

Editorial Comment

How Best to Identify Prognostically Important Left Ventricular Hypertrophy: A Cut to the Chase*

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Determinants of left ventricular mass. After birth, myocardial growth largely occurs due to an increase in myocyte size (hypertrophy) rather than myocyte number (hyperplasia) (1). During childhood and adolescence, left ventricular mass enlarges in tandem with increasing body size (2,3). Among the various measures of body size, left ventricular mass tracks most closely with lean body mass (2). Myocardial mass is similar in boys and girls but begins to diverge during adolescence, with the greater increase in left ventricular mass in men due to the proportionally greater increases in body height and weight (3). With aging, left ventricular wall thicknesses increase, whereas cavity size tends to decrease in normotensive adults, resulting in no change in overall ventricular mass but a progressive increase in relative wall thickness (concentric remodeling) (4).

The relation between body size and left ventricular mass becomes less close in adults because of the superimposition of conditions predisposing to left ventricular hypertrophy, such as obesity and hypertension. Obesity is associated with an increase in left ventricular mass in both normotensive and hypertensive populations, independent of blood pressure (5,6). Left ventricular hypertrophy in obesity is most commonly eccentric (6,7), emphasizing the importance of volume load in determining left ventricular mass (8). The extent to which hypertension induces myocardial growth and results in left ventricular hypertrophy is quite variable, depending on the severity of hypertension and the patient population (9).

Among asymptomatic, mildly hypertensive patients, left ventricular mass was found to be 13% greater than in normotensive subjects similar in age, gender and body size, whereas frank left ventricular hypertrophy was present in 12% of hypertensive patients (10).

“Normalization” of left ventricular mass. Because of its strong relation to body size, a variety of methods have been utilized to adjust left ventricular mass for differences in body size. The goals of such “normalization” include the development of accurate reference standards for normality and quantification of the impact of disease states, such as hypertension and obesity, on left ventricular growth. Traditional methods for adjustment of left ventricular mass have utilized either height or body surface area, which is determined by both height and weight. Controversy regarding the preference between these simple methods centers on the extent to which the impact of obesity on left ventricular mass is explained: division of absolute left ventricular mass by body surface area “forgives” or underestimates the influence of obesity by proportionally lowering ventricular mass, whereas division by height accentuates the impact of obesity by proportionally elevating ventricular mass.

An attractive alternate method for normalization of left ventricular mass involves the use of lean body mass. Adjustment of left ventricular mass by lean body mass, measured using 24-h urinary creatinine excretion, better diminished observed differences between adult men and women and between obese and nonobese subjects than did adjustment by body surface area, height or weight (7). When measured by dual-energy X-ray absorptiometry, lean body mass explained 75% of the variance in left ventricular mass in black and white boys and girls (2). Although newer methods of determining lean body mass, such as bioimpedance and dual-energy X-ray absorptiometry, may speed the measurement of lean body mass, the time, expertise, and expense involved may continue to limit the use of this measure of body size as the optimal method of adjustment.

More recently, de Simone et al. (11) have utilized the concept of allometric relations among body parts to identify a more ideal method of adjustment. In this approach, left ventricular mass may be related by nonlinear regression analysis to a regression coefficient or constant (b1) times a given measure of body size raised to the power of an allometric signal (b2) that gives the best fit:

Left ventricular mass = b1 \times \text{Measure of body size}^{b2}.

Because left ventricular mass is a volumetric, or three-dimensional measure, whereas body surface area is two-dimensional, and height is one-dimensional, one might expect that the allometric signal for left ventricular mass in relation to body surface area would be 1.5 and that for height would be 3. In fact, in a large population of normotensive adults and children, left ventricular mass most closely related to body surface area to the 1.5 power and height to the 2.7 power (11). Variability among normal subjects was best minimized, and the increase in left ventricular mass attributable to obesity (as estimated using ideal ventricular mass predicted from ideal weight based on observed height) was most accurately predicted, by adjustment by height1.57 (11). A similar approach was subsequently applied to normal, young adults in the Framingham population, and although a different allometric signal was derived (height1.97), variability in left ventricular mass was again considerably diminished (12). Although a subsequent
study by de Simone et al. (13) found the allometric signals to be lower (and more comparable to the Framingham data) when children and adults were analyzed separately (height\(^{2.3}\) and height\(^{2.13}\), respectively), cardiovascular risk tended to be best predicted by adjustment of left ventricular mass by the allometric signal (height\(^{2.7}\)) derived using the entire age spectrum (partition value of 51 g/m\(^{2.7}\)).

**Prognostic importance of left ventricular hypertrophy.**

The debate concerning the optimal method of adjustment of left ventricular mass for differences in body size and the development of partition values for normality is of clinical relevance in view of the well established independent contribution of the presence of echocardiographic left ventricular hypertrophy to an increase in all-cause mortality and cardiovascular morbidity and mortality both in the general population and among hypertensive patients (14–16). The increased risk associated with left ventricular hypertrophy is roughly twofold greater in the general population (15) and even higher when analyses are limited to hypertensive patients (16). Furthermore, the presence of left ventricular hypertrophy in the absence of coronary artery disease appears to confer a greater risk than in the presence of significant coronary disease or significant left ventricular dysfunction (17), and it may be of greater prognostic significance in women than in men (18).

The potential mechanisms whereby left ventricular hypertrophy might increase morbidity and mortality include 1) hemodynamic alterations, such as reduced ventricular compliance and elevated filling pressures; 2) a lowered ischemic threshold of the hypertrophied myocardium; 3) enhanced arrhythmogenesis; and 4) an association with an increase in both coronary and extracardiac vascular disease. The evidence supporting these postulated mechanisms has been recently reviewed (9).

**Current study.**

The study by Liao et al. (19) in this issue of the Journal represents an effort to “cut to the chase.” Acknowledging the debate concerning the optimal method of adjustment of left ventricular mass and cognizant of the importance of the presence of left ventricular hypertrophy in influencing outcome, the authors compared the predictive value of left ventricular mass adjusted by various methods for all-cause and cardiac mortality. Although one might quibble endlessly about which method results in the least variability and best accounts for obesity, the ultimate clinical goals are to stratify risk, target therapy and improve outcome.

The study is a retrospective analysis of 988 consecutive patients studied with both coronary angiography and echocardiography over a 9.5-year period at Cook County Hospital in Chicago. Obstructive coronary artery disease was present in 54% of patients, and all results are subdivided according to its presence or absence. During an average follow-up of 7 years, 202 patients died, 127 of cardiac disease and 75 of other causes.

Not surprisingly, when left ventricular mass was considered a continuous variable (log-transformed and standardized into a Z score), the relative risks for all-cause and cardiac mortality were increased with increasing left ventricular mass, regardless of the method of adjustment, with no differences among the six methods considered (height, height\(^{2}\), height\(^{2.13}\), height\(^{2.7}\), body surface area, body surface area\(^{1.5}\)). Seven different partition values (five gender specific) for adjusted left ventricular mass derived from analyses of the Framingham (20) and Cornell (13,14,16) populations were then evaluated: three adjusting by body surface area, two adjusting by height and two adjusting by height\(^{2.7}\). Although statistical comparisons are not provided, the presence of left ventricular hypertrophy appeared to carry a greater risk in the patients without, as opposed to those with, coronary artery disease, in keeping with a previous report from the same group (17). Among patients without coronary artery disease, all partition values conferred an increased risk of all-cause and cardiac mortality; in general, partition values based on indexation by body surface area tended to identify higher risk associated with hypertrophy than those based on adjustment for height, although the differences were rarely significant. Among patients with coronary artery disease, relative risks were again largely similar, and only adjustment by height\(^{2.7}\) failed to increase relative risk.

Very few patients had left ventricular hypertrophy detected only by body surface area adjustment. Patients in whom left ventricular hypertrophy was detected only by height-based methods of adjustment did not have an increase in relative risk of death, most likely due to the overall lower left ventricular mass in this group compared with the group with hypertrophy also detected by adjustment by body surface area.

**In summary,** the study demonstrates that increasing left ventricular mass, regardless of the method of adjustment, is associated with increasing risk of death. Differences in the predictive values of the different methods of adjustment arise only when specific partitions are evaluated, and these differences are probably attributable to the generally lower absolute left ventricular mass among patients with height-based rather than body surface area-based criteria in this predominantly obese population. The study would appear to confirm the results of a previous analysis confined to nonhospitalized hypertensive patients wherein major differences in risk among the various methods of adjustment were not readily discernible (13).

**Study limitations.** One of the major limitations of the study concerns the highly select nature of its cohort: inner-city, hospital-based patients, of whom >80% were black, >80% hypertensive, >50% obese and ~50% had left ventricular hypertrophy. Furthermore, by definition, all patients must have undergone coronary angiography for presumed coronary artery disease. Cardiac deaths are not further characterized, and significant valvular heart disease does not appear to be an exclusion criterion and may account for ventricular hypertrophy and some of the cardiac deaths among the noncoronary artery disease group. Despite the unrepresentative nature of the cohort, it is reassuring that the relative risks associated with left ventricular hypertrophy are in the same range as those previously reported.

The relative risk data are exclusively presented after adjustment for age and gender. Given the lack of a clear, much less strong, association of age with left ventricular mass and the fact
that most partition values are gender specific, it is unclear why such adjustment is necessary, and whether it might have influenced the results. Unfortunately, the relative risks of partition values based on absolute left ventricular mass were not fully explored. Finally, as the authors acknowledge, cardiovascular morbidity is not considered an end point. Whether such analyses would enhance or lessen differences in predicting risk among the different methods of adjustment is uncertain, although one might predict that obesity-related morbidity might lessen the differences.

Future directions. The predictive value of the refreshingly simple measure of absolute left ventricular mass has not been adequately examined. Despite its dependence on body size, there may be threshold levels of ventricular mass that exceed the ability of the microvasculature to adequately sustain and thereby increase risk. In addition, not only the size but also the geometry of the left ventricle may be of importance, as suggested by the enhanced concentration of disease and risk among hypertensive patients with the concentric pattern of left ventricular hypertrophy (16,21). Finally, the development and ready availability of accurate methods to determine lean body mass may provide the optimal method of adjustment of left ventricular mass.

Although analyses similar to those in the current study, as well as assessment of absolute left ventricular mass and geometric pattern, should certainly be performed in other populations, one wonders whether an attempt should be made to pool data from several of the large population-based studies that have included echocardiography to 1) more confidently define the limits of normality over a broad range of age, race and socioeconomic status; 2) further explore the utility of allometric relations in reducing the variability of left ventricular mass attributable to body size; and 3) consider development of partition values based on outcome rather than “normality” using longitudinal data. Until such time, the presence of left ventricular hypertrophy, however defined, should alert the clinician and should stimulate efforts at regression, at least in the setting of hypertension, in view of preliminary data suggesting benefit and pending the outcomes of large, ongoing trials designed to evaluate this potential.

I thank Richard B. Devereux, MD for thoughtful review of this editorial.

References

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