Determinants of Cardiac Involvement in Children and Adolescents With Essential Hypertension

Stephen D. Daniels, MD, PhD, Richard A. Meyer, MD, and Jennifer M.H. Loggie, MD

Left ventricular hypertrophy is often found in association with systemic hypertension and may be an independent risk factor for cardiovascular disease morbidity and mortality. Few studies have investigated the determinants of left ventricular mass (LVM) in young patients with essential hypertension. Therefore, we studied 104 children and adolescents with blood pressure persistently greater than the 90th percentile for age and sex and with no known cause of blood pressure elevation. LVM was determined by echocardiography and was indexed by height to account for body size. The mean LVM index was 90.2 ± 26.0 g/m. Using the gender-specific 95th percentile from normal children, 40 subjects (38.5%) had left ventricular hypertrophy. Using multiple regression analysis, the significant independent direct correlates of LVM index were male sex, body mass index, dietary sodium intake, age at diagnosis, and systolic blood pressure at maximum exercise. The significant independent inverse correlate of LVM index was resting heart rate (p < 0.05). These variables accounted for a substantial portion of the LVM index variance in this population (multiple R² = 0.56, p < 0.001). The results indicate that left ventricular hypertrophy is prevalent in children and adolescents with essential hypertension. The direct association of LVM index with body mass index and dietary sodium intake suggests weight reduction and dietary salt restriction might be useful to prevent or treat the development of left ventricular hypertrophy in pediatric patients with essential hypertension. (Circulation 1990;82:1243–1248)

Systemic hypertension is one of the leading causes of morbidity and mortality among adults in the United States. The Framingham Study has shown that hypertension precedes clinically significant heart failure in 75% of cases, and that there is a direct relation between the level of blood pressure and the incidence of congestive heart failure. Furthermore, adults with hypertension and evidence of left ventricular hypertrophy had a 10-fold greater risk of developing congestive heart failure than did hypertensive adults without hypertrophy. Recent research has indicated left ventricular hypertrophy may be an independent risk factor for cardiovascular morbidity and mortality.

Human and animal studies have demonstrated that left ventricular hypertrophy, even when provoked by hypertension, is not solely dependent on the level of blood pressure or the duration of blood pressure elevation. This has led to studies of the LVM correlates in an attempt to characterize the subset of hypertensive patients who are prone to develop left ventricular hypertrophy and to identify potential mechanisms of cardiac hypertrophy. However, few studies have been conducted in young patients with essential hypertension, and little is known about the early pathophysiological processes that lead to overt end-organ pathology.

Therefore, the present study was designed to first determine the prevalence of left ventricular hypertrophy in a population of children and adolescents with essential hypertension and second to identify independent correlates of LVM index in this population.

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Methods

Study Population and Protocol

Children and adolescents with essential hypertension followed in the Hypertension Clinic of the

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Children's Hospital Medical Center were invited to participate in this study. All had systolic and/or diastolic blood pressure greater than the 90th percentile for age and gender on at least three occasions over a 3-month period or longer. None of the subjects had a known secondary cause of blood pressure elevation as determined by routine clinical and laboratory examinations. Of the 123 subjects asked to participate, 104 agreed (84%) and were included in the study after written informed consent was obtained. Subjects were admitted to the Clinical Research Center for a 36-hour period.

**Echocardiography**

LVM was calculated from M-mode echocardiographic measurements of the left ventricle. M-mode echocardiograms were performed using standard techniques previously described. Measurements were made according to the American Society of Echocardiographic Convention using leading-edge to leading-edge methodology. All echocardiographic measurements were made during the expiratory phase of respiration. Each measurement was made three times, and the average of those measurements was used to calculate LVM. This was done using the formula of Devereux et al:

\[
LVM (g) = 0.80 \times 1.04 \times \left[(\text{interventricular septum} + \text{left ventricular internal dimension} + \text{posterior wall thickness})^3 - (\text{left ventricular internal dimension})^3\right] + 0.06
\]

This equation has been anatomically validated for children with normal hearts. LVM was divided by height to index for body size as suggested by Levy et al.

**Independent Variables**

Nine categories of potential left ventricular hypertrophy correlates were studied: demography, body size, blood pressure and heart rate, family history of cardiovascular disease, treatment with antihypertensive medication, sodium intake and use of tobacco and alcohol, laboratory tests, cardiovascular reactivity to playing a video game under challenging conditions, and cardiovascular reactivity to maximal exercise.

The demographic variables included age, race, sex, and socioeconomic status measured by family income and parental education. Body size variables included height, weight, body surface area, and body mass index. The mean systolic and diastolic blood pressures during follow-up in the Hypertension Clinic, as well as the age at diagnosis of hypertension and the known duration of hypertension, were obtained from clinic records. Heart rate and blood pressure were measured according to the guidelines presented by the National Heart, Lung, and Blood Institute Task Force on Blood Pressure Control in Children.

Families were questioned about hypertension, dyslipoproteinemia, or early (before age 65) cardiovascular morbidity or mortality in first-degree relatives of the subject (parents, grandparents, or siblings). Subjects were characterized with respect to treatment with antihypertensive medication, the number and type of medications used, and the duration of treatment. They were also questioned without the parents present about smoking tobacco and drinking alcohol. Dietary sodium intake was estimated in two ways. First, sodium excretion in the urine over a 24-hour period was taken as an index of dietary salt intake. Urine collections were obtained in the Clinical Research Center. Samples from four subjects were excluded because of inadequate collections indicated by urinary creatinine excretion greater than 30 or less than 8 mg/kg/day. Second, subjects were allowed to select their diet while in the Clinical Research Center. The type and amount of foods consumed were observed by a trained dietician, and the intake of sodium over a 24-hour period was calculated from the known sodium composition of each food. The amount of table salt added to the food was also measured.

Venipuncture was performed after 8–10 hours in the supine position before arising after awakening and after a 12-hour fast. A second blood sample was then obtained after the subject had been ambulating for 15 minutes.

Several laboratory analyses were performed on these blood samples, including fasting plasma glucose, hemoglobin (a measure of blood viscosity), plasma renin activity, plasma aldosterone, plasma catecholamines, and a lipid profile.

Basal plasma renin activity and plasma aldosterone were measured by radioimmunoassay in the endocrinology laboratory of the University of Cincinnati Hospital. Plasma catecholamine concentrations (dopamine, epinephrine, and norepinephrine) were measured in both the basal and ambulatory conditions. The assay was performed by high-pressure liquid chromatography using electrochemical detection at the Smith Kline Clinical Laboratories (St. Louis).

Measurements of a full lipid profile (total cholesterol, high density lipoprotein [HDL] cholesterol, and triglycerides) were conducted in a laboratory standardized by the Centers for Disease Control (CDC). Low density lipoprotein (LDL) cholesterol was then calculated from those measurements.

A video game (PAC-Man) with an adjustable skill level was used to measure cardiovascular reactivity to a task requiring sustained concentration under challenging conditions. Previous studies have demonstrated this stressor elicits cardiovascular changes comparable to those observed during mental arithmetic. Testing was performed in the Clinical Research Center. The instructions emphasized this was a measure of hand-eye coordination and skill and the subject was to attempt to achieve the highest possible score. Baseline blood pressure and heart rate were measured at 2-minute intervals for 10 minutes before playing the game with the subject sitting quietly. Measurements were then taken at
1-minute intervals for 5 minutes while playing the game. The mean systolic and diastolic blood pressures, pulse pressure, and heart rate during mental stress, as well as the mean change in blood pressure and heart rate from rest to playing the video game, were used in the analysis.

A graded bicycle ergometer exercise protocol in which subjects perform at 50%, 75%, and 100% of predicted maximal workload was used in the investigation. During the test, the subject’s blood pressure, heart rate, and cardiac output were measured at rest and at 50%, 75%, and 100% of predicted maximal workload. The predicted maximal workload was calculated from a regression equation based on age, sex, and body size previously derived in this laboratory from studies of exercise in normal children. If the subject was able to perform at greater than 100% of the predicted workload, additional measurements were taken at increasing workloads until exhaustion. The amount of exercise performed by each subject was recorded. During the 15-minute postexercise recovery period, measurements of heart rate and blood pressure were also made. The working capacity as well as heart rate, blood pressure, and cardiac output were measured as described previously. Peripheral vascular resistance was calculated from the above variables. Values for heart rate, systolic blood pressure, diastolic blood pressure, cardiac output, and peripheral vascular resistance at maximal exercise, as well as the change in these parameters from rest to maximal exercise and the amount of exercise performed, were used as independent variables in the analysis.

Statistics

All values are given as mean ± SD. The prevalence of left ventricular hypertrophy was calculated using the 90th and 95th percentile of LVM index for normal children as cutoff points. Ninety-five percent confidence intervals for the prevalence were calculated using a test-based calculation.

The correlations between the LVM index and the individual independent variables were determined using the Pearson correlation coefficient. Multiple linear regression was used to examine the relation between the independent variables and the dependent variable to determine which variables were significant independent determinants of LVM index. An all-possible-regressions multiple regression procedure was used. The regression model selected as the ‘best’ model was the one that produced the highest multiple $R^2$ and also contained only independent variables with regression coefficients that statistically were significantly different from zero. An all-possible-regressions analysis considers all combinations of independent variables and their ability to explain the variance of the dependent variable. This involves both a qualitative and statistical evaluation of the multiple correlation coefficient ($R^2$). The increase in $R^2$ for the addition of an independent variable to a regression model was evaluated compared with the regression model without that variable. An incremental increase in $R^2$ of 10% was considered to be important. A statistical test that the $R^2$ was significantly different from zero was also performed for models that were judged to be candidates for the “best” regression model for explaining the variance of LVM index. For candidate models, $t$ tests for each of the regression coefficients were performed to test the null hypothesis that the regression coefficients were significantly different from zero. Only models in which all of the regression coefficients were significantly different from zero were considered. A probability value of less than 0.05 was used to indicate statistical significance.

Results

Eighty of the 104 subjects were boys, and 54 were white. The mean age of the subjects was 14.9 ± 3.5 years. Thirty-two subjects were on antihypertensive medication at the time of the study. Seventeen subjects (16%) reported use of alcohol, and eight (8%) reported cigarette smoking. Descriptive statistics for the study population are presented in Table 1.

The mean LVM index was 90.2 ± 26.0 g/m. The range was 33.8–162.6 g/m. The prevalence of left ventricular hypertrophy was determined using sex-specific percentiles derived from a study of normal children. Using the 90th percentile as a cutoff (91.0 g/m for boys, 76.7 g/m for girls), the prevalence of left ventricular hypertrophy was 51% (95% confidence interval [CI], 41–61%). Using the 95th percentile (99.8 g/m for boys, 81.0 g/m for girls), the prevalence was 38.5% (95% CI, 19–48%). The prevalence of left ventricular hypertrophy by race and sex is presented in Table 2. There was no statistically significant differences in the prevalence of left ventricular hypertrophy by race or sex by χ² analysis.

The correlates of LVM index are presented in Table 3. The strongest direct correlate of LVM index was the systolic blood pressure at maximum exercise ($r = 0.59$). The strongest inverse correlate was resting heart rate ($r = -0.47$). Race, family history, duration of hypertension, treatment with antihypertensive medi-
TABLE 3. Significant Univariable Correlates of Left Ventricular Mass Index

<table>
<thead>
<tr>
<th>Variable</th>
<th>Correlation Coefficient</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.38</td>
<td>&lt;0.011</td>
</tr>
<tr>
<td>Sex</td>
<td>0.37</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SES (maternal education)</td>
<td>-0.20</td>
<td>&lt;0.050</td>
</tr>
<tr>
<td>Body size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td>0.47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight</td>
<td>0.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean SBP-during course in Hypertension Clinic</td>
<td>0.29</td>
<td>&lt;0.010</td>
</tr>
<tr>
<td>Age of diagnosis of hypertension</td>
<td>0.32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resting heart rate at time of study</td>
<td>-0.47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family history*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet and Lifestyle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium intake</td>
<td>0.39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24-hour urinary sodium excretion</td>
<td>0.26</td>
<td>&lt;0.050</td>
</tr>
<tr>
<td>Laboratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>0.32</td>
<td>&lt;0.010</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>-0.26</td>
<td>&lt;0.010</td>
</tr>
<tr>
<td>Cardiovascular reaction to mental stress</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP during stress</td>
<td>0.33</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulse pressure during stress</td>
<td>0.28</td>
<td>&lt;0.010</td>
</tr>
<tr>
<td>Heart rate during stress</td>
<td>-0.43</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular reaction to exercise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP at maximum exercise</td>
<td>0.59</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiac output at maximum exercise</td>
<td>0.47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral vascular resistance at maximum exercise</td>
<td>-0.29</td>
<td>&lt;0.020</td>
</tr>
<tr>
<td>Change in SBP from rest to exercise</td>
<td>0.31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in cardiac output from rest to exercise</td>
<td>0.42</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Exercise performed</td>
<td>0.46</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

SES, socioeconomic status; SBP, systolic blood pressure; HDL, high density lipoprotein.

*None of the family history or treatment variables were associated with left ventricular mass index.

The summary of the multiple regression analysis for LVM index is presented in Tables 4 and 5. Two regression models were found to have similar capacity to explain the variance of LVM index. The models are the same, except age at diagnosis is included in the first model (Table 4) and systolic blood pressure at maximum exercise is substituted for age at diagnosis in the second model (Table 5). The regression coefficient for systolic blood pressure at maximum exercise is of borderline significance (p=0.07) in this model. Sex, body mass index, resting heart rate, and dietary sodium intake are significant independent determinants of LVM index in both of the models. In this analysis, a positive regression coefficient denotes a direct association between the independent variable and LVM index, whereas a negative regression coefficient indicates an inverse relationship between the two. The multiple R² for both of these regression models is approximately 0.55; this means the regression equation including those variables accounts for approximately 55% of LVM index variance. The fact that the regression coefficients are significantly different from zero indicates the variables make a significant, independent contribution to the explanation of the variance of the dependent variable (LVM index). The variance inflation factors associated with the independent variables ranged from 1.0 to 2.1. This means it is unlikely that multicollinearity presents a problem in this analysis.

TABLE 5. Alternate Multiple Regression Model for Left Ventricular Mass Index

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>SE</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>47.254</td>
<td>25.631</td>
<td>&lt;0.07</td>
</tr>
<tr>
<td>Sex (boys, 1; girls, 0)</td>
<td>13.591</td>
<td>5.064</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Body mass index (wt/ht²)</td>
<td>1.162</td>
<td>0.380</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Resting heart rate (beats/min)</td>
<td>-0.525</td>
<td>0.155</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sodium intake (mg/24 hr)</td>
<td>0.004</td>
<td>0.002</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Systolic blood pressure at maximum exercise (mm Hg)</td>
<td>0.175</td>
<td>0.095</td>
<td>&lt;0.07</td>
</tr>
</tbody>
</table>

Multiple R²=0.54.
Discussion

The range of LVM index was broad. Compared with normals, the range was from approximately the 10th percentile to greater than the 99th percentile. This is not unexpected given the heterogeneous nature of essential hypertension. The prevalence of left ventricular hypertrophy in this study was 38.5%. In studies of adults with essential hypertension, the prevalence of hypertrophy measured by echocardiography has ranged from 23–48%.17 When the results from several studies were combined, 42% of 450 hypertensive adult patients and 3.6% of 251 controls exhibited left ventricular hypertrophy.18 In echocardiographic studies of children, Laird and Fixler found 16% of children with elevated blood pressure had left ventricular hypertrophy. Culpepper et al reported 11% of subjects with borderline blood pressure had indexed LVM more than 2 SDs above predicted normals.19 The differences in prevalence may be explained by a number of factors including patient selection and the cutoff points for LVM used to define hypertrophy. Neither of the pediatric studies included subjects with moderate or more severe essential hypertension. Most of the subjects in the study of Culpepper et al had top normal blood pressure.19

In the present study, the estimates of LVM were indexed by height, and sex-specific criteria for left ventricular hypertrophy were applied to account for the effects of body size and sex on LVM. None of the previously published studies of LVM in children with hypertension has used sex-specific criteria as were used in the present investigation.

In this study, LVM index was significantly correlated with average systolic blood pressure in the univariable analysis. However, this relation did not persist after inclusion of other significant variables in the multiple regression model. In the Bogalusa Heart Study,20 systolic blood pressure was associated with left ventricular wall thickness, but not LVM. One aspect of the present study and some previous studies of adult subjects is that only hypertensive subjects were included; thus, the range of blood pressure is restricted. Restricting the range of an independent variable in this fashion may bias the results toward no association, making it more difficult to detect an association between level of blood pressure and LVM. Nevertheless, because of this restriction of subjects to those with elevated blood pressure, an element of blood pressure level underlies the remaining analysis.

Blood viscosity and neurohumoral factors have been associated with LVM in previous studies.21,22 In the present study, hemoglobin concentration was directly associated with LVM in the univariable analysis. However, this relation did not persist in the multivariable analysis. Neither plasma catecholamine concentrations nor basal plasma renin activity were associated with LVM index.

The results of the multivariable analysis for LVM index can be compared with previously reported results. In the present study, sex, but not race, was associated with LVM index. This is similar to the previous findings of Daniels et al.23 in normal children as well as results from the population-based Bogalusa Heart Study.20 The independent association of body mass index with LVM index is similar to the findings of Hammond et al who found body mass index to be an important determinant of left ventricular muscle mass in hypertensive employed adults.23 These findings also confirm the results of MacMahon et al who demonstrated a reduction in LVM after weight loss in young obese hypertensive subjects. The results of the present study would suggest that obesity may have an independent adverse effect on the left ventricle in children and adolescents with essential hypertension.

The finding of a direct relation between sodium intake and LVM index is similar to that of previous studies in both laboratory animals and adult human subjects. Lindpaintner and Sen25 have shown sodium intake is directly associated with LVM in rats. Schmieder et al26 found dietary sodium intake assessed by urinary sodium excretion over 24 hours was a powerful determinant of posterior wall thickness and LVM. Ferrara et al27 found sodium restriction resulted in decreased LVM in men with essential hypertension.

Cardiovascular responses to both mental stress and physical exercise were associated with LVM index in this study. The response of systolic blood pressure to maximum exercise was the strongest univariable correlate of LVM index and was an independent determinant in the alternate multiple regression model. These results are similar to those of Papademetriou et al who found systolic blood pressure at 3 minutes of exercise was correlated (r=0.48) with LVM in adults with hypertension.28

The age at diagnosis was used as a measure of the onset of hypertension. However, it is difficult to know the precise onset of hypertension in these subjects. It is possible that those who were diagnosed later in childhood had a longer duration of hypertension than was known because their blood pressure elevation remained undetected due to a paucity of blood pressure measurements before diagnosis. The observed association between the age at diagnosis of hypertension and LVM index is the opposite of what was hypothesized. It was expected that a younger age at diagnosis and a longer duration of hypertension would be associated with increased LVM index. The observed relation of an older age at the time of diagnosis with increased LVM index and the finding of no association between duration of hypertension and LVM index remain unexplained.

LVM index was inversely related to resting heart rate in the multivariable analysis. This relation also remains unexplained. It is possible that rate resting heart rate may be a marker of physical fitness. This would mean that increased fitness (lower heart rate)
was associated with increased LVM index. This is consistent with previous studies of LVM index in athletes.\(^{29}\) The amount of exercise performed (another measure of fitness) was a significant correlate of LVM index in the univariable, but not in the multivariable analysis.

We conclude that left ventricular hypertrophy is prevalent in US children and adolescents with essential hypertension. The identification of independent correlates of LVM index may provide the basis for future clinical strategies to manage pediatric patients with essential hypertension. The independent effects of sodium intake and body mass index suggest that restriction of dietary intake of sodium and programs to reduce obesity may provide important nonpharmacological means for preventing and/or treating development of left ventricular hypertrophy.

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