Sex Differences in the Determinants of Left Ventricular Mass in Childhood

The Medical College of Virginia Twin Study

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Background. Left ventricular (LV) hypertrophy is a predictor of cardiovascular events in adults and has been observed in children and adolescents with hypertension. We wanted to establish the determinants of LV mass in normotensive preadolescent children. Our objectives were 1) to produce a simplified and generalizable model of the clinical variables that determine normal cardiac growth during childhood and 2) to understand better why males have an increased LV mass relative to females, even as children.

Methods and Results. In a group of 243 eleven-year-old children, we analyzed anthropometric, hemodynamic, and echocardiographic data to define which variables were predictors of echocardiographically determined LV mass. Stepwise regression was used to predict LV mass overall, by sex, and by body size (body mass index). Overall, LV mass was directly related to weight, male sex, and systolic and diastolic blood pressure and inversely related to resting heart rate and skin-fold thicknesses. Systolic blood pressure was a determinant in boys but not in girls. Heart rate was a weak inverse correlate in both sexes. When the data were analyzed by body mass index quartile, weight was the sole predictor of LV mass in the largest children.

Conclusions. We conclude that in normotensive preadolescent children, 1) weight, but not ponderosity, is a strong predictor of LV mass; 2) body fat is negatively associated with LV mass; 3) boys have an increased LV mass relative to girls; and 4) boys and girls have similar anthropometric determinants and may have different hemodynamic determinants. Our data suggest that body size, and in particular lean body mass, explains much of the variability in cardiac growth seen in children. The influence of hemodynamic variables seems to be more limited. Our findings are of general interest because, although hypertensive heart disease is well described, the early developmental stages are not well understood.

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KEY WORDS • hypertension • weight • mass, body • mass, left ventricular

Recent studies have shown that left ventricular (LV) hypertrophy is an even stronger predictor of cardiovascular events in adults than systolic or diastolic blood pressure.1,2 This relation persists even after adjustments are made for blood pressure, obesity, sex, and other cardiovascular risk factors.3 Across all age groups, LV mass varies with body surface area and increases as a function of age.4,5 Although many investigators have studied LV mass in children, most have studied a cross section of children of all ages. Some investigators have studied more specific groups: Daniels et al6 recently demonstrated that LV hypertrophy is prevalent in children and adolescents with essential hypertension. Radice et al7 showed that normotensive adolescent offspring of hypertensive parents also have a significantly increased LV mass compared with controls. Schicken et al8 showed that in school-age children, LV mass, corrected for body size, is significantly greater in children in the upper blood pressure quintile than for children in the lower blood pressure quintiles.

We chose to study a group of normotensive 11-year-old children to establish the determinants of LV mass in normotensive preadolescent children. Our main objective was to produce a simplified and generalizable model of the clinical variables that determine normal cardiac growth during childhood. A secondary objective was to ascertain whether preadolescent girls have a smaller LV mass than boys, as has been reported for most other study populations, and whether variations in the determinants of LV mass underlie this sex difference. We hypothesized that even in such a homogeneous group, weight would be the strongest predictor of LV mass.

Methods

Study Population

Two hundred forty-three 11-year-old children participating in the Medical College of Virginia Twin Study...
were enrolled in the current study. Specifically, a random twin was selected from each twin pair. Subjects were examined as close as possible to their 11th birthday, and all were healthy by history and physical examination. Parents were asked about the family medical history, including the incidence of heart disease. A positive family history was defined as hypertension or cardiovascular death in a parent or in a first-degree relative of the parent or heart disease in either parent. Parents were asked to state how many times per week their child exercised "long enough to sweat."

**Anthropometry**

Height, weight, and Tanner stage\(^9\) were recorded. Tanner stage of sexual development is based on a scale ranging from 1 to 5, where stage 1 is prepubertal and stage 5 represents adult status. Skin-fold thicknesses of triceps, biceps, subcapular, and suprailiac areas were measured by the technique of Tanner with Holtain skin-fold calipers designed to exert a constant pressure of 10 g/mm\(^2\) over a range of 0–48 mm. All anthropometric data were obtained in duplicate and averaged. Body mass index was defined as weight divided by height squared (wt/ht\(^2\)). Ponderosity index was defined as weight divided by height cubed (wt/ht\(^3\)).

**Hemodynamics**

Blood pressure was measured in the sitting position using a mercury sphygmomanometer with the appropriate size compression cuff. The fourth Korotkoff phase was used as the diastolic blood pressure. The mean of two measurements was used for blood pressure. Heart rate was measured with a cardiotachometer.

**Echocardiography**

M-mode echocardiograms of the left atrium and LV were performed with the subject in the supine position. Left atrial diameter was measured by M mode from the parasternal long-axis view. LV dimensions were measured with a digitizing tablet by standard criteria.\(^10\) Values were measured for three cycles and averaged. Test–retest reliability of subjects and of measured dimensions disclosed an intraclass correlation of 0.92. LV mass (g) was calculated by the Penn convention:\(^11\)

\[
{\text{LV mass}} = 1.04 \left( {\text{LVEDD} + \text{IVS} + \text{PWT}^3} \right) - \text{LVEDD}^3 - 13.6
\]

where LVEDD is the LV end-diastolic dimension, IVS is the interventricular septal dimension, and PWT is the LV posterior wall thickness. This equation has been anatomically validated.\(^11\) LV wall stress was determined by the method of Grossman et al, as recommended by Reichek.\(^12\)

**Exercise Testing**

Dynamic exercise testing was performed with a bicycle ergometer calibrated to indicate the workload in kilogram-meters per minute. Children cycled at 60–80 rpm, beginning at a work load of 150 kg-m/min (stage 1) and increasing every minute by 100 kg-m/min (to the next stage). Heart rate was measured at each stage with a cardiotachometer, and blood pressure was measured with a Critikon monitor. Each child was encouraged to exercise to maximal exercise tolerance.

### Table 1. Demographic Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Boys</th>
<th>Girls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>243</td>
<td>124</td>
<td>119</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>11.2±0.01</td>
<td>11.2±0.02</td>
<td>11.2±0.02</td>
</tr>
<tr>
<td>Tanner stage</td>
<td>2.0±0.10</td>
<td>1.8±0.06</td>
<td>2.2±0.09*</td>
</tr>
<tr>
<td>Exercise ×/wk</td>
<td>4.1±0.20</td>
<td>4.3±0.24</td>
<td>3.8±0.30</td>
</tr>
<tr>
<td>Positive FH</td>
<td>0.56±0.03</td>
<td>0.57±0.04</td>
<td>0.55±0.05</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

Tanner stage of sexual development ranges from stages 1 through 5 (stage 1 is prepubertal and stage 5 represents adult status); Exercise ×/wk, number of times per week subjects exercised enough to "work up a sweat"; Positive FH, positive family history of heart disease or hypertension (0, none; 1, positive).

\(*p<0.05, \text{boys vs. girls.}"

**Statistical Analysis**

Statistical analysis consisted of stepwise regression of the possible determinants of LV mass. The variables entered into the equation included the variables shown in Tables 1 and 2 and the resting hemodynamic variables shown in Table 3. Skin-fold thicknesses (sum and individual), wall stress, left atrial diameter, and shortening fraction were also included. A preliminary analysis showed that exercise hemodynamic variables were no more important than resting variables, and exercise variables were therefore eliminated from the analysis. A variable was added to the model if its associated F statistic was ≤0.15. Once a new variable was added to the model, only those variables with an F statistic of ≤0.05 were retained. Mean square estimates for these variables were used to calculate their relative contributions to the variance of LV mass. Pooled t tests were used to test for differences in variables between boys and girls. Predictor models of LV mass were constructed by stepwise linear regression for the whole sample and by sex. Models were similarly constructed for the lowest weight quartile, for the middle two quartiles, and for the highest weight quartile.

**Results**

The demographic characteristics of the children enrolled in this study are shown in Table 1. The children ranged in age from 10.9 to 11.9 years. The girls were slightly more sexually developed than the boys (mean Tanner stage 2.2 versus 1.8). There were no significant differences by sex in any of the indexes of body size (Table 2). There were, however, significant sex differences in skin-fold thicknesses, a measure of body fat, with girls having greater biceps, triceps, subcapular, and total skin-fold thicknesses (Figure 1).

### Table 2. Anthropometric Variables

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Boys</th>
<th>Girls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>36.9±0.5</td>
<td>36.7±0.74</td>
<td>37.1±0.7</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>145.31±0.39</td>
<td>144.50±0.57</td>
<td>145.52±0.64</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.22±0.01</td>
<td>1.22±0.01</td>
<td>1.23±0.01</td>
</tr>
<tr>
<td>BMI (wt/ht²)</td>
<td>17.41±0.16</td>
<td>17.45±0.22</td>
<td>17.37±0.24</td>
</tr>
<tr>
<td>Pond (wt/ht³)</td>
<td>12.0±0.10</td>
<td>12.07±0.14</td>
<td>11.92±0.15</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

BSA, body surface area; BMI, body mass index; Pond, ponderosity index.
The hemodynamic variables of the subjects are shown in Table 3. The average resting heart rate was lower in the boys. There was no sex difference in resting blood pressure. The boys significantly outdistanced the girls during exercise testing. Similarly, the submaximal heart rate (measured at 350 kg-m/min) was significantly lower in the boys.

Echocardiographic measurements are shown in Table 4. The LV mass and LV mass indexed for body surface area were significantly different between boys and girls, averaging almost 9 g greater for boys than for girls. Each of the variables used in the equation to calculate LV mass was significantly larger in the boys except for septal thickness. There were no significant differences between boys and girls in shortening fraction, wall stress, left atrial diameter, or relative wall thickness.

The determinants of LV mass in our population, by stepwise multiple regression, explained 49% of the variance among individuals overall. The determinants, in order of significance, were weight, suprailiac skin-fold thickness, sex, heart rate, systolic blood pressure, and diastolic blood pressure (Figure 2). None of the exercise variables were better predictors of LV mass than were the resting parameters.

The determinants of LV mass were different for boys and girls (Figure 2). For boys, the determinants explained 41% of the total variance and included weight, suprailiac skin-fold thickness, systolic blood pressure, and heart rate. In girls, 48% of the variance was explained by weight, suprailiac skin-fold thickness, and heart rate; blood pressure was not a determinant. Of note, suprailiac skin-fold thickness and heart rate were negatively correlated with LV mass in all groups. The variables that did not contribute to the variance in LV mass beyond those in our models included height, family history, Tanner stage, body mass index, ponderosity index, wall stress, left atrial diameter, and shortening fraction.

To examine whether the determinants of LV mass differed in thin children compared with heavier children, subjects were grouped by body mass index quartile: Group 1 comprised subjects in the lowest quartile, group 2 the 25th–75th percentile, and group 3 the highest quartile (Table 5). The ratio of boys to girls was similar in each group. LV mass increased across the groups, but when indexed by body surface area there were no longer any differences. Weight became a more significant predictor in children with the largest body mass index; in group 3 it was the sole predictor. Significant hemodynamic predictors included heart rate (inversely correlated) in group 2 and systolic blood pressure in group 1. LV mass was highly dependent on weight in all three groups but was not otherwise related to markers of obesity. In all groups, skin-fold thicknesses were inversely associated with LV mass, although in group 3 this was not statistically significant ($p=0.06$). This suggests that in thinner children, lean body mass (represented by the inverse of suprailiac skin-fold thickness) is a more important determinant of LV mass than it is for heavier children.

**Discussion**

In the present study of LV mass in 243 eleven-year-old children, we found that 1) weight, but not ponderosity...
ity, is a strong predictor; 2) body fat is negatively associated with LV mass; 3) boys have an increased LV mass relative to girls; and 4) boys and girls have similar anthropometric determinants and may have different hemodynamic determinants.

Our findings are of general interest because although hypertensive heart disease is well described, the early developmental stages are not well understood. In adults and in children, body size and obesity may confound the classification of normal versus abnormal LV mass, making it difficult to know the independent effect of variables such as blood pressure on LV mass. By studying a group of preadolescent normotensive children with a body size distribution similar to that of the general population of 11-year-olds, we minimized the potential confounding effects of puberty and body size.

Anthropometric and Hemodynamic Variables

In our study, the following variables explained 49% of the variation in LV mass: weight, suprailiac skin-fold thickness, sex, heart rate, and systolic and diastolic blood pressure. Suprailiac skin-fold thickness and heart rate were each inversely correlated with LV mass. The strong inverse relation between skin-fold thickness and LV mass (overall and by sex) has not previously been shown in children. LV mass was more dependent on the inverse of suprailiac skin-fold thickness in every analysis than on total or other individual skin-fold thicknesses. This suggests that in our study, suprailiac skin-fold thickness was the most useful indirect measure of total body fat. Boys had a lower resting heart rate and less total skin-fold thickness than girls and had a greater LV mass. Systolic blood pressure was a determinant in boys but not in girls. Weight was a stronger predictor in girls, and perhaps this variable, which is highly correlated with blood pressure, absorbed the effects of systolic blood pressure in girls.

The Bogalusa Heart Study of normotensive school-age children found that systolic blood pressure was associated with LV wall thickness but not with LV mass. In Daniels et al’s study of determinants of LV mass in a young hypertensive population (ages, 6–23 years), systolic blood pressure was correlated with LV mass (indexed by height) in univariate analyses only. As in our study of normotensive children, Daniels et al found that body size and male sex were strong predictors of LV mass and that resting heart rate was an independent inverse correlate. The authors suggested that systolic blood pressure may not have been a strong predictor because the blood pressure range of their subjects was restricted (hypertensives only). In our study of normotensive children, systolic blood pressure remains a weak predictor.

Genetic Influence

The association of LV mass and weight has a strong genetic component. Verhaaren et al demonstrated that genes common to LV mass and weight significantly influence the covariation of these variables, and more than 90% of the correlation of LV mass and weight is a result of genes common to weight and LV mass. In preadolescent children, skin-fold thickness variability is also strongly influenced by genes.

Sex Differences

Many investigators have found substantial sex differences in LV mass, with males having consistently larger LV dimensions beyond the effects of body size. We now believe that this finding is related to increased lean body mass in normotensive preadolescent boys. Skin-fold thicknesses have been shown to correlate highly with percentage of total body fat in children. In contrast to other measurements such as height and weight, females at all ages have greater skin-fold thickness at virtually every site than do males; by adulthood, men have 40% greater lean body mass than women. Because there were no weight differences between boys and girls in our population, the finding that the boys had significantly smaller skin-fold thicknesses than the girls suggests that their “fat-free” (i.e., muscle) mass was greater.

Devereux et al demonstrated in healthy adults that sex differences in LV mass are closely related to differ-
ences in lean body mass (estimated from 24-hour urine creatinine excretion) and that indexing of LV mass by lean body mass results in the elimination of sex differences. He suggested that an explanation for the sex difference of 15–20% in LV mass index (indexed by body surface area) is that lean body mass and maximal oxygen consumption are 15% lower in women than in men at any given level of body weight. Our findings in children are consistent with his. We suspect that other unmeasured variables also contribute to the sex difference observed in our population.

In our population, the boys appeared to be better conditioned than the girls, on the basis of lower resting and submaximal exercise heart rates. Heart rate was inversely associated with LV mass, suggesting that physical conditioning may alter LV mass even at this age. Rowland et al.21 showed that features of “athlete’s heart,” such as bradycardia and cardiomegaly, do occur in athletic prepubertal children. In the Framingham study,22 an association between level of physical activity and LV mass was observed in men but not in women. Furthermore, analyses of body mass index and subcuticular skin-fold thickness suggested that lean body mass was correlated with LV mass.

The regression coefficient for sex in the overall equation for LV mass was significantly different from zero, indicating that sex explains a portion of the variation in LV mass that is not explained by other measured variables. Unmeasured variables that might also contribute to this sex difference include differing genetic influences23 and adrenal androgen levels.24 Supporting a hormonal influence on LV mass is the finding that at menopause, the increase in LV mass related to age is accelerated in women.22

Conclusions

We found that in preadolescent children, LV mass is directly related to weight and male sex and inversely related to resting heart rate and body fat. Our data suggest that body size, and in particular lean body mass, explains much of the variability in cardiac growth seen in children. Hemodynamic variables contribute more to LV mass in thinner children and in boys; weight is a stronger predictor in bigger children and in girls. The reason for a greater LV mass in preadolescent boys is not well explained. It may relate to sex differences in genetic regulation, in physical conditioning, and/or in lean body mass. The potential roles of other hemodynamic variables, such as stroke volume and systemic vascular resistance, and of hormonal control on cardiac growth warrants further investigation.

Acknowledgments

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References

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