Prevalence of Cardiac Structural and Functional Abnormalities in Untreated Primary Hypertension

Eljas Laufer, Garry L. Jennings, Paul I. Korner, and Elizabeth Dewar

We examined the prevalence of left ventricular structural and functional abnormalities in previously untreated subjects by performing echocardiography in 89 normal volunteers, 57 patients with established hypertension, and 38 patients with mild or borderline hypertension. We measured left ventricular mass, wall thickness, internal diameter, and wall thickness/radius ratio. Because of intergroup differences in body size, we used covariance analysis to index these variables to a common value of 1.8 m². No adjustment was needed for the wall thickness/radius ratio. Functional variables determined were fractional shortening and transmitral early/late flow velocity ratio (the latter was standardized by analysis of covariance to age 40 years). The prevalence of left ventricular mass index values more than 2 SD above the mean of the normal group was 30% in the patients with established hypertension and 12–15% in the patients with mild hypertension. Corresponding figures for wall thickness index were 65% and 32% and for the wall thickness/radius ratio 60% and 40%. The prevalence of abnormality in the transmitral flow velocity was 28% in the patients with established hypertension and 12% in the patients with mild hypertension. A multivariate discriminant function that used combined anatomic and functional variables provided the most reliable classification; it was correct in 82% of normal subjects, 65% of patients with established hypertension, and 61% of patients with mild hypertension. The majority of patients with hypertension have cardiac structural or functional abnormalities, or both. (Hypertension 1989; 13:151-162)

In human primary hypertension the reported prevalence of left ventricular hypertrophy (LVH) ranges between 20 and 80%.

The majority of investigators suggest that the prevalence is closer to the lower end of this range. However, even the upper end of the range is below the almost universal prevalence of LVH in animals with genetic or experimental hypertension. Hypertension is usually more severe in the experimental models, which could account for the greater incidence of LVH. In addition, most experiments are performed in inbred strains of animals, where the normal range of variation of left ventricular size may be smaller than in a mixed population where genetic or environmental factors are not as well controlled. Many of the previous human series have included patients previously treated with antihypertensive drugs, which could have resulted in regression of LVH and underestimation of the prevalence rate.

The purpose of the present study was to examine these structural abnormalities by two-dimensional and M-mode echocardiography. We examined patients with established chronic hypertension and with mild or “borderline” hypertension and compared the different variables with those obtained in a group of normal subjects. In addition to various intergroup comparisons of individual variables (e.g., wall thickness, wall thickness/radius ratio, and left ventricular mass index [LVMI]), we compared the normotensive and hypertensive groups by means of multivariate discriminant function analysis to determine whether this analysis allowed a clearer intergroup differentiation. We also examined to what extent various indexes of left ventricular function, which included the measurement of fractional systolic shortening as determined by echocardiography and the early/late ratio of transmitral diastolic blood flow velocities as determined by Doppler measurement, would help to differentiate the groups, either alone or in combination with the different structural indexes.
Subjects and Methods

We studied 89 normal volunteers (average age 30.6 years, range 14–69 years) (Table 1). The subjects had no history of cardiovascular or other major disease, and no abnormality was detected on physical examination or on a resting 12-lead electrocardiogram. Consecutive patients with previously untreated hypertension and normal subjects were recruited from June 1984 to February 1987 from our Risk Clinic where the general population is screened for conventional cardiovascular risk factors. Blood pressure was measured in the supine position after 10 minutes rest with a random zero sphygmomanometer. Patients with blood pressure elevated above 160/95 mm Hg on three consecutive visits 2 weeks apart were classified as having established hypertension. Patients with blood pressure above those values on the first two visits, but with a diastolic blood pressure below 95 mm Hg on the third visit were classified as having mild or borderline hypertension. After classifying each subject, we excluded secondary causes of hypertension by physical examination, urinalysis, serum biochemistry, hematological examination, and chest x-ray.

Echocardiographic studies were performed in all 38 patients with mild hypertension and 57 with established hypertension; the Doppler equipment did not become available until after the study had begun, so that combined Doppler, M-mode, and two-dimensional echocardiographic studies were performed in only 54 normal subjects, in only 24 patients with mild hypertension, and in only 38 with established hypertension. The characteristics of the subset of subjects who underwent both echocardiographic and Doppler studies were similar to that of the total group (Table 1).

**Echocardiography**

Echocardiographic and Doppler recordings were made with a Hewlett-Packard (Andover, Massachus-
estimated by the above formula and the actual weight of the left ventricle. The regression equation was

\[ LVE = 1.2LVO - 10.1, \]

where LVE and LVO were the estimated and observed left ventricular mass, respectively; the regression coefficient did not differ significantly from 1.0, with the regression accounting for 81% of the total variance (r = 0.9, SE = 0.11, p < 0.001), the standard error of a single observation was ±6.5% of the mean value.

Left ventricular mass measurements were indexed (1) conventionally by dividing by body surface area (left ventricular mass index [LVMI]), (2) by dividing by height, as described by Levy et al,22 and (3) by a covariance method (see below). We determined systolic function by measuring fractional shortening.13

The echocardiographic records were coded and measurements were made by two "blinded" observers. The measurements of the two observers were averaged to a between-observer variation of 1 mm wall thickness or LVID. Larger differences were reevaluated by the two observers together, and the final estimate arrived at by consensus. No subject in this series had segmental wall motion abnormalities.23

The Penn convention21 per se was not used because there were a number of hypertensive patients whose endocardial echoes could not be clearly separated. However, an estimate of LVMI "Penn"15 was derived from the conventional method of indexing left ventricular mass/body surface area (LVM/BSA) by multiplying LVMI by 0.8, which is the regression coefficient of the regression equation that Devereux et al24 described to correct values of left ventricular mass obtained by the present American Society of Echocardiography17 technique to Penn convention values. In four patients with established hypertension and in three with mild hypertension, left ventricular wall thickness could not be accurately determined either because of problems with resolution or difficulty in obtaining a true short-axis view. These patients all had LVH on qualitative examination of the two-dimensional images, but their results were not included in the main analysis because of the difficulty of quantification.

**Doppler Measurements**

We determined early (E) and late (a-wave, A) transmirtal diastolic peak flow velocities by using both pulsed and continuous wave Doppler measurements.14-16 Differences between observers were averaged and were less than 5 cm/sec. There were no patients in the series in whom Doppler measurements could not be obtained on technical grounds. We used the ratio of early-to-late peak flow velocities (E/A), which becomes altered when left ventricular diastolic function changes.15,16

**Statistical Methods**

The results of the various measurements have been expressed as mean ± SEM. In comparing the intergroup differences of single variables, we used one-way analysis of variance (ANOVA) or unpaired t test. Because of the significant differences in mean ages and body surface area in the three groups, we examined the effects of these variables and sex on wall thickness, LVID, WT/R ratio, left ventricular mass, and E/A ratio in the entire group and also separately in men and women (see Results). We used covariance analysis25 to determine an appropriate index of left ventricular mass that could be applied to all the groups. We first determined the relation of left ventricular mass to body surface area in each group. From this we then derived an overall regression function from the intragroup variances and covariance SS from the total (Table 2). We used the equation to obtain a left ventricular mass index (LVM*) for correcting the observed left ventricular mass to a body surface area (BSA) of 1.8 m², which was close to the average value of all three groups

### Table 2. Regression Equations

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Equation</th>
<th>SEM₀</th>
<th>SEM₁</th>
<th>t</th>
<th>r</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>89</td>
<td>LVM = 1.42.3BSA-46.1</td>
<td>±20.0</td>
<td>±36.1</td>
<td>7.11</td>
<td>0.62</td>
<td>50.5</td>
</tr>
<tr>
<td>Mild</td>
<td>35</td>
<td>LVM = 78.3BSA +87.9</td>
<td>±43.3</td>
<td>±80.8</td>
<td>0.08</td>
<td>0.28</td>
<td>3.27</td>
</tr>
<tr>
<td>Established</td>
<td>53</td>
<td>LVM = 230.1BSA -164.5</td>
<td>±35.3</td>
<td>±68.2</td>
<td>6.52</td>
<td>0.69</td>
<td>42.6</td>
</tr>
<tr>
<td>Intragroup</td>
<td>177</td>
<td>LVM = 158.8BSA -58.6</td>
<td>±17.4</td>
<td>±42.6</td>
<td>3.01</td>
<td>0.57</td>
<td>9.12</td>
</tr>
<tr>
<td>Intragroup</td>
<td>177</td>
<td>LVM = 2.9height +26.5</td>
<td>±0.40</td>
<td>±45.5</td>
<td>2.68</td>
<td>0.49</td>
<td>7.2</td>
</tr>
<tr>
<td>Intragroup</td>
<td>177</td>
<td>LVID = 1.10BSA +2.86</td>
<td>±0.15</td>
<td>±0.39</td>
<td>6.97</td>
<td>0.47</td>
<td>48.58</td>
</tr>
<tr>
<td>Intragroup</td>
<td>177</td>
<td>WT = 0.22BSA +0.68</td>
<td>±0.22</td>
<td>±0.53</td>
<td>5.05</td>
<td>0.36</td>
<td>25.51</td>
</tr>
<tr>
<td>Normal</td>
<td>54</td>
<td>E/A = -0.16Age +2.21</td>
<td>±0.003</td>
<td>±0.112</td>
<td>4.93</td>
<td>-0.58</td>
<td>24.4</td>
</tr>
<tr>
<td>Mild</td>
<td>24</td>
<td>E/A = -0.02Age +2.26</td>
<td>±0.005</td>
<td>±0.184</td>
<td>4.83</td>
<td>-0.70</td>
<td>23.7</td>
</tr>
<tr>
<td>Established</td>
<td>38</td>
<td>E/A = -0.16Age +1.88</td>
<td>±0.003</td>
<td>±0.157</td>
<td>4.58</td>
<td>-0.60</td>
<td>21.0</td>
</tr>
<tr>
<td>Intragroup</td>
<td>116</td>
<td>E/A = -0.012Age +2.22</td>
<td>±0.002</td>
<td>±0.301</td>
<td>9.6</td>
<td>-0.66</td>
<td>92.9</td>
</tr>
</tbody>
</table>

LVID and WT had intragroup relations only (to BSA). Equations show relation of left ventricular mass (LVM) to body surface area (BSA) and height, left ventricular internal diameter (LVID) and wall thickness (WT) to BSA, and transmirtal early/late flow velocity ratio (E/A) to age.
[LVM* = LVM + b(1.8 - BSA), where b is slope of the intragroup equation]. As both wall thickness and LVID were also significantly related to body surface area in the whole population by analysis of covariance, they were also indexed in each subject to a common body surface area of 1.8 m² (WT* and LVID*, respectively).

Similarly, because a relation between E/A ratio and age has previously been demonstrated in normal subjects, and in the light of significant differences in the mean age of the three groups of subjects in this study, we used covariance analysis to correct E/A ratio to a common age of 40 years (E/A*); where E/A* = E/A + b(40 - age).

For the multivariate analysis we used the method of linear discriminant function analysis, which was performed by using the computer program provided in the Statistical Package for the Social Sciences microcomputer version (SPSS/PC+). We calculated a three-group discriminant function analysis to differentiate the groups on the basis of (1) anatomic criteria with WT* and LVID* as the predictor variables, (2) functional criteria with E/A* and FS, and (3) combined anatomic and functional criteria with the predictor variables WT*, E/A*, and FS.

For the three-group discriminant analysis we derived two discriminant functions: D₁ and D₂. Statistics used to assess these functions included (1) the eigenvalue, that is, the ratio of intergroup-to-intragroup SS, (2) %Vx is percentage of intergroup variance attributable to each function, (3) the canonical correlation coefficient, which is a measure of the degree of association between the discriminant scores and the groups, and (4) Wilks λ, that is, the ratio of the intragroup SS to total SS, which is the proportion of the total variance not explained by the intergroup differences. Wilks λ is transformed into a variable distributed in accordance with the χ² distribution; a high value of χ² suggests that the discriminant scores of individuals from the different groups attributable to the equations are likely to be different.

To assess whether the proportion of men and women differed significantly in the three groups, we used the likelihood ratio (G statistic) calculated from the frequencies as described by Sokal and Rohlf.

**Results**

**Characteristics of Groups**

The subjects with mild or borderline and established hypertension were on the average older than the normal subjects (both p < 0.001), although there was reasonable overlap in the age range of the different groups. The hypertensive groups were significantly heavier (p < 0.0001), and their body surface area was greater (p < 0.05 and p < 0.001, respectively) than the normotensive subjects. The mean arterial pressures of the patients with mild and established hypertension were 13 and 28 mm Hg, respectively, above the values of the normal subjects (p < 0.01). The characteristics of the subset of normal subjects and hypertensive subjects in whom Doppler measurements were performed were similar to that of the larger group (Table 1). There were more men than women in the study (123 and 61, respectively).

**Indexing of Anatomic and Functional Data**

We examined the relation between body surface area and left ventricular mass, wall thickness, LVID, and WT/R ratio. By using the combined data of normal and hypertensive subjects, men as well as women, we determined that WT/R ratio was unrelated to body surface area, whereas left ventricular mass had both an intergroup and intragroup relation to body surface area (Table 2). For left ventricular mass there were significant differences in the regression coefficients and in the intercept values of the three intergroup regression equations, and only in the normal group did the intercept not differ significantly from zero (Table 2). However, the intercept of the intergroup regression equation was also not significantly different from zero, thus providing support for the use of either LVM* or of the conventional index LVMI (LVM/BSA). None of the above variables were related to age. The effect of sex on the different variables is best seen in the anatomic data of the normal subjects. There was no significant difference in the regression coefficients relating body surface area to left ventricular mass between the sexes (t = 0.43) but there was a significant difference in intercept (t = 2.28, p < 0.05). The best fitting regression equations were: LVM*n = 74.8 + 80BSA and LVM*w = 47 + 80BSA, where LVM*n and LVM*w are left ventricular mass in men and women, respectively. Thus for any given body surface area, left ventricular mass was about 15% higher in men than women. This is evident in the individual results of the normal subjects in Figure 1 where the difference between the sexes is evident in the distribution of the points of LVM* and, to a lesser degree, when the conventional index LVMI was used. The sex differences still remained when indexing was performed by dividing left ventricular mass by height, which is in agreement with the results of Devereux et al. (see Discussion). Sex differences were minimal and not significant in normal subjects in relation to WT*, LVID*, and WT/R (Figures 1 and 2), and these variables are best used to consider the combined data for men and women in normal and hypertensive subjects, particularly in relation to the multivariate analysis. As regards the use of either LVM* or LVMI when considering the differences between normal subjects and the two hypertensive groups, we compared the results in men only as well as the results from the combined data. Comparison of the pooled data for these variables among the three groups is valid, because although the number of men exceeded that of women in all three groups, the proportion of men and women did not differ signif-
significantly, as assessed by G statistic (G=2.49, 2 df, \( p=0.3 \)) for the larger anatomic group in Table 1 and (G=2.62, 2 df, \( p=0.2 \)) for the smaller group who had functional studies. There were no sex differences in the relation between E/A ratio and age.

Anatomic Differences

The mean values of the individual variables are summarized in Table 3. The differences in \( WT/R \) ratio and \( WT^* \) were most striking \((F=41.2 \) and 38.2, respectively; both \( p<0.00001 \)). \( LVID^* \) also differed significantly \((F=6.86; p=0.0014) \) with the differences most evident on comparison of the normal group where values were significantly higher than the two hypertensive groups, \( p=0.02 \) (mild) and \( p=0.001 \) (established), respectively. \( LVM^* \) averaged 210, 227, and 265 g/1.8 m\(^2\) body surface area, respectively, in the normal subjects and in the subjects with mild and established hypertension (Figure 1). These differences in mean value were highly significant by one-way ANOVA \((F\text{ ratio}=25.1, \ p<0.00001) \). This was also the case for the standard index LVMI expressed as g/m\(^2\). As left ventricular mass was related to body surface area differently in each sex we examined \( LVM, LVM^* \), and LVMI in men alone, and similar intergroup differences were observed (Table 3). Similar differences in other variables between normal and hypertensive subjects occurred in both sexes (Figures 1 and 2).

![Figure 1](http://hyper.ahajournals.org/)

**Figure 1.** Individual values for left ventricular mass (LVM) (upper left panel) and wall thickness/radius (WT/R) ratio (lower left panel) in normal subjects (NORM) and patients with mild (MILD) and established (ESTAB) hypertension. Right panels are the LVM indexed by the covariance method described in the text \((LVM^*)\) (upper right) or the conventional left ventricular mass/body surface area \((LVMI)\) (lower right). Dashed lines are the upper and lower 2 SD limits in the normal group. •, indicate men; ○, indicate women; *, the mean value of each group.

![Figure 2](http://hyper.ahajournals.org/)

**Figure 2.** Values of uncorrected wall thickness (WT) and left ventricular internal diameter (LVID) in normal subjects (NORM) and patients with mild (MILD) or established (ESTAB) hypertension (left panel). Right panel shows the same variables indexed for body surface area. •, indicate men; ○, indicate women.
Table 3. Structural and Functional Variables in Normal Subjects and in Patients With Mild and Established Hypertension

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal</th>
<th>Mild</th>
<th>Established</th>
<th>F from one-way ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT (cm)</td>
<td>1.00±0.009</td>
<td>1.10±0.019</td>
<td>1.21±0.022</td>
<td>55.3</td>
</tr>
<tr>
<td>WT* (cm/1.8 m²)</td>
<td>1.00±0.008</td>
<td>1.09±0.018</td>
<td>1.17±0.022</td>
<td>38.2</td>
</tr>
<tr>
<td>LVID (cm)</td>
<td>4.95±0.045</td>
<td>4.76±0.069</td>
<td>4.94±0.061</td>
<td>3.05</td>
</tr>
<tr>
<td>LVID* (cm/1.8 m²)</td>
<td>4.95±0.040</td>
<td>4.69±0.067</td>
<td>4.79±0.053</td>
<td>6.86</td>
</tr>
<tr>
<td>WT/R ratio</td>
<td>0.04±0.005</td>
<td>0.47±0.012</td>
<td>0.50±0.010</td>
<td>41.2</td>
</tr>
<tr>
<td>LVM (g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men &amp; women</td>
<td>210±4.62</td>
<td>233±7.09</td>
<td>285±9.57</td>
<td>33.2</td>
</tr>
<tr>
<td>Men alone</td>
<td>230±5.27</td>
<td>241±7.43</td>
<td>312±9.82</td>
<td>36.4</td>
</tr>
<tr>
<td>LVM* (g/1.8 m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men &amp; women</td>
<td>210±3.78</td>
<td>227±6.95</td>
<td>265±7.60</td>
<td>25.1</td>
</tr>
<tr>
<td>Men alone</td>
<td>220±5.13</td>
<td>228±7.87</td>
<td>282±8.38</td>
<td>24.2</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men &amp; women</td>
<td>116±2.15</td>
<td>126±3.83</td>
<td>143±3.62</td>
<td>22.8</td>
</tr>
<tr>
<td>Men alone</td>
<td>122±2.75</td>
<td>126±4.13</td>
<td>152±3.90</td>
<td>22.2</td>
</tr>
<tr>
<td>LVMI/height (g/cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men &amp; women</td>
<td>1.21±0.024</td>
<td>1.36±0.044</td>
<td>1.60±0.049</td>
<td>31.9</td>
</tr>
<tr>
<td>Men alone</td>
<td>1.29±0.029</td>
<td>1.38±0.046</td>
<td>1.73±0.056</td>
<td>32.6</td>
</tr>
<tr>
<td>LVMI&quot;Penn&quot; (g/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men &amp; women</td>
<td>93±1.72</td>
<td>101±3.07</td>
<td>115±2.89</td>
<td>22.8</td>
</tr>
<tr>
<td>Men alone</td>
<td>98±2.21</td>
<td>101±3.31</td>
<td>122±3.12</td>
<td>22.2</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.70±0.052</td>
<td>1.41±0.080</td>
<td>1.20±0.063</td>
<td>19.16</td>
</tr>
<tr>
<td>E/A* ratio</td>
<td>1.87±0.080</td>
<td>1.45±0.118</td>
<td>1.16±0.096</td>
<td>16.58</td>
</tr>
<tr>
<td>FS</td>
<td>0.36±0.007</td>
<td>0.39±0.011</td>
<td>0.37±0.010</td>
<td>1.86</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

ANOVA, analysis of variance; WT, wall thickness; WT*, wall thickness index; LVID, left ventricular internal diameter; LVID*, left ventricular internal diameter index; WT/R, wall thickness/radius ratio; LVM, left ventricular mass; LVM*, left ventricular mass indexed by covariance method described in text; LVMI, left ventricular mass indexed by conventional method; E/A, transmitral early/late flow velocity ratio; E/A*, transmitral early/late flow velocity ratio index, standardized by analysis of covariance to age 40 years; FS, fractional shortening.

The least intergroup overlap in plots of the individual values occurred with uncorrected wall thickness where 71% of patients with established hypertension and 26% of those with mild hypertension showed values 2 SD above the mean in normal subjects. After correction of wall thickness to allow for the confounding effect of body size, WT* was 2 SD above the mean in normal subjects in 65% of patients with established hypertension and 32% with mild hypertension (Figure 2). The distribution of WT/R ratio, which was not related to sex, is shown in Figure 1. WT/R ratio was greater than the mean+2 SD in 8 of 25 men and 6 of 10 women with borderline hypertension and in 24 of 40 men and 8 of 13 women with established hypertension and 32% with mild hypertension (Figure 2). The distribution of WT/R ratio, which was not related to sex, is shown in Figure 1. WT/R ratio was greater than the mean+2 SD in 8 of 25 men and 6 of 10 women with borderline hypertension and in 24 of 40 men and 8 of 13 women with established hypertension; for the combined group the figures came to 14 of 35 (40%) in borderline hypertension and 32 of 53 (60%) in established hypertension. The differences between the prevalence values for each sex were not significant. The individual values showed the greatest overlap occurred with LVM* or LVMI where only 30% of patients with established hypertension and 12% (LVM*) and 15% (LVMI), respectively, with mild hypertension were 2 SD above the mean in normal subjects. There was no improvement in the classification when left ventricular mass was indexed for height (33% established, 16% mild).

We examined whether the separation between the three groups was improved by multivariate discriminant function analysis with WT* and LVID* as predictor variables. The two discriminant functions required for the analysis are given in Table 4. The first of these functions (D1) provided the major differentiation between the groups and accounted for 95.5% of the intergroup variance (p<0.00001). The second function (D2) accounted for 4.5% of the variance, but still provided useful discrimination (p=0.008). The discriminant functions correctly classified 70% of patients with established hypertension and only misclassified 14% of these as normal (Figure 3, left panel). Similarly, 72% of normal subjects were correctly classified and only 8% were misclassified into the established hypertension group. However, in the subjects with mild hypertension discrimination was poor and the assignment into the three possible categories was random (not significant). A virtually identical classification was obtained when LVM* and WT/R ratio were used instead of WT* and LVID*. The percentage of correctly classified subjects in all three groups was 63%. 

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TABLE 4. Results From Three-Group Linear Discriminant Analysis Using Structural, Functional, and Combined Predictor Variables

<table>
<thead>
<tr>
<th>Discriminant functions</th>
<th>Eigenvalue</th>
<th>Canonical Wilks A (Di+DJ</th>
<th>$\chi^2$ (D1)</th>
<th>$\chi^2$ (D2)</th>
<th>Group (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural predictor variables alone</td>
<td>D1 = -8.61 + 9.08 WT* - 0.23 LVID*</td>
<td>0.569</td>
<td>0.602</td>
<td>0.612</td>
<td>(D1+D2)</td>
</tr>
<tr>
<td></td>
<td>D2 = -15.49 + 2.53 WT* + 2.64 LVID*</td>
<td>0.042</td>
<td>0.200</td>
<td>0.960</td>
<td>(D1)</td>
</tr>
<tr>
<td>Functional predictor variables alone</td>
<td>D1 = -2.42 + 1.73 E/A* - 0.78 FS</td>
<td>0.300</td>
<td>0.480</td>
<td>0.746</td>
<td>(D1+D2)</td>
</tr>
<tr>
<td></td>
<td>D2 = -6.56 + 0.12 E/A* + 17.12 FS</td>
<td>0.031</td>
<td>0.173</td>
<td>0.970</td>
<td>(D1)</td>
</tr>
<tr>
<td>Combined predictor variables</td>
<td>D1 = -9.25 + 10.43 WT* - 3.73 FS - 0.27 E/A*</td>
<td>0.919</td>
<td>0.692</td>
<td>0.500</td>
<td>(D1+D2)</td>
</tr>
<tr>
<td></td>
<td>D2 = -5.05 - 9.96 WT* + 17.34 FS - 0.24 E/A*</td>
<td>0.043</td>
<td>0.203</td>
<td>0.959</td>
<td>(D1)</td>
</tr>
<tr>
<td></td>
<td>D3 = -6.23 + 0.01 LVM* + 11.79 WT/R - 3.22 FS - 0.66 E/A*</td>
<td>0.924</td>
<td>0.693</td>
<td>0.477</td>
<td>(D1+D2)</td>
</tr>
<tr>
<td></td>
<td>D4 = -6.29 - 0.01 LVM* + 10.53 WT/R + 9.46 FS + 0.37 E/A*</td>
<td>0.089</td>
<td>0.286</td>
<td>0.918</td>
<td>(D1)</td>
</tr>
</tbody>
</table>

Eigenvalue, ratio of intergroup-to-intragroup sums of squares (SS); %Vx, percentage of intergroup variance attributable to each function; Canonical $\lambda$, canonical correlation coefficient, which measures degree of association between the discriminant scores and the groups; Wilks $\lambda$, ratio of intragroup SS to total SS, which is proportion of total variance not explained by intergroup differences; D1 and D2, discriminant functions; df, degrees of freedom; WT*, wall thickness index; LVID*, left ventricular internal diameter index; E/A*, transmitral early/late flow velocity ratio index; FS, fractional systolic shortening; LVM*, left ventricular mass indexed by covariance method described in text; WT/R, wall thickness/radius ratio.

Functional Data

The transmitral diastolic flow velocity ratio (E/A) was lower in the two hypertensive groups than in the normal group (Figure 4). This was due to progressive reduction in the early velocity (E) as well as a progressive increase in the late velocity (A). However, the decline in E/A ratio with increasing severity of hypertension was partly confounded by the intergroup differences in age, which influenced E/A ratio in the normal subjects. By using analysis of covariance (Table 2), we were able to determine that the E/A ratio, adjusted to a common age of 40 years (E/A*), still declined significantly with increasing severity of hypertension (Table 3; $F=16.58$ for differences between group means; $p<0.00001$). However, the age-adjusted ratio was reduced by 2 SD or more below the mean of the normal group in only 12% of patients with mild hypertension and 28% of patients with established hypertension (Figure 5).

We found no significant relation between fractional systolic shortening and age, sex, or body size. There was marked overlap of the values of fractional shortening of the two hypertensive groups and the normal subjects (Figure 5). However, in the patients with mild hypertension fractional shortening was higher than in the other two groups ($p=0.045$). Normal subjects and patients with established hypertension had very similar mean values of fractional shortening and there was almost complete overlap between the groups (Table 3; $F=1.86$; $p=0.16$).

Functional data as predictor variables in a discriminant function analysis did not improve intergroup differentiation and was not as satisfactory as with the anatomic variables alone. With E/A* and fractional systolic shortening, 65% of normal subjects were correctly classified and 21% were misclassified into the established hypertension group. Established hypertension was correctly classified in 59% of patients and misclassified as “normal” in 24%. Before, patients with mild hypertension were randomly classified with no discriminative capacity between the groups. The average percentage of correctly classified subjects in the three groups (56%) was less than that found with the anatomic variables alone (Figure 3, center panel).

Combined Anatomic and Functional Discriminant Analysis

When we combined the anatomic and functional predictor variables WT*, E/A*, and fractional systolic shortening, the main improvement was in the capacity to classify correctly a higher proportion of patients with mild hypertension. The combined anatomic and functional discriminant analysis resulted in correct classification of 61% of mild
hypertensive patients (13% misclassified as established hypertension and 26% as normal), with 72% of the total group correctly classified. This analysis also resulted in correct classification of 82% of normal subjects and 65% of patients with established hypertension (Figure 3, right panel). Both E/A* and fractional systolic shortening contributed nearly equally to the discrimination power of the combined anatomic and functional analysis. When only WT* and E/A* were used as predictor variables, 52% of the mild hypertensive group were correctly classified within their own group, and 68% of the total group were correctly classified. When only WT* and fractional systolic shortening were used as predictor variables, the results showed closely similar frequencies of 54% and 67%, respectively. In these latter two analyses, 77% of normal subjects and 64% of established hypertensive subjects were correctly classified within their own groups.

Almost the same proportion of correct classifications was achieved with the four predictor variables, LVM* (LVMI or left ventricular mass/height), WT/R ratio, E/A*, and fractional systolic shortening (Table 4) as with the three simpler predictor variables of WT*, E/A*, and fractional systolic shortening in the combined anatomic and functional discriminant analysis. In general, when men alone were examined by combined anatomic and functional discriminant analysis, the classification was slightly better, irrespective of the particular variables included. For example, in men alone the percentage of the grouped cases correctly classified was 74% (Figure 3) when determined with the variables WT*, E/A*, and fractional systolic shortening (FS).

Discussion

In the present study we compared the wall thickness and LVID as well as left ventricular mass and WT/R ratio and functional variables of patients with mild and established hypertension with corresponding variables of a well-matched group of normal subjects. All the subjects in the study had been classified prospectively. From the differences in blood pressure at the time of the screening and at the time of the echocardiographic measurements, it is clear that the patients with mild hypertension had only a slight elevation of blood pressure and, as judged from the decline in pressure between screening and echocardiography, there could well have been a proportion of “normal” subjects included in this group. However, the patients with established hypertension were of similar severity to patients included in previously published series.14,5,32,33 The patients in both hypertensive groups were somewhat heavier and older than the normal subjects and had larger body surface area, similar to most reported series.

Our major findings with single variables were that with LVM* (or LVMI) only about 30% of patients with established hypertension and 12% of those with mild hypertension had values that were 2 SD
above the normal range. With WT/R ratio or WT*, corresponding values were about 65% of patients with established hypertension and about 30% with mild hypertension. With E/A* 28% of patients with established hypertension and 12% with mild hypertension had values more than 2 SD below the normal range. With the anatomic predictor variables WT* and LVID*, multivariate discriminant function analysis improved classification of normal subjects and those with established hypertension, but did not help further classify patients with mild hypertension. The use of several functional variables (E/A*, FS) by discriminant function analysis resulted in little improvement in classification over the single variables. Analysis with combined anatomic and functional variables gave the best separation of normal and hypertensive subjects and was the only method of correctly classifying the majority of patients with mild hypertension. The variables WT*, E/A*, and FS, correctly classified 82% of normal, 61% of mild, and 65% of established subjects with hypertension.

Because of the relation of structural variables to body surface area and of E/A to age, it was important to standardize these measurements to allow valid intergroup comparisons. The use of covariance analysis based on a regression function derived from the combined intragroup data appears the best empirical approach in making these adjustments rather than the more arbitrarily obtained indexes. There were significant differences in the regression coefficients and in the intercept values of each of the three regression equations relating left ventricular mass and body surface area derived from the results of the subjects of each group. The non-zero intercepts in the equations for each of the two hypertensive groups and the significantly different regression coefficients suggest that factors other than body surface area (e.g., LVH) contributed to the relation. The non-zero intercept suggests non-linearities in the relation, which were removed once the "intergroup" factors had been eliminated in the covariance analysis. In practice, the function LVM* gave a very similar proportion of abnormalities as the conventional index LVM/BSA (LVMI). The covariance analysis validated the use of the latter index by demonstrating that the intercept from the combined intragroup data did not differ significantly from zero. Because of the intergroup differences in body surface area and age, some adjustment of left ventricular mass and of E/A is essential; without this adjustment there is an increase in the proportion.
of apparent abnormalities obtained. We have preferred to use the indexes of LVM* and E/A* close to the mean body surface area and age, respectively, of the three groups. As the results in men and women were fairly similar and the number of women in some groups was small, we have, in the main, presented results for men and women together.

In agreement with previous studies\(^{31}\) we found, however, that there were significant sex differences in the relation between left ventricular mass and body surface area. Sex differences were not significant in the other anatomic variables WT*, WT/R ratio or LVID*. Devereux et al\(^{31}\) have shown that the differences in left ventricular mass are largely accounted for by the proportion of body fat and can be reduced by indexing left ventricular mass to lean body mass. We preferred to examine the prevalences in each sex by using anatomic indexes where a sex difference in the relation to body surface area is absent. When men alone were examined by the multivariate discriminant analysis, the resultant classification was closely similar to that of the population as a whole (Figure 3), which suggests that there was no significant increase in variance when the data were combined for both sexes.

WT* and WT/R ratio provided better intergroup anatomic differentiation than LVM*, LVMI, or LVM/height. With LVM* only 30% of patients with established hypertension and only 12% with mild hypertension had values above the normal range (i.e., 2 SD above the mean) and a similar proportion was obtained in LVMI or LVM/height. These results are close to the values given in another large study on the prevalence of LVH.\(^5\) The low prevalence in the present series occurred despite the exclusion of any previously treated patients, which suggests that inclusion of previously treated patients cannot have been the prime factor accounting for the relatively low prevalence of left ventricular mass abnormality in earlier reports.\(^5\) However, the prevalence of high wall thickness or WT/R ratio was higher than in other studies that have included previously treated patients.\(^5,7\) This difference may reflect an effect of treatment in the early stages that is apparent on examination of wall thickness, but not left ventricular mass.

The Penn convention\(^{21}\) per se for the measurement of left ventricular wall thickness was not used in the present study as a number of hypertensive subjects would have been excluded because of difficulties in distinguishing endocardial echoes. Whether the Penn convention or the present method is used, the estimates of prevalence would not be affected. Our data relates well to previous studies that have used the Penn convention,\(^{21,31}\) given the difference in techniques. However, as our method resulted in slightly higher average LVMI values in normal subjects in our series, we also estimated LVMI-'Penn'\(^{25}\) (Table 3) as described by Devereux et al.\(^{24}\) Although applying this correction\(^{24}\) to the measurements in dogs in our validation experiments does result in a slightly better estimate of anatomic mass, the differences were not significant.

The results of the present study also suggest that early in mild hypertension wall thickness increases, but LVID slightly decreases\(^{33}\) and leads to a relatively small increase in left ventricular mass as calculated by Devereux and Reicheck\(^{2}\) and other D\(^3\) formulae.\(^{18,23,34,35}\) One problem in assessing the "true" prevalence of LVH in hypertensive patients is the relatively high variance in LVM* or LVMI in the normal population (Figure 1). The range of normal LVMI* values (Figure 1) appears greater than in inbred strains of experimental animals.\(^8,9\) The greater the variance in the normal population, the more likely it is that the "true" incidence of abnormality is underestimated if abnormal variables are required to be more than 2 SD above the mean of the normal group. Hence, WT* and WT/R ratio, where the normal variance is smaller, may be preferable to LVM* or LVMI as measures of LVH when hypertension is relatively mild.\(^36\) Particularly as WT/R ratio was independent of sex in the present as well as previous studies.\(^31\) One reason why a higher proportion of abnormalities in mild hypertension was detected by the multivariate analysis may be because it examines the overall anatomic pattern. The use of this technique provides a more subtle means of assessing the prevalence of LVH than univariate analysis.

When we used WT* and LVID* as anatomic predictor variables, 70% of normal subjects and a similar proportion of those with established hypertension were classified correctly. The relatively low value of the Wilks \(\lambda\) (Table 4) is consistent with the decrease in the intragroup variance and suggests that the multivariate analysis technique allows better discrimination between normal subjects and patients with established hypertension than the univariate analysis. We conclude that in patients with established hypertension the prevalence of LVH is higher than reported from the differences when using LVM* or LVMI alone. However, our results indicate that, purely on these anatomic criteria, the prevalence of LVH in patients with mild hypertension is low.\(^4,2\)

For the functional variables we used E/A transmitral diastolic flow velocity ratio and fractional systolic shortening. In chronic hypertension a decrease in the E/A* ratio probably denotes, for the most part, abnormal left ventricular diastolic function.\(^{14,16,37,39}\) As a single variable there was a lower incidence of left ventricular abnormality in mild or established hypertension (Figures 4 and 5) than with structural variables such as WT* or WT/R ratio, but the incidence was closely similar to that of LVM* (Figure 1). With fractional systolic shortening, the intergroup differences were minimal. Patients with the highest fractional systolic shortening fell into the mild hypertensive group, with the average value significantly higher than that of the normal subjects. This is in keeping with the previously described hypercontractile state in early human
and experimental hypertension.40-45 Despite the modest degree of "supernormal" systolic function in mild hypertension, E/A* ratio was reduced on average even in the group with mild hypertension, which is consistent with the findings of previous studies where parameters of diastolic function have been examined.14,33,36,39,46

Again, the multivariate analysis improved the intergroup classification. However, its discriminant capacity was well below that obtained with the structural variables, and it did not help in the classification of patients with mild hypertension.

The best overall classification was obtained by using a combination of the structural and functional predictor variables. This produced some improvement in correct classification of normal subjects and had very little effect on the classification of patients with established hypertension. However, by the use of both structural and functional variables we correctly classified more patients with mild hypertension. This suggests that the patients diagnosed as having mild hypertension are a heterogeneous group, and it will be important to determine whether chronic hypertension develops49 in the 74% classified by the discriminant analysis into a hypertensive group. Although the results on cardiac structure from our univariate analysis and multivariate analysis suggest a prevalence of 65-70% of LVH in untreated established hypertension, this is probably the minimum estimate of "true" prevalence as the hypertension in patients in this study was only moderate (Table 1). As a corollary there was no evidence of ventricular dilatation or impairment of systolic function, which have been reported in more severe hypertension48 (Table 3).

Some previous studies have shown a significant frequency of asymmetric septal hypertrophy, especially in borderline hypertensive patients.3,32 By contrast, we found this type of hypertrophy in only one of our mildly hypertensive patients, and the high frequency in earlier studies may have been due to the inclusion of previously treated patients,3 inclusion of the right ventricular tricuspid valve apparatus in the septal thickness measurement, or improper beam angulation that would lead to a false positive diagnosis of asymmetric septal hypertrophy,49 particularly in M-mode studies. Most two-dimensional and M-mode studies assume that wall thickness is uniform around the left ventricle and that hypertrophy develops uniformly in hypertension. This premise has been questioned by Salcedo et al,48 who found that early development of LVH in dogs with hypertension was neither concentric nor symmetric, and estimates of septal thickness and posterior left ventricular wall thickness alone could potentially underestimate wall thickness and left ventricular mass. We assessed wall thickness from five different wall thickness segments to minimize errors due to nonuniformity. Our method differed slightly from that of Salcedo et al48 as short axis measurements were at the mitral chordae level and not leaflet and papillary muscle level.18 Our method did not assume that the left ventricular long axis is twice the minor axis as this assumption is probably only valid in a "normal" size heart22 and not when the geometry is altered in hypertension.30 Our left ventricular mass measurements, which were a modified combination of two previous methods,18,21 produced satisfactory estimates of left ventricular mass in both normal dogs and those with LVH in the validation experiment.

In agreement with previous studies, we have found, when using univariate analysis, that about 30% of patients with established primary hypertension have a high LVMI. This finding indicates that previous antihypertensive treatment alone cannot account for this low prevalence. Our results suggest that left ventricular mass is not as good an indicator of cardiac structural change in hypertension as the WT/R ratio. With the latter variable, which has a lower variance in the normal group, the prevalence of structural abnormality was 60%, which was higher than in previous studies that included treated patients. With multivariate discriminant function analysis the minimum prevalence of left ventricular abnormalities in untreated established hypertension was 65-70%, which is consistent with the suggestion that most patients had evidence of LVH or abnormal diastolic function. About 60% of patients with borderline hypertension have an abnormality that is distinct both from normal and established hypertensive subjects.

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