Why Is Left Ventricular Hypertrophy So Predictive of Morbidity and Mortality?

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ABSTRACT: The prevalence, prognosis, and predictors of left ventricular hypertrophy (LVH) are reviewed, and theories of the pathogenesis of the relation between LVH and poor prognosis are summarized to highlight controversies in the field. In the Framingham Heart Study, which consists largely of white people, echocardiographic LVH has a prevalence of 14% in men and 18% in women. The prevalence of LVH is reported to be elevated in African Americans compared with whites, although the higher prevalence has been attributed to the increased prevalence of hypertension and obesity. Echocardiographic LVH is independently associated with a variety of cardiovascular endpoints, including coronary heart disease and stroke. Furthermore, after adjusting for other cardiovascular disease risk factors, LVH is associated with a doubling in mortality in both white and African American cohorts. Despite the intensive investigation of LVH, there remain many unanswered questions: To what extent do genetic or other factors account for the large portion of the variance in LVH that remains unexplained? What is the prognosis of LVH and left ventricular geometry in a population-based African American cohort? How does the development and progression of LVH relate to other risk factors and their treatment? What is the relation of LVH to poor prognosis? The proposed Jackson Heart Study will help address many important unanswered questions regarding LVH.

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The prevalence of left ventricular hypertrophy (LVH) depends upon the population studied and the modality used for its diagnosis. In the Framingham Heart Study's predominantly white cohort, the prevalence of LVH on the electrocardiogram (ECG LVH) was 2.9% in men and 1.5% in women. In comparison, the echocardiogram proved more sensitive for the detection of LVH, diagnosing the condition in 14.2% of men and 17.6% of women with technically adequate echocardiograms.[1]

The prevalence of ECG LVH in African Americans has been demonstrated to be higher than in whites.[2,3] Data from the Atherosclerosis Risk in Communities Study suggest that even after adjusting for blood pressure and other risk factors for LVH, African-Americans have a higher prevalence of ECG LVH than whites.[4] Racial differences in echocardiographic left ventricular mass (LVM) are more complex. Although studies have shown a higher prevalence of echocardiographic LVH in African Americans than in whites,[5] LVM indexed for body surface area has been reported to be similar between the races.[3,6–9] However, there is a tendency for African Americans to have higher mean levels of wall thickness.[3,6–8]

Prognosis of LVH

ECG LVM. The first insights into the worsened survival associated with LVH came from the ECG literature. In Framingham Heart Study subjects, definite ECG LVH was associated with about a three-fold risk of developing clinically overt coronary heart disease, including angina, myocardial infarction, stroke, and congestive heart failure.[10–13] Furthermore, ECG LVH was a highly lethal attribute; ECG LVH was associated with an age-adjusted, five-fold risk of all-cause mortality in both men and women.

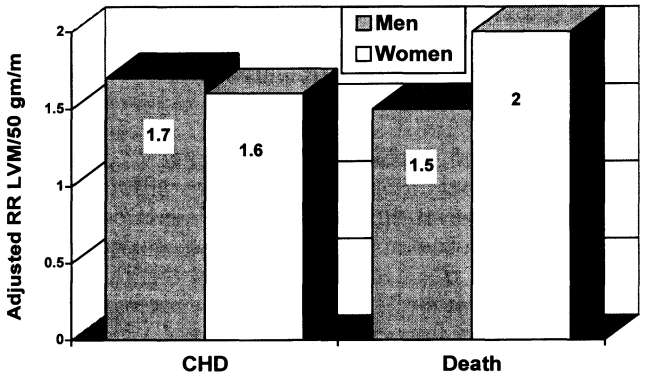

Figure 1. Risk of left ventricular mass; The Framingham Heart Study.[15] RR, relative risk; CHD, coronary heart disease; death, all-cause mortality.

A more recent series from the Bronx Longitudinal Aging Study suggests that ECG LVH remains an important prognostic indicator.[14] In a community-based cohort of men and women, 75 to 85 years of age at baseline, the prevalence of ECG LVH was 9.2%. The mortality rate was 11.7 per 100 person years versus 4.9 per 100 person years, for subjects with and without baseline ECG LVH, respectively. Persistent LVH was an independent predictor of all-cause mortality, as well as myocardial infarction and cardiovascular disease.

Echocardiographic Left Ventricular Mass. The prognosis of echocardiographic LVM has been studied in three settings; in patients with hypertension, in patients referred for coronary angiography, and in population-based samples. In these studies, echocardiographic LVM conveyed a worse prognosis after adjusting for coexistent risk factors. LVM predicts cardiovascular events, including coronary heart disease, stroke, sudden death, and all-cause mortality.

In the Framingham Heart Study, subjects aged ≥40 years with technically adequate echocardiograms who were free of clinically evident cardiovascular disease (n = 3220), were observed for up to 4 years.[15] As Figure 1 illustrates, increasing LVM was associated with coronary heart disease and all-cause mortality in both men and women, after adjusting for other risk factors. For each 50 gm/m (corrected for height) increment in LVM, the risk-factor-adjusted relative risk for death was 1.5 in men and 2 in women.

In a subsequent study from Framingham, echocardiographic LVH was also found to be predictive of incident stroke.[16] After adjusting for other risk factors, the hazard ratio for stroke and transient ischemic attack was 1.5 [95% confidence interval (CI), 1.2 to 1.8] for each quartile increment in LVM (height adjusted).

Liao and colleagues[17,18] examined the prognosis of echocardiographic LVH in an African American angiography cohort at Cook County Hospital, a large inner-city public hospital (Figure 2). The authors followed, for a mean of 5 years, the cases of 1089 consecutive black patients who underwent both echocardiography and coronary angiography. In this angiography referral cohort, the investigators found a 50% prevalence of echocardiographic LVH [LVM indexed to body surface area (BSA) > 131 g/m^2 in men and > 100 g/m^2 in women]. The relative risk of echocardiographic LVH for death was 2.4. More importantly, because of the high prevalence of the condition, they estimated that 37 of 100 deaths in the cohort were attributable to LVH. Furthermore, both the attributable risk and relative risk for echocardiographic LVH were greater than for the other cardiovascular conditions studied, including multivessel coronary artery disease and decreased ejection fraction.

In another study from the Cook County Hospital investigators, in subjects free of significant coronary artery disease, the relative risk of elevated LVM was higher in women than in men.[19] Adjusting for cardiovascular risk factors, the relative risk of all-cause mortality was 2.0 in men and 4.3 in women.

In a cohort of patients with uncomplicated hypertension, echocardiographic LVH was a significant independent predictor of cardiovascular events and all-cause mortality.[20,21] Koren et al further suggested that the pattern of echocardiographic LVH was important.[21] They divided the subjects into four categories: normal left ventricular geometry [LVM index < 125 g/m^2, relative wall thickness (RWT) < 0.45], concentric remodeling (LVM index < 125 g/m^2, RWT ≥ .45), eccentric hypertrophy (LVM index ≥125 g/m^2, RWT < .45), and concentric hypertrophy (LVM index > 125 g/m^2, RWT ≥.45). Subjects with concentric LVH had the highest all-cause mortality (Figure 3), followed by intermediate mortality with eccentric hypertrophy and concentric remodeling (P < 0.001, by analysis of variance). In

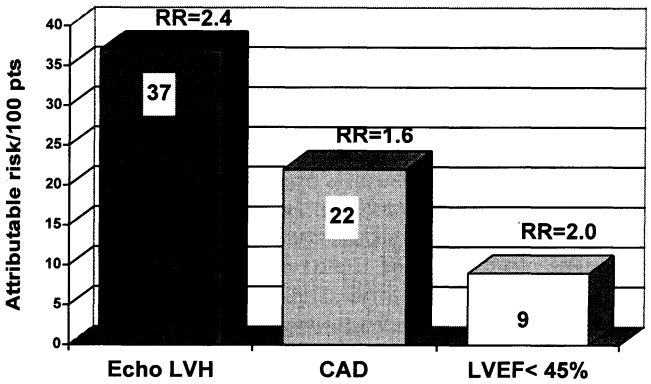

Figure 2. Mortality of consecutive African Americans referred for cardiac catheterization.[18] RR, relative risk; echo LVH, echocardiographic LVH; CAD, multivessel coronary artery disease; LVEF, left ventricular ejection fraction.

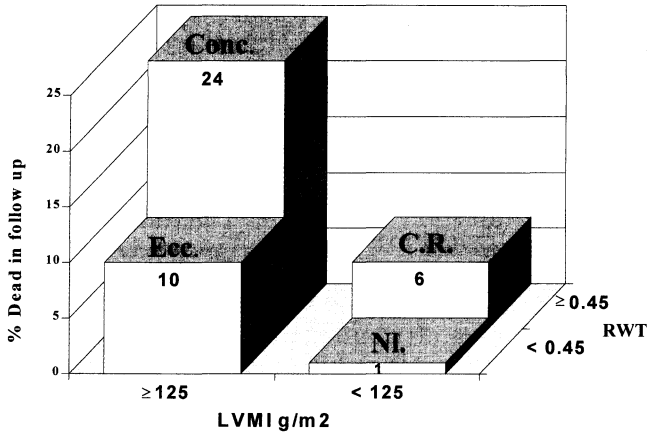

Figure 3. Relation of left ventricular geometry to mortality in patients with uncomplicated hypertension. LVMI, left ventricular mass indexed for body surface area; RWT, relative wall thickness (ratio of the posterior wall thickness to one-half the left ventricular internal dimension at end-diastole); *Conc.*, concentric hypertrophy; *Ecc.*, eccentric hypertrophy; *C.R.*, concentric remodeling. (Adapted with permission from Koren MJ, Devereux RB, Casale PN, et al. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. Ann Intern Med 1991;114:345–52. Copyright © 1991 American College of Physicians.)

addition, they found that LVM and geometry were more strongly predictive of outcome than traditional cardiovascular risk factors; ECG LVH was not predictive of outcome, partly because of its low prevalence.

The importance of left ventricular geometric patterns, as opposed to LVM, has not been universally supported. Examining the issue in a population-based sample, investigators from the Framingham Heart Study explored the relation of left ventricular geometry to outcome in 3216 subjects observed for up to eight years.[22] They found that subjects with concentric LVH had the highest mortality, but these subjects also had the highest LVM. Adjusting for baseline LVM largely attenuated the relations of left ventricular geometry to cardiovascular disease incidence and mortality. Compared with normal geometry, the odds ratio for incident cardiovascular disease with concentric LVH was 1.3 in men (95% CI, 0.8 to 2.1) and 1.2 in women (95% CI, 0.6 to 2.3).

Investigating the relation of left ventricular geometry to outcome in the PIUMA database of hypertensive patients, Verdecchia et al studied 274 consecutive subjects with hypertension and LVM index ≥ 125 g/m^2 followed for up to 8 years.[23] In multivariable analyses, the investigators found that LVM index above the median (145 g/m^2) was associated with adverse outcome (relative risk 2.61; 95% CI, 1.02 to 6.63), whereas left ventricular geometry was not a significant prognostic indicator (the incidence of major cardiovascular morbid events was 2.2 and 3.3 per 100 patient-years in eccentric versus concentric hypertrophy, respectively; P-values were not statistically significant). However, the small sample size may have limited the power of the study to detect an impact of LV geometry.

Predictors of Left Ventricular Hypertrophy

An appreciation of the risk factors for LVH is critical to understanding the possible confounders of the relation between LVH and poor prognosis, and potentially to discerning strategies for preventing the complications of LVH. The literature examining the risk factors for echocardiographic LVH is extensive and comes from a variety of settings, including epidemiologic investigations[5,7,24–29] and hypertension[3,6,30] and angiography patient cohorts.[31]

Demographic Variables. The influence of race on LVM has been discussed above. Sex-related differences in LVM have been described consistently; men have higher LVM, even after differences in body size are accounted.[5,6,32] The prevalence of elevated LVM increases with age.[24,27] However, in adults, in multivariable models, age either does not predict or is only a modest predictor of LVM. The lack of a major age effect suggests that increasing LVM is not an obligatory part of 'normative' aging; rather, it is largely a reflection of the increasing prevalence of cardiovascular conditions associated with aging, such as hypertension, valvular heart disease, and myocardial infarction.[3,6,27,32–35]

Blood Pressure. Surprisingly, blood pressure explains only a relatively modest percentage of the observed variance in LVM, regardless of the method of blood pressure assessment or the study setting.[28,35,36] Contemporary resting blood pressure has consistently been found to be associated with LVM,[24] yet the correlations are not very strong (r values in the .13−.30 range.[5,26,27,35]

One possible explanation for the modest correlation between contemporary blood pressure and LVM is the potential for misclassification of blood pressure exposure by a single assessment. Yet, although the average of 30-year longitudinal systolic blood pressure readings at the Framingham Heart Study was a better predictor of LVM ($p < 0.01$) than contemporary blood pressure, the correlation remained modest at $r = 0.27$ in men and $r = 0.31$ in women.[26] Similarly, several investigators have examined the relation between ambulatory blood pressure and LVM index and have found that the correlation is somewhat higher than with resting systolic blood pressure, but the correlations have all been ≤ 0.50.[7,30] Blood pressure response on the treadmill has also been examined. Although the exaggerated blood pressure response to exertion is related to LVM, the relation is largely attenuated after adjusting for age, resting blood pressure, and body mass.[37]

In several studies of normotensive individuals, increased LVM predicted the incidence of hyperten-

sion in follow-up.[38–40] In normotensive adults in the Framingham Heart Study, after adjusting for risk factors for hypertension, the odds ratio for developing hypertension was 1.2 per one standard deviation in LVM index (95% CI, 1.04 to 1.39).[38] Data suggesting that LVM predicts the incidence of hypertension, and that the converse is true (hypertension is associated with the development of LVH), may suggest that both hypertension and LVM share common antecedents.

Anthropometric Variables. After adjusting for age and blood pressure, obesity remains significantly correlated with LVM;[28,41] a number of investigations have found that LVM was more highly correlated with weight (or body mass index) than with blood pressure.[3,27,28,41] The most appropriate anthropometric variable by which to index LVM is controversial and unresolved.[42] Although weight and body mass index are more highly correlated with LVM than is height, investigators have argued that indexing by BSA inappropriately 'forgives' for obesity.[34] Furthermore, the prognostic advantage of adjusting for body size by any particular method is small, presumably because the anthropometric variables are highly correlated and because increasing LVM per se overwhelms the contribution of the indexing method.[31,34,42]

Miscellaneous Variables. LVM has been associated with a wide variety of other variables, including alcohol intake in men,[25] diabetes,[29,43] smoking,[27] urinary sodium,[6] insulin resistance,[44] hematocrit,[3] blood viscosity,[45] physical activity (particularly among elite athletes),[5,46,47] cardiac disease (including valvular disease,[24,27] prevalent myocardial infarction,[24] and congestive heart failure[27]), and echocardiographic variables (including Doppler stroke volume and afterload-independent midwall fractional shortening).[28]

How Much of the Variance in LVM Is Currently Explained?. A number of investigators have performed careful multivariable modeling to elucidate how much of the variance in LVM can be explained by demography, anthropometry, cardiovascular risk factors and cardiovascular disease. Surprisingly, about 50-75% of the variance remains unexplained by variables that are currently assessed.[5,27,28,36]

Ongoing investigations are examining the influence of genetic factors on LVM. Twin studies and epidemiologic investigations have provided suggestive evidence for a genetic contribution to LVM.[36,48–50] However, the genetic basis of LVM remains unknown.

Why Is Left Ventricular Hypertrophy so Predictive of Poor Prognosis?

The cause of the excess morbidity and mortality associated with LVH is incompletely understood, complex, and reviewed elsewhere.[51,52] Most investigators suggest that the poor prognosis is multifactorial and includes the burden of cardiovascular risk factors associated with LVH, the relation of LVH to myocardial ischemia and arrhythmias, and LVH as a marker for subclinical disease.

LVM Provides a Time-Integrated Measure of the Exposure to Other Risk Factors. Although the studies demonstrating a worsened prognosis with LVM, adjusted for standard cardiovascular risk factors, undoubtedly the poor prognosis of LVH is partially mediated through the excess mortality associated with the factors that predispose to LVH. Many experts have proposed that LVM may integrate longitudinal exposures to risk factors such as hypertension and obesity.

LVH Relation to Ventricular Irritability. In the Framingham Study, ECG LVH[53] and echocardiographic LVH in men[15] have been demonstrated to be predictive of sudden death in the community. In both hypertensive[54,55] and population-based[56,57] cohorts, echocardiographic LVH has been associated with increased risk for ventricular arrhythmias after adjusting for other risk factors for ventricular ectopy. Animal models have demonstrated that LVH increases the myocardial vulnerability to ventricular arrhythmias and sudden death. A recent study by Rials et al, performed in rabbits, suggested that the vulnerability to ventricular fibrillation is related to increased dispersion of refractoriness, action potential prolongation, and lowering of the ventricular fibrillation threshold; intriguingly, these electrical abnormalities were reversed after LVH regression induced by angiotensin-converting enzyme inhibitor.[58]

LVH Relation to Myocardial Ischemia. In the Framingham Study, both ECG[11] and echocardiographic LVH[59] have been shown to predispose to the development of coronary heart disease. Further, survivors of myocardial infarction with increased LVM have been shown to have excess cardiac events.[60] The mechanisms of the relation between LVH and coronary heart disease are still being elucidated and are complex.[61] LVH, by virtue of increased muscle mass and myocardial fibrosis, and increased pressure load, places excess oxygen demands on the coronary vasculature.[52] Furthermore, studies have demonstrated that subjects with LVH have compromised myocardial oxygen supply by virtue of endothelial dysfunction and diminished coronary vasodilator reserve, even in the absence of angiographic coronary artery disease.[62–64] Finally, animal models have also suggested that myocardial ischemia may induce LVH,[65] and, conversely, that LVH may result in more extensive myocardial infarct size.[66]

LVH as an Indicator of Subclinical Disease. The prognostic value of LVH may in part reflect its role as a marker of subclinical disease.[51,67] LVH has been demonstrated to correlate with extracardiac athero-

sclerosis. In a longitudinal study derived from an employed population, LVM was correlated with carotid arterial wall thickness ($r = 0.37$, $P < 0.0005$) and luminal diameter ($r = 0.33$, $P < 0.005$).[68] In a subsequent larger study from the same group, in multivariable modeling, carotid atherosclerosis was predicted by both LVM [odds ratio per 1 standard deviation (SD) LVM 1.5; 95% CI, 1.1–2.0], and ECG LVH (odds ratio 7.8; 95% CI, 1.3–45.0).[69] Similarly, in the much larger population-based sample of the Cardiovascular Health Study, both carotid artery diameter (partial $r = 0.17$, $P < 0.0001$) and carotid intimal medial thickness (partial $r = 0.07$; $P = 0.0001$) were significant predictors of LVM.[70] The relation between carotid disease and LVH may partly reflect the burden of shared risk factors that predispose to both LVH and carotid pathology.

Left Ventricular Hypertrophy: Unanswered Questions

What Accounts for the 50–70% of the Variability in LVM That Is Unknown?. Although the correlates of LVM have been investigated in hundreds of studies, the source of much of the observed subject-to-subject variability in LVM remains unknown. In addition to mechanical factors, ongoing investigations are exploring the contribution of neural, endocrine, and genetic factors to LVM.

What Is the Genetic Contribution to the Development and Progression of LVH?. Phenotypic studies have demonstrated a genetic influence on LVM, but the genes remain unknown. The portion of the variability caused by genes regulating LVM, as opposed to genes for risk factors for LVM (such as hypertension and obesity), is poorly understood. It is unclear whether there are race-based genetic differences in LVH and, if present, whether these differences are independent of risk factors for LVH (eg, obesity and hypertension).

What Is the Morbidity and Mortality of Echocardiographic LVM in An Unselected Population-Based Sample of Minorities?. Studies investigating the relation of LVM to prognosis have been conducted in cohorts based on largely white populations, hypertension cohorts, or angiography referral cohorts. The prognosis of LVM in a community-based cohort of African Americans or other minorities is largely unexplored.

Does Left Ventricular Geometry Provide Prognostic Information Independent of Baseline LVM? Do the Prognostic Insights Vary by Age, Ethnicity or Sex?. Although there is not a major age or ethnic influence over echocardiographic LVM, the literature suggests that left ventricular geometry may vary by age, ethnicity, and sex. Although some investigators have described prognostic variation in relation to the pattern of left ventricular geometry, other investigators studying largely white samples have suggested that these differences are markedly attenuated if one adjusts for baseline LVM. Whether age, sex, or ethnicity modifies the relation of left ventricular geometry to prognosis is largely unexplored.

What Is the Etiology of the Relation of LVH to Poor Prognosis?. Investigators have hypothesized that LVH predisposes to myocardial ischemia and ventricular arrhythmias and that LVH is related to subclinical cardiovascular disease. However, there remains an incomplete understanding of the cause of the relation between LVH and poor prognosis.

Will Screening for LVM Provide a Cost-Effective Way to Target Risk Factor Modification?. There is an imperfect relation between risk factors and events, such that primary prevention results in the costly strategy of needing to treat many patients to prevent one event.[67] Some experts have advanced the concept that echocardiography be utilized to screen certain subsets of hypertension patients to identify high- and low-risk patients, so as to more effectively target patients for preventive therapy.[71] However, echocardiography as a screening tool for LVH remains controversial because of scientific uncertainty as to whether the regression of LVM per se alters prognosis.

Does the Regression of LVM Improve Prognosis? Studies have demonstrated that the regression of LVH is feasible in hypertensive patients by both weight loss in overweight patients[72] and by antihypertensive medication.[73] Two observational studies following ECG LVH[14,74] and three hypertension treatment trials following changes in echocardiographic LVM[75-77] suggest that regression of LVH, as opposed to persistence of this pattern, is associated with improved survival. It remains undetermined whether regression of LVM should be an important goal of treatment. An alternative perspective maintains that LVM regression should be regarded as a surrogate endpoint that accompanies hypertension treatment. It is inadequately understood whether the regression of LVM is an independent predictor of improved prognosis; this is an objective of several ongoing investigations.[78]

Summary

Despite intensive inquiry into LVH, a number of unanswered questions remain. Unequivocally, however, LVH is a lethal attribute and is associated with a doubling in mortality. Although treatment directed toward the regression of LVH is controversial, given its poor prognosis, it seems prudent to prevent the development of LVH through the prevention of obesity and the prevention and adequate control of hypertension.

While this article was being prepared for publication, Ghali et al [79] reported an examination of the impact of left ventricular geometry in a prospective African American cohort of patients receiving cardiac catheterization. As with similar work at the

Framingham Heart Study,[22] after adjustment for left ventricular mass, relative wall thickness was no longer predictive of outcome.

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