Impact of Left Ventricular Structure on the Incidence of Hypertension

The Framingham Heart Study

Wendy S. Post, MD; Martin G. Larson, ScD; Daniel Levy, MD

Background Left ventricular hypertrophy is often found very early in the course of hypertension. It is not known whether increased left ventricular mass contributes to the pathogenesis of hypertension. The purpose of this study was to examine the impact of left ventricular mass and other echocardiographically assessed cardiac structural features on the incidence of hypertension.

Methods and Results Subjects for this investigation included participants in the Framingham Heart Study and the Framingham Offspring Study who were normotensive at the baseline examination (systolic blood pressure, <140 mm Hg; diastolic blood pressure, <90 mm Hg; not receiving antihypertensive medications) and free of coronary heart disease, congestive heart failure, valvular heart disease, hypertrophic cardiomyopathy, diabetes mellitus, and renal insufficiency. The study sample included 1121 men (mean age, 44.4 years) and 1559 women (mean age, 45.6 years). Four years after the baseline examination, 202 men (18.0%) and 257 women (16.5%) were hypertensive (systolic blood pressure, ≥140 mm Hg; diastolic blood pressure, ≥90 mm Hg; or use of antihypertensive medications). Baseline echocardiographic left ventricular mass (P = .01) and the sum of septal and posterior left ventricular wall thicknesses (P = .02) were associated with progression to hypertension. After adjusting for sex, baseline age, systolic and diastolic blood pressures, body mass index, alcohol intake, and systolic blood pressure from an examination 8 years earlier, the odds ratio for developing hypertension for a 1-SD increment in left ventricular mass index was 1.20 (95% confidence interval, 1.04 to 1.39), and the odds ratio for a 1-SD increment in left ventricular wall thickness was 1.16 (95% confidence interval, 1.02 to 1.33).

Conclusions In these normotensive adults, increased left ventricular mass and wall thickness were associated with the development of hypertension. Further studies are warranted to examine the utility of echocardiography in determining the need for antihypertensive therapy and to assess the effect of earlier intervention on the course of progression to hypertension. (Circulation. 1994;90:179-185.)

Key Words: hypertension • left ventricle • hypertrophy • Framingham Heart Study • echocardiography

Hypertension is a disease with multiple etiologies, some of which are incompletely understood. Left ventricular hypertrophy is often found very early in the course of hypertension. In addition, a few studies have documented elevated left ventricular mass before the development of hypertension, suggesting a possible role of left ventricular hypertrophy in the pathogenesis of hypertension.

Although left ventricular hypertrophy develops as a result of pressure overload, systemic blood pressure correlates only modestly with left ventricular mass. The pathogenesis of hypertrophy not only is related to elevated systemic blood pressure but also is influenced by other factors such as catecholamines, the renin-angiotensin system, loading conditions of the ventricle, and genetics. These factors may help explain the poor correlation between systemic blood pressure and left ventricular mass, and they may contribute to an elevation in left ventricular mass before the development of hypertension.

The purpose of this study was to evaluate the associations between left ventricular mass, internal diameter, wall thickness, and relative wall thickness and the incidence of hypertension in normotensive adults. These data may provide insights into the pathogenesis of hypertension and enhance our understanding of the clinical significance of left ventricular hypertrophy.

Methods

The Framingham Heart Study is a prospective epidemiological study that was established in 1948 to evaluate potential risk factors for coronary heart disease. The original cohort included 5209 residents of Framingham, Mass, who were between the ages of 28 and 62 years. Selection criteria and study design have been reported. An additional 5135 subjects, who were offspring of original Framingham Heart Study participants and spouses of offspring, were entered into The Framingham Offspring Study in 1971. The present sample was derived from original Framingham Heart Study subjects who attended a routine biennial examination between 1979 and 1981 and Offspring Study subjects who were examined between 1979 and 1983. Subjects who met any of the following criteria were excluded: (1) systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, (2) use of antihypertensive medication, (3) coronary heart disease or congestive heart failure, (4) diabetes mellitus, (5) renal insufficiency (creatinine ≥2.0 mg/dL), (6) valvular heart disease, (7) age <20 years, or (8) an inadequate echocardiogram.

Body height and weight measurements, medical history, physical examination, serum creatinine, fasting glucose, and

Received October 15, 1993; revision accepted March 28, 1994.
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echocardiography were obtained routinely at the baseline examination. Body mass index was used as a measure of obesity, calculated as weight (in kilograms) divided by the square of height (in meters). Resting systolic and diastolic blood pressures were measured twice by a physician, at the first and fifth Korotkoff phases, during each clinic examination. The mean values of the two measurements were used to determine systolic and diastolic blood pressures. The diagnoses of coronary heart disease and congestive heart failure were established in accordance with published criteria after review by a committee of three physicians who evaluated records from the Framingham Heart Study clinic, interim hospitalizations, and visits to nonstudy physicians. Diabetes was defined as a fasting blood glucose level $\geq 140$ mg/dL ($7.77$ mmol/L), a random nonfasting blood glucose level $\geq 200$ mg/dL ($11.11$ mmol/L), or the use of insulin or an oral hypoglycemic agent. The diagnosis of valvular heart disease was based on clinical examination evidence of a systolic murmur of intensity graded $\geq 3$ on a 6-point scale or any diastolic murmur. Information regarding alcohol consumption was obtained at the baseline examination for the Offspring Study participants. Because this information was not available at the baseline examination for original Framingham Heart Study subjects, for these subjects alcohol intake was obtained from an examination 2 years earlier. Alcohol consumption was calculated in ounces per week using a published estimation formula.

**Echocardiographic Methods**

Standard M-mode echocardiographic techniques were used in this study as previously described. Measurements of left ventricular wall thickness and chamber diameter were made in diastole in accordance with methods outlined by the American Society of Echocardiography. Left ventricular mass was estimated by the modified cubed formula using measurements obtained in accordance with the "Penn" convention: left ventricular mass ($g$) = 1.04 ([LVMI + VST + PWT]$^3$) - (LVMI)$^3$ - 13.6, where LVMI is left ventricular internal dimension, VST is ventricular septal thickness, and PWT is posterior left ventricular wall thickness. Left ventricular mass was indexed to height rather than body surface area because the latter approach is insensitive to changes in left ventricular mass that are observed in the setting of obesity. Left ventricular wall thickness was defined as the sum of VST and PWT. Relative wall thickness was defined as (left ventricular wall thickness/LVMI)$\times 100\%$.

**Follow-up**

Four years after the baseline examination, subjects returned for follow-up examinations that included blood pressure measurements. In accordance with criteria put forth by the Fifth Report of the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure, hypertension was defined as systolic blood pressure $\geq 140$ mm Hg, diastolic blood pressure $\geq 90$ mm Hg, or current use of antihypertensive medications. Subjects who developed coronary heart disease or congestive heart failure during follow-up were excluded because of the potential antihypertensive effects of pharmacological therapies for these disease entities.

**Statistical Analysis**

Hypertension detected at the follow-up examination was analyzed in the pooled sample of men and women using logistic models to adjust for the influences of sex, baseline age, systolic and diastolic blood pressures, body mass index, and alcohol consumption. This model also adjusted for systolic blood pressure from an examination 8 years earlier. These variables were chosen because they influenced left ventricular mass and/or hypertension. Their influence on hypertension was very similar in men and women, except that an age-sex interaction term was needed to account for sex differences in the relation of age to the development of hypertension.

Echocardiographic variables first were analyzed individually in multivariable logistic models that included the clinical variables. To determine which combination of echocardiographic variables produced the best prediction of hypertension, all the echocardiographic variables were entered into a stepwise analysis, in which the clinical variables were forced into the model to control for potential confounders. Because the echocardiographic variables differ with regard to mean values and units of measurement, we computed the odds ratio for development of hypertension and a 95% confidence interval (CI) for a 1-SD increment of each variable. Among subjects who were not using antihypertensive medications at the follow-up examination, changes in systolic and diastolic blood pressures from baseline values were analyzed with multiple linear regression models. Changes in blood pressure differed between men and women regarding the influence of age, baseline blood pressure, and body mass index. Therefore, men and women were analyzed separately. As before, echocardiographic variables were assessed separately in multivariable models adjusting for the clinical variables described above. A stepwise model was used subsequently.

Several techniques were used to evaluate the fitted models, including the following methods: tests for sex-specific regression coefficients for clinical and echocardiographic variables; graphical analysis to check for a linear relation between logits of probability and values of predictor variables; examination of deviance residuals, leverage, and influence statistics; and computation of the Hosmer-Lemeshow goodness-of-fit statistic.

In all analyses, a value of $P<.05$ was considered statistically significant.

**Results**

The study sample was derived from 2805 men and 3413 women who had a baseline examination (Table 1). There were 1111 men and 1314 women excluded at the baseline examination due to hypertension. An additional 215 men and 120 women were excluded due to coronary heart disease, congestive heart failure, diabetes mellitus, renal insufficiency, valvular heart disease, or age $<20$ years. Inadequate echocardiograms resulted in the exclusion of 176 men and 178 women; these subjects tended to be older and more obese than subjects with better-quality echocardiograms. There were 2 subjects who had extreme values for left ventricular mass and were therefore excluded from analysis. During follow-up, 58 men and 31 women died or developed coronary heart disease or congestive heart failure, and 124 men and 209 women did not attend the follow-up examination. Therefore, the study sample comprised 1121 men and 1559 women.

**Clinical and Echocardiographic Characteristics**

At the baseline examination, subjects ranged in age from 20 to 88 years. The mean age was 44.4 years for men and 45.6 years for women. Mean systolic blood pressure was 120 mm Hg in men and 115 mm Hg in women; corresponding diastolic values were 77 and 73 mm Hg.

At the 4-year follow-up examination, 202 men (18.0%) and 257 women (16.5%) were hypertensive, of whom 352 (76.7%) had elevated blood pressure and 107 (23.3%) were receiving antihypertensive medication. Subjects with hypertension at follow-up had higher mean age, baseline blood pressure, body mass index, and alcohol...
intake than those who remained normotensive (Table 2). Baseline measures of left ventricular mass, left ventricular mass index, left ventricular wall thickness, and relative wall thickness were higher in subjects who developed hypertension, but left ventricular internal dimension was similar in the groups (Table 3).

**Progression to Hypertension**

Observed (crude) probabilities of progression to hypertension as a function of baseline left ventricular mass index are displayed in Fig 1. There was a steep, positive, curvilinear relation between baseline left ventricular mass and the probability of hypertension. The rapid rise in the probability of hypertension at higher levels of left ventricular mass was largely due to the clustering of hypertension risk factors among subjects with higher left ventricular mass.

Separate multiple logistic regression analyses were used to examine the association of each echocardiographic variable with the development of hypertension, adjusting for sex, baseline age, systolic and diastolic blood pressures, body mass index, alcohol consumption, and systolic blood pressure from an examination 8 years before the baseline examination. Both baseline left ventricular mass index and left ventricular wall thickness were associated with the development of hypertension. Table 4 shows the odds ratios corresponding to a 1-SD increment of each echocardiographic variable. A 26.5-g/m increase in indexed left ventricular mass was associated with an odds ratio of 1.20 (95% CI, 1.04 to

<table>
<thead>
<tr>
<th>TABLE 1. Derivation of the Study Sample</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Total no. of subjects attending index examination</td>
<td>2805</td>
<td>100</td>
</tr>
<tr>
<td>Serial exclusions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensive medication use</td>
<td>500</td>
<td>17.8</td>
</tr>
<tr>
<td>SBP ≥140 mm Hg or DBP ≥90 mm Hg</td>
<td>611</td>
<td>21.8</td>
</tr>
<tr>
<td>CHD or CHF</td>
<td>120</td>
<td>4.3</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>68</td>
<td>2.4</td>
</tr>
<tr>
<td>Creatinine &gt;2.0 mg/dL</td>
<td>2</td>
<td>0.1</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>19</td>
<td>0.7</td>
</tr>
<tr>
<td>Age &lt;20 y</td>
<td>6</td>
<td>0.2</td>
</tr>
<tr>
<td>Inadequate echocardiogram</td>
<td>176</td>
<td>6.3</td>
</tr>
<tr>
<td>Left ventricular mass outliers</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Died before follow-up examination</td>
<td>28</td>
<td>1.0</td>
</tr>
<tr>
<td>Developed CHD or CHF</td>
<td>30</td>
<td>1.1</td>
</tr>
<tr>
<td>Did not attend follow-up examination</td>
<td>124</td>
<td>4.4</td>
</tr>
<tr>
<td>Total no. of participants</td>
<td>1121</td>
<td>40.0</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; CHD, coronary heart disease; and CHF, congestive heart failure.

<table>
<thead>
<tr>
<th>TABLE 2. Clinical Characteristics of Subjects at Baseline Examination According to Blood Pressure Status at Follow-up Examination</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normotensive</td>
<td>Hypertensive</td>
</tr>
<tr>
<td></td>
<td>at Follow-up</td>
<td>at Follow-up</td>
</tr>
<tr>
<td></td>
<td>(n=919)</td>
<td>(n=202)</td>
</tr>
<tr>
<td>Age, y</td>
<td>43.1±11.7</td>
<td>50.6±12.5</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>79.7±10.9</td>
<td>82.2±11.6</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.76±0.07</td>
<td>1.75±0.08</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.7±3.2</td>
<td>26.8±3.2</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>118±10</td>
<td>126±9</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>76±7</td>
<td>81±6</td>
</tr>
<tr>
<td>SBP, 8 y previous, mm Hg</td>
<td>120±11</td>
<td>127±12</td>
</tr>
<tr>
<td>DBP, 8 y previous, mm Hg</td>
<td>78±8</td>
<td>82±8</td>
</tr>
<tr>
<td>Alcohol intake, oz/wk</td>
<td>4.6±5.1</td>
<td>5.2±5.4</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure. Values are given as mean±SD.
TABLE 3. Echocardiographic Characteristics of Subjects at Baseline Examination According to Hypertension Status at Follow-up Examination

<table>
<thead>
<tr>
<th>Baseline Echocardiographic Characteristic</th>
<th>Men (n=919)</th>
<th>Hypertensive at Follow-up (n=202)</th>
<th>Women (n=1302)</th>
<th>Hypertensive at Follow-up (n=257)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV mass, g</td>
<td>186±43</td>
<td>202±51</td>
<td>121±29</td>
<td>136±35</td>
</tr>
<tr>
<td>LV mass index, g/m</td>
<td>106±24</td>
<td>115±28</td>
<td>75±18</td>
<td>85±21</td>
</tr>
<tr>
<td>LV wall thickness, mm</td>
<td>16.9±2.3</td>
<td>17.9±2.7</td>
<td>14.3±1.9</td>
<td>15.4±2.5</td>
</tr>
<tr>
<td>LV internal dimension, mm</td>
<td>52.7±3.8</td>
<td>52.7±3.9</td>
<td>47.4±3.4</td>
<td>47.7±3.5</td>
</tr>
<tr>
<td>Relative wall thickness, %</td>
<td>32.2±5.2</td>
<td>34.1±6.2</td>
<td>30.3±4.7</td>
<td>32.6±6.2</td>
</tr>
</tbody>
</table>

LV indicates left ventricular. Values are given as mean±SD.

1.39) for the development of hypertension. Similarly, each 2.5-mm increment in left ventricular wall thickness was associated with an odds ratio of 1.16 (95% CI, 1.02 to 1.33) for progression to hypertension. Neither relative wall thickness nor left ventricular internal dimension was significantly associated with the incidence of hypertension. When all the echocardiographic variables were considered in a stepwise logistic regression model that controlled for the clinical variables, indexed left ventricular mass was the only echocardiographic variable significantly associated with the development of hypertension. There were no appreciable changes in the odds ratios when left ventricular mass was indexed to body surface area or to higher powers of height.

Marginal effects of left ventricular mass on the predicted probabilities of developing hypertension are shown in Fig 2 at various levels of systolic blood pressure after adjusting for baseline age, body mass index, diastolic blood pressure, alcohol intake, and systolic blood pressure from an examination 8 years before the baseline examination. The marginal effects of left ventricular mass on the probability of developing hypertension approached a linear relation after adjusting for the clinical variables. Note that the absolute impact of left ventricular mass on the probability of developing hypertension was greatest at higher baseline levels of systolic blood pressure.

Change in Blood Pressure

The impact of cardiac structure on blood pressure changes as a continuous variable (follow-up value minus baseline) was analyzed using multiple linear regression analysis. Left ventricular mass index and left ventricular wall thickness were predictive of an increase in systolic blood pressure at follow-up after controlling for clinical variables; however, the changes in systolic blood pressure per 1-SD increments in echocardiographic variables were small (0.7 to 1.1 mm Hg). This was due, in part, to the exclusion from this analysis of hypertensive subjects who were receiving antihypertensive drug therapy at the follow-up examination. As such, subjects with the greatest rise in serial blood pressure, necessitating initiation of drug treatment for hypertension, were excluded from consideration. None of the echocardiographic variables was associated with a change in diastolic blood pressure.

Discussion

This study identifies cardiac structural precursors of hypertension in normotensive adults. A 26.5-g/m increase in left ventricular mass was associated with a 20% greater odds of developing hypertension during 4 years of follow-up, and a 2.5-mm increment in left
ventricular wall thickness was associated with a 16% increase in the odds of developing hypertension. In contrast, left ventricular internal dimension and relative wall thickness were not associated with the odds of developing hypertension after controlling for associated clinical variables. Left ventricular mass and left ventricular wall thickness also were associated with serial changes in systolic blood pressure but not changes in diastolic blood pressure.

This study confirms the findings of de Simone et al., who demonstrated that left ventricular mass predicted the development of hypertension in 132 normotensive employed adults, of whom 15 developed hypertension. The present study has a larger sample size (2680 versus 133), with a greater number of hypertensive subjects at follow-up (459 versus 15). The larger study sample provides greater precision in the estimation of risks and allows more extensive multivariable analyses that adjust for factors known to predispose to hypertension. We also have quantified the magnitude of the effect of left ventricular mass and wall thickness on the likelihood of developing hypertension by computing odds ratios using multiple logistic regression, and we have demonstrated that the absolute impact of left ventricular mass on the probability of developing hypertension is most pronounced at higher baseline levels of systolic blood pressure. A recent study found that increased left ventricular mass predicted a subsequent increase in blood pressure in Japanese urban men.

Some hemodynamic studies have reported increased cardiac output and normal peripheral vascular resistance early in the course of hypertension. Later, peripheral vascular resistance is elevated and cardiac output may be normal or depressed. An increase in left ventricular mass in the preclinical stages of hypertension may promote hypertension by providing the contractile force necessary to elevate systemic blood pressure before the vascular changes that raise systemic vascular resistance.

The results of the present study are consistent with, but do not imply, causality between increased left ventricular mass and progression to hypertension. An alternative explanation to the hypothesis that left ventricular mass promotes hypertension is that normotensive subjects with increased left ventricular mass may have elevated blood pressures at other times. Causal blood pressure measurements record only one point in time and may result in misclassification. Left ventricu-

### Table 4. Odds of Progression to Hypertension Based on Echocardiographic Variables

<table>
<thead>
<tr>
<th>Echocardiographic Variable</th>
<th>Incremental Unit*</th>
<th>Odds Ratio per Increment†</th>
<th>95% Confidence Interval</th>
<th>Lower</th>
<th>Upper</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV mass index, g/m</td>
<td>26.5 g/m</td>
<td>1.20</td>
<td>1.04</td>
<td>1.39</td>
<td>.01</td>
<td></td>
</tr>
<tr>
<td>LV wall thickness, mm</td>
<td>2.5 mm</td>
<td>1.16</td>
<td>1.02</td>
<td>1.33</td>
<td>.02</td>
<td></td>
</tr>
<tr>
<td>LV internal dimension, mm</td>
<td>4.4 mm</td>
<td>1.07</td>
<td>0.93</td>
<td>1.24</td>
<td>.32</td>
<td></td>
</tr>
<tr>
<td>Relative wall thickness, %</td>
<td>5.2%</td>
<td>1.08</td>
<td>0.97</td>
<td>1.21</td>
<td>.15</td>
<td></td>
</tr>
</tbody>
</table>

LV indicates left ventricular.

*Incremental unit for each echocardiographic variable reflects 1 SD.

†Results of separate multivariable logistic regression models for each echocardiographic variable, adjusted for sex, baseline age, systolic and diastolic blood pressures, body mass index, alcohol consumption, and systolic blood pressure from 8 years before the index examination.
ular mass may reflect the summation of pressure in the systemic circulation over longer periods of time. In an attempt to account for antecedent blood pressure, values from an examination 8 years before the baseline examination were entered into the regression model for predicting incident hypertension.

An additional, alternative explanation to the hypothesis that left ventricular hypertrophy promotes hypertension is that there may be a common factor that is associated with the development of both hypertension and left ventricular hypertrophy. The pathogenesis of essential hypertension is multifactorial and is not completely understood. Left ventricular hypertrophy is a frequent finding in hypertensive patients, but the degree of hypertrophy is only partially explained by the level of blood pressure. It has been suggested that in addition to elevated blood pressure, numerous factors contribute to the development of hypertrophy. Alterations in the renin-angiotensin system and catecholamines have been implicated in both the etiology of hypertension and the development of hypertrophy. It is possible that abnormalities in these humoral systems that lead to hypertension also directly stimulate myocardial hypertrophy; however, some studies have not supported this concept. In addition, genetic factors play an important role in the development of both hypertension and myocardial hypertrophy.

A large majority of Framingham Heart Study subjects are white, so these results do not necessarily apply to other ethnic or racial groups. Another limitation of this study is that in the analysis of echocardiographic predictors of incremental changes in blood pressure as a continuous variable, changes in blood pressure from baseline to follow-up could not be measured in subjects who developed hypertension and were receiving antihypertensive medications. These individuals were excluded from the analysis of change in blood pressure but were included in the analysis of incident hypertension.

**Summary**

In normotensive adults, increased left ventricular mass and wall thickness were associated with a subsequent increase in blood pressure and the development of hypertension. In borderline hypertensive patients in whom echocardiographic information is available, left ventricular mass and wall thickness may be helpful in determining the need for antihypertensive therapy. Further studies are warranted to determine the clinical usefulness of earlier interventions on the course of progression to hypertension.

**Acknowledgments**

This work was supported in part by National Institutes of Health contract N01-HC-38038. We give special thanks to Thomas P. Rocco, MD, for his assistance in the formulation of this manuscript.

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Impact of left ventricular structure on the incidence of hypertension. The Framingham Heart Study.
W S Post, M G Larson and D Levy

Circulation. 1994;90:179-185
doi: 10.1161/01.CIR.90.1.179

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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