVIDs is LVID in systole and PWTs is posterior wall thickness in systole.
Supplementary Table S1. Relationships between baseline indexes of left ventricular mass (LVM) and baseline LV ejection fraction (EF) or LV midwall fractional shortening (FSmid) with LVM expressed as an inappropriate increase in LVM (LVM_{inappr}), absolute LVM or LVM indexed to height$^{2.7}$ (LVMI) in mild-to-moderate hypertensives (n=168).

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Adjustors*</th>
<th>Partial r</th>
<th>Confidence intervals</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline EF versus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVM_{inappr}</td>
<td>+LVM</td>
<td>-0.61</td>
<td>-0.70 to -0.50</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVM_{inappr}</td>
<td>+LVMI</td>
<td>-0.62</td>
<td>-0.70 to -0.51</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVM</td>
<td>*</td>
<td>-0.05</td>
<td>-0.20 to 0.11</td>
<td>=0.56</td>
</tr>
<tr>
<td>LVMI</td>
<td>*</td>
<td>-0.01</td>
<td>-0.16 to 0.15</td>
<td>=0.91</td>
</tr>
<tr>
<td>Baseline FSmid versus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVM_{inappr}</td>
<td>+LVM</td>
<td>-0.39</td>
<td>-0.51 to -0.24</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVM_{inappr}</td>
<td>+LVMI</td>
<td>-0.36</td>
<td>-0.49 to -0.32</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVM</td>
<td>*</td>
<td>0.08</td>
<td>-0.08 to 0.23</td>
<td>=0.33</td>
</tr>
<tr>
<td>LVMI</td>
<td>*</td>
<td>0.08</td>
<td>-0.08 to 0.23</td>
<td>=0.33</td>
</tr>
</tbody>
</table>

* Adjustors are for age, sex, circumferential LV systolic wall stress, diabetes mellitus, pulse rate, previous treatment for hypertension, regular smoking, regular alcohol intake, body weight, and body height (when assessing relations with LVM).
**Supplementary Table S2.** Antihypertensive drug classes at the end of 4-months of therapy, received by participants with an increased or normal inappropriate increase in left ventricular mass ($LVM_{\text{inappr}}$) or LVM index ($LVMI$) at baseline.

<table>
<thead>
<tr>
<th>Drug class</th>
<th>$LVM_{\text{inappr}}$ (%)</th>
<th>LVMI (g/m$^{2.7}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;150 (n=33)</td>
<td>≤150 (n=135)</td>
</tr>
<tr>
<td>Hydrochlorothiazide (n, [%])</td>
<td>8 (24)</td>
<td>40 (30)</td>
</tr>
<tr>
<td>Nifedipine GITS (n, [%])</td>
<td>22 (67)</td>
<td>80 (59)</td>
</tr>
<tr>
<td>Enalapril (n, [%])</td>
<td>5 (15)</td>
<td>25 (19)</td>
</tr>
<tr>
<td>Verapamil SR (n, [%])</td>
<td>6 (18)</td>
<td>31 (23)</td>
</tr>
<tr>
<td>Reserpine (n, [%])</td>
<td>1 (3)</td>
<td>10 (7)</td>
</tr>
<tr>
<td>Carvedilol (n, [%])</td>
<td>6 (18)*</td>
<td>7 (5)</td>
</tr>
</tbody>
</table>

GITS, gastrointestinal system, SR, slow release. *p<0.05 vs $LVM_{\text{inappr}}$ ≤150%.