Normalization for Body Size and Population-Attributable Risk of Left Ventricular Hypertrophy

The Strong Heart Study

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**Background:** Left ventricular hypertrophy (LVH) is identified by left ventricular mass (LVM) normalized by body surface area (BSA) or height (in meters) also raised to allometric powers. The presence of LVH detected by these indices predicts increased cardiovascular (CV) events. Whether different indexations of LVH differ in their ability to predict excess risk is unknown.

**Methods:** A total of 2400 subjects, (1589 women and 811 men), 59 ± 8 years of age and without prevalent CV disease, valvular disease or wall motion abnormalities and high prevalence of obesity were followed for an average of 86 months. Reference values (mean ± 1.96 SD) for LVM/BSA, LVM/BSA\(^{1.5}\), LVM/m, LVM/m\(^{2.7}\), and LVM/m\(^{2.13}\) were obtained in 251 normal participants and population-attributable risk percent (PAR%) for fatal and nonfatal CV events were calculated from prevalence of LVH and hazard ratios (HR).

**Results:** In the entire population or in hypertensive participants, prevalence of LVH was higher for LVM/m\(^{2.7}\) (20% and 28%) and LVM/m\(^{2.13}\) (18% and 25%) than for BSA (7% and 11%). Age and sex-adjusted PAR% for LVM/m\(^{2.7}\) or LVM/m\(^{2.13}\) were on average 1.8-fold greater than for LVM/BSA in the entire population, and 1.6-fold greater in hypertensive participants, differences that were statistically significant.

**Conclusions:** The presence of LVH identified by LVM normalized for height to allometric powers is associated with a higher proportion of incident CV events than is LVH detected by normalization for BSA and is convenient for identification of individuals at high risk and in need of preventive intervention in populations with high prevalence of obesity. Allometric power methods allow detection of prognostically adverse, obesity-related LVH, which is unidentified using BSA. Am J Hypertens 2005; 18:191–196 © 2005 American Journal of Hypertension, Ltd.

**Key Words:** Cardiovascular risk, echocardiography, obesity, prognosis, arterial hypertension, risk factors.
definitions of LVH in the Strong Heart Study cohort to maximize prediction of CV events that might be potentially prevented by regression of LVH.

Methods

Population

The Strong Heart Study (SHS) is a cohort survey of CV risk factors and disease in American Indians from three communities in Arizona, seven in southwestern Oklahoma, and three in South and North Dakota, as extensively described. Participants 47 to 80 years of age underwent echocardiography in 1993 to 1995 during the second SHS examination.

Participants without prevalent CV disease (CVD) at the time of echocardiographic examination were selected for the present analysis. Additional exclusion criteria included aortic valve disease of any degree, more than mild mitral regurgitation, and any wall motion abnormality. Thus, 2400 participants (1589 women and 811 men, mean age 59 ± 8 years, followed for 86 ± 11 months) were available. The average time from the echocardiographic examination to the first CV event in this cohort was 38 ± 7 months.

Arterial hypertension was defined according to the guidelines of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure VII (JNC-7). Obesity was identified by the 1998 National Institutes of Health classification (body mass index [BMI] ≥30 kg/m²). Diabetes was defined on the basis of the 1997 guidelines by the American Diabetes Association or current use of hypoglycemic therapy. Fatal and nonfatal CV end-points were established as previously reported in detail. Deaths were identified through tribal and Indian Health Service hospital records, and by direct contact by study personnel with participants and their families. Possible CV-related deaths were identified from death certificates as described previously. Medical records were reviewed at the second examination to identify nonfatal CV events that occurred after the first SHS examination. All materials were reviewed independently by physician members of the Strong Heart Study Mortality and Morbidity Committees to confirm the cause of death or to establish the specific CVD-related diagnosis.

Echocardiographic Methods

Echocardiography was performed according to standardized procedures, as previously reported in detail. The LV internal dimension and wall thickness were measured at end-diastole and end-systole by American Society of Echocardiography recommendations on up to three cardiac cycles.

The LVM was measured by an anatomically validated method and was normalized by a number of measures of body size, including BSA, BSA in meters (ie, m² raised to the allometric power of 1.5), height, height in meters (all theometric signal of the LVM/height relation over the entire life span) and meters (the allometric signal identified for adults only).

As previously reported, LVM was measurable in 3188 of 3487 participants in the SHS (91%). Nonmeasurable LVM was weakly and independently associated with male sex, older age, greater body mass index, and lower forced expiratory volume but not other risk factors, and it was more frequent when BMI was >35 kg/m² (14%) compared with 6% to 8% of other participants. Inter-observer variability concerning the SHS has been previously reported; intra-observer variability has also been reported.

Statistical Analysis

Data were analyzed using SPSS 11.0 software (SPSS Inc., Chicago, IL). Data are expressed as mean ± SD and range. Categories were compared by χ² statistics. Population-specific partition values for clear-cut definition of LVH were obtained in 251 normal SHS participants (57% women and 43% men who were normotensive, nondiabetic, with normal renal function [serum creatinine <1.2 mg/dL], no valve disease or wall motion abnormality, body mass index <28 kg/m², and no prevalent or incident CV events), using mean ± 1.96 SD of the distribution of LVM normalized for each measure of body size, without sex distinction, consistent with previous reports. For every normalization of LVM and corresponding definition of LVH, adjusted hazard ratios (HR) were computed for the entire population and separately for hypertensive participants, for composite fatal and nonfatal CV events associated with presence of LVH, using Cox proportional hazard models.

We used LVH population-attributable risk percentage (PAR%) as the measure of the impact of LVH on composite fatal and nonfatal CV events. We calculated PAR% assuming that individuals with LVH can regress to normal LV geometry and that the excessive event rate associated with LVH would be eliminated. The formula of Levin was used:

\[
PAR\% = \frac{P(HR - 1)}{P(HR - 1) + 1} \times 100
\]

where P is the prevalence of LVH by different normalizations. The HR for composite fatal and nonfatal CV events were generated by the two Cox models described above. To generate 95% confidence intervals (CI) for PAR%, we used the exponential transformation of standard error (SE) of the β-coefficient of Cox regression for each given measure of LVH, which represents the SE of the HR (SE_HR). Thus, SE_HR * 1.96 was added or subtracted from the formula for PAR%, to generate lower and upper bounds (B_low/high) of the PAR% distribution (95% CI):

\[
B_{\text{low/high}} = \frac{P(HR - 1)}{P(HR - 1) + 1} \pm 1.96 \text{SE}_{\text{HR}}
\]

The null hypothesis was rejected at two-tailed α ≤0.05.
Table 1. Left ventricular mass (LVM) normalized for different measures of body size in the reference population (n = 251)

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVM (g)</td>
<td>134.34 ± 31.54</td>
</tr>
<tr>
<td>LVM/BSA (g/m²)</td>
<td>76.17 ± 14.79</td>
</tr>
<tr>
<td>LVM/BSA¹.⁵ (g/m³)</td>
<td>57.54 ± 10.84</td>
</tr>
<tr>
<td>LVM/height (g/m)</td>
<td>80.53 ± 17.00</td>
</tr>
<tr>
<td>LVM/height².⁷ (g/m².⁷)</td>
<td>33.95 ± 6.78</td>
</tr>
<tr>
<td>LVM/height².¹³ (g/m².¹³)</td>
<td>45.32 ± 9.02</td>
</tr>
</tbody>
</table>

BSA = body surface area.

Results

Among the 2400 participants, 43% were hypertensive, 32% overweight, 56% obese (72% women and 28% men; OR = 1.8, P < .002), and 53% diabetic. Composite fatal and nonfatal CV events occurred in 131 participants (5.5%), 85 of whom were women (65%; P = .742 v men). The risk of CV events was 2.8-fold higher (95% CI = 1.9 to 4.1, P < .0001) in hypertensive and 2.4 (95% CI = 1.6 to 3.5, P < .0001) in diabetic participants, but no difference was found between obese and nonobese individuals (OR = 0.97 [95% CI = 0.83 to 1.13], P > .6).

Table 1 presents the mean (± 1 SD) of each index of LVM in the reference population. Men exhibited greater values than women (all P < .0001, not shown), but this difference was minimized using normalizations based on allometric signals (both P < .01).

Table 2 shows the sex-specific prevalence of LVH in relation to type of normalization for body size in the entire study population and in normotensive or hypertensive participants. When using common partition values, LVM by BSA or height was more prevalent in men than in women. In contrast, when sex-specific partition values were used, LVH was substantially more prevalent in women than in men with all measures. Whatever partition value was used, the use of allometric signals highlighted a higher prevalence of LVH in women than in men. The prevalence of LVH substantially increased with normalization for all measures of body height and was lower with normalizations for BSA, which is related also to body weight. Nonindexed LVM identified an intermediate prevalence of LVH between that recognized by BSA and those by height-based normalizations. The next analyses will be conducted on definition of LVH by common partition values in women and men, adjusting for sex.

Prospective Risk Attributable to LVH

Age- and sex-adjusted HR and corresponding PAR% for composite fatal and nonfatal CV events for each measure of LVH are displayed in Table 3. The PAR% obtained using normalization for height raised to allometric powers were on average 1.8-fold greater than those obtained by normalizing for BSA in the whole population, and 1.6-fold greater in hypertensive participants, differences that could be considered statistically significant, given the lack of overlap between the respective confidence intervals. Notably, performances of indexation for height to the first power and BSA to the power of 1.5 were disappointing, whereas those of unindexed LVM were comparable to normalization for BSA to the first power. As compared with the number of events that could be prevented assuming regression of LVH by LVM/BSA, an additional seven events per 100 individuals attributable to LVH might be prevented using LVM/height to allometric power.

Discussion

Normalization of LVM for body size is widely used to compare individuals with different body builds and to generate partition values to identify groups at high risk for CV events. The challenge of scaling organ weight for body size in studies of comparative physiology in mammals has generally been overcome by using body weight. In humans, however, the problem of scaling is more complex, as body size varies markedly because of variable amounts of body fat resulting from environmental influences and genetic selection.

Although the rationale of indexing LVM for height raised to its allometric power is strong, as we and others have suggested, results of longitudinal analyses have not confirmed a clear advantage of one indexation over others or shown a better definition of high CV risk.

Despite the similarity in the HR, the different methods of definition of LVH cannot reflect the same impact in populations because of the substantial difference in hypertrophy prevalence, as previously reported and as shown in Table 2 of the present study. Combining HR and prevalence of the indicator, PAR% helps to identify which risk predictors are most relevant for public health and thereby warrant allocation of resources for prevention.

The analysis developed in this study demonstrates that different indexations of LVM for measures of body size are not interchangeable for identification of the excessive risk associated with LVH in a population with substantial prevalence of obesity. Compared with other commonly used normalizations of LVM, indexation of LVM for height to the powers representing the allometric signal, either across the entire life span or in adults, identifies a higher proportion of incident CVD attributable to LVH in our entire study population and in hypertensive individuals as well.

Allometric signals of height minimize gender difference in LVM index, as already shown in an ethnically different normal population. In general, hypertensive women show higher prevalence of LVH when an obesity-dependent normalization is adopted. Because, in the SHS cohort, obesity was significantly more prevalent in women than in men, a higher proportion of LVH could be identified in women using allometric power methods. In fact,
Table 2. Crude prevalence of left ventricular hypertrophy (LVH) in normotensive and hypertensive individuals, according to partition values reported in Table 1

<table>
<thead>
<tr>
<th></th>
<th>Normotensive (n = 1374)</th>
<th>Hypertensive (n = 1026)</th>
<th>Overall prevalence of LV hypertrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men (n = 457)</td>
<td>Women (n = 917)</td>
<td>Men (n = 354)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>53.56 ± 6.81</td>
<td>53.88 ± 7.07</td>
<td>54.35 ± 7.30</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.00 ± 5.01</td>
<td>31.31 ± 6.34</td>
<td>31.41 ± 5.59</td>
</tr>
<tr>
<td>Obesity (%)</td>
<td>38.9</td>
<td>56.5</td>
<td>56.5</td>
</tr>
<tr>
<td>Non-sex-specific partition value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVM (%)</td>
<td>14</td>
<td>3</td>
<td>24</td>
</tr>
<tr>
<td>LVM/BSA (%)</td>
<td>6</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>LVM/BSA².5 (%)</td>
<td>4</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>LVM/Height (%)</td>
<td>13</td>
<td>23</td>
<td>23</td>
</tr>
</tbody>
</table>
| LVM/Height²⁻²⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻˓
indexation of LVM for height to allometric signals identifies a higher proportion of incident CVD attributable to hypertensive LVH by including 7% of preventable events attributable to obesity-related LVH, a share that is missing when using BSA.

Thus, the PAR% using height^{2.7} or height^{2.13} were about 16% in the Strong Heart Study cohort, a population with high prevalence of obesity, generally mild hypertension, and relatively good control of blood pressure (BP) with therapy. This impact of PAR% might be even higher in other populations with less successful control of hypertension and more prevalent LVH, or even lower when obesity is less prevalent. This study suggests that identification of LVH using normalization of LVM for height to its allometric power is preferable to normalization for BSA in populations with the SHS characteristics. Because the magnitude of PAR% is strongly influenced by population prevalence of the specific risk predictor, this conclusion cannot be automatically extended to other populations, although previously reported relative risks and population prevalence of the specific risk predictor, this conclusion cannot be automatically extended to other populations and clinical characteristics, especially concerning prevalence of obesity.

Normalization for BSA tends to blunt the effect of obesity, and the resulting prevalence of LVH is substantially attributable to hypertension. Using BSA-based PAR% for primary prevention substantially speaks to decreasing BP to regress LVH and reduce adverse events attributable to pure hypertensive LVH. In contrast, if the height^{2.7}-based PAR% is taken as the basis of a program of CVD prevention, reducing BP is no longer sufficient to eliminate incident events attributable to LVH, and intervention regarding reduction of obesity might also be required. Identification of a marker of preclinical CVD with a population-attributable risk as high as 16% to 17% opens up the possibility of targeting primary prevention interventions different from, or in addition to, the general preventive measure of reducing causal CV risk factors.

### References

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