

Left ventricular hypertrophy and cardiovascular prognosis

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SUMMARY Left ventricular hypertrophy is an important independent predictor of cardiovascular risk. The therapeutic implications of this remain to be explored.

KEY POINTS Electrocardiographic left ventricular hypertrophy has long been known to be a risk factor for adverse cardiovascular events; however, electrocardiography is not very sensitive for detecting this condition. More recently, echocardiography has been found to provide a more accurate and sensitive estimation of left ventricular mass than electrocardiography does. Both electrocardiographic and echocardiographic left ventricular hypertrophy independently predict a higher risk of coronary artery disease, cardiovascular disease, and total mortality. These associations have been noted in the general population, in patients with hypertension, and in patients undergoing coronary angiography. Important clinical correlates of left ventricular hypertrophy include hypertension, obesity, genetic predisposition, and, possibly, advanced age.

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LEFT VENTRICULAR hypertrophy (LVH) is a cardiovascular risk factor, but what exactly constitutes LVH? Classic electrocardiographic criteria, which provide a yes-or-no answer to the question of whether LVH is present, are highly specific but not very sensitive. Echocardiography is more sensitive, but does the finding of LVH on echocardiography carry the same prognostic significance? Does it help to consider left ventricular mass as a continuous variable in estimating risk, and if so, should it be indexed to height, body surface area, or height squared? What factors predict LVH?

MEASURING LEFT VENTRICULAR MASS

In clinical practice the two primary methods for detecting LVH are electrocardiography¹ and echocardiography.^{2,3} Electrocardiography suffers from a low sensitivity and produces a relatively low estimate of prevalence in population studies.⁴ Echocardiography is more sensitive but is considerably more labor-intensive and expensive. In the Framingham cohort of 4684 subjects who had adequate echo-

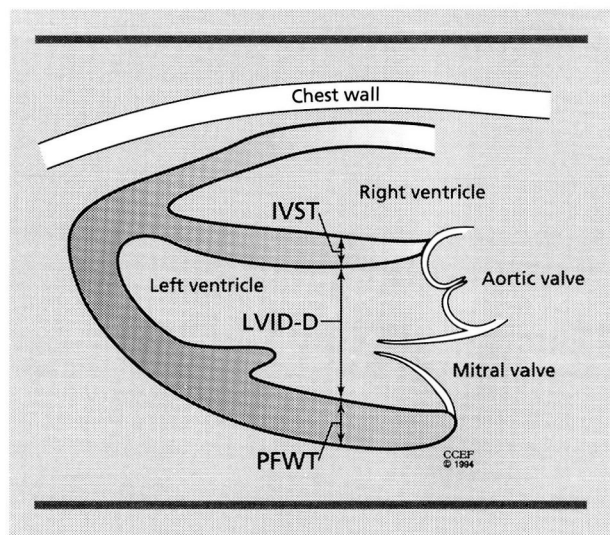


FIGURE 1. Schematic of the heart as it would be seen in an echocardiographic parasternal long-axis view, illustrating how left ventricular mass can be estimated from echocardiographic data. All Penn Convention measurements (in centimeters) are made at the end of diastole, coincident with the peak of the R wave on a simultaneous electrocardiogram. The left ventricular mass (in grams) is estimated as $1.04[(\text{LVID-D} + \text{IVST} + \text{PFWT})^3 - (\text{LVID-D})^3] - 13.6$; where LVID-D is the left ventricular internal dimension at end-diastole, IVST is the interventricular septal thickness, and PFWT is the posterior free-wall thickness.

TABLE 1
UPPER NORMAL LIMITS
FOR LEFT VENTRICULAR MASS IN THE FRAMINGHAM
STUDY*

Measurement	Men	Women
Unadjusted	248 g	155 g
Adjusted for body surface area	130 g/m ²	96 g/m ²
Adjusted for height	138 g/m	95 g/m
Adjusted for height to 2.0 power	78 g/m ²	58 g/m ²

*Data from Lauer et al, reference 8

cardiograms, 755 met echocardiographic criteria for LVH. Electrocardiography had a sensitivity of only 6.9% and a specificity of 98.8%.

Echocardiographic methods

All echocardiographic methods for measuring left ventricular mass estimate the left ventricular muscle volume by subtracting the cavity size from the "total" (ie, cavity plus walls) left ventricular size. The left

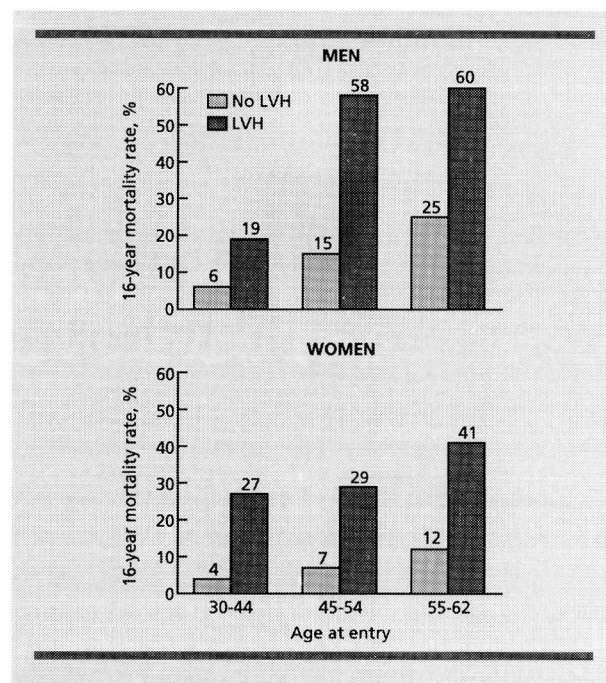


FIGURE 2. Electrocardiographic left ventricular hypertrophy (LVH) and mortality in the Framingham Heart Study. From Kannel et al, reference 12.

ventricular muscle volume is then multiplied by the density of the muscle to obtain the left ventricular mass. A particularly useful method for population studies is the Penn Convention (Figure 1).²

Adjusting for body size. Many authors have used a "left ventricular mass index" in which the left ventricular mass is divided by the body surface area; others have advocated dividing by height.⁵ However, because LVH may well be related to obesity (see below), adjusting by body surface area may inappropriately attenuate the association between left ventricular mass and body mass.^{5,6} One group has advocated dividing the left ventricular mass by the height raised to a power of 2.7,⁷ but recent analysis of a young, healthy Framingham cohort has suggested that dividing by the height to a power of 2.0 may be best.⁸ Upper normal limits of left ventricular mass, based on this last study, are given in Table 1.

Unfortunately, many people have technically inadequate echocardiographic studies—nearly 21% in the Framingham study.⁹ Subjects with inadequate studies tended to be older; thus, epidemiologic studies that rely on echocardiography for estimation of left ventricular mass are limited by an inherent selection bias.

TABLE 2
SUMMARY OF EPIDEMIOLOGIC STUDIES RELATING
ECHOCARDIOGRAPHIC LEFT VENTRICULAR MASS WITH LONG-TERM PROGNOSIS

Investigator	Type of cohort	N	Follow-up, years	Endpoint	Total events	Relative risk with left ventricular hypertrophy	
Levy ¹⁷	General population	1911	4	CAD*	70	Men:	1.67 [†]
						Women:	1.60 [†]
Levy ⁹	General population	3220	4	Cardiovascular disease	208	Men:	1.49 [†]
						Women:	1.57 [†]
				All deaths	124	Men:	1.73 [†]
						Women:	2.12 [†]
Casale ¹⁸	Hypertensive patients	140	4.8	Cardiovascular disease	14	Men:	3.83
Koren ¹⁹	Hypertensive patients	280	10.2	Cardiovascular disease	40	All:	2.17
				Cardiovascular death	11	All:	14.00
				All deaths	19	All:	3.50
Ghali ²⁰	Hypertensive patients, mostly black, had angiography	785	4	Cardiac death	—	With CAD:	2.73 [§]
						Without CAD:	2.80 [§]
				All deaths	80	With CAD:	2.14 [§]
						Without CAD:	4.14 [§]

*Coronary artery disease

[†]Relative risks for each increment of 50 g/m of left ventricular mass after adjustment for age, systolic blood pressure, smoking, and ratio of total to high-density lipoprotein cholesterol

[‡]Relative risks for each increment of 50 g/m of left ventricular mass after adjusting for age, blood pressure, antihypertensive treatment, ratio of total to high-density lipoprotein cholesterol, number of cigarettes smoked per day, diabetes, body mass index, and electrocardiographic left ventricular hypertrophy

[§]Adjusted for age, sex, and hypertension

Electrocardiographic methods

Rautaharju and colleagues¹⁰ have derived regression models that relate electrocardiographic parameters to echocardiographic left ventricular mass. According to one such regression equation, which applies to white and black men, the left ventricular mass index (in g/m² of body surface area) = $-36.4 + 0.010(R \text{ in } V_5) + 0.020(S \text{ in } V_1) + 0.028(S \text{ in III}) + 1.82(T_{\text{neg}} \text{ in } V_6) - 0.148(T_{\text{pos}} \text{ in aVR}) + 1.049(\text{QRS duration in milliseconds})$. Norman and colleagues¹¹ have incorporated age and body mass into an improved regression equation, derived from Framingham data. The role such regression equations will play in research and in clinical practice remains to be explored.

PROGNOSTIC IMPLICATIONS OF ELECTROCARDIOGRAPHIC LVH

In a 14-year Framingham follow-up, men age 55 to 62 with "definite" electrocardiographic LVH¹² had a relative risk of developing coronary artery disease ranging from 2.2 to 5.1, depending on the length of time after LVH first appeared; in women the relative

risk ranged from 1.4 to 2.5. Sudden death was the first sign of coronary artery disease in 29% of men with definite electrocardiographic LVH, compared with only 10% in those without LVH. Definite electrocardiographic LVH was also associated with a markedly higher risk of dying of any cause (Figure 2).¹² In a 30-year Framingham follow-up, electrocardiographic LVH carried an adverse prognosis as bad as did pathologic Q waves indicative of previous myocardial infarction, especially in men.¹³

Univariate analyses of elderly hypertensive patients found electrocardiographic LVH predictive of coronary events ($P = .056$) and stroke ($P < .05$) in black patients; in white patients LVH was predictive of congestive heart failure ($P < .05$), coronary events ($P < .02$), and stroke ($P < .01$).¹⁴ In multiple logistic regression analyses controlling for age and standard cardiovascular risk factors, electrocardiographic LVH was independently predictive only of stroke (odds ratio 2.10, $P = .034$); however, all multivariate models also included echocardiographic LVH as a covariate.¹⁴

In a subset of subjects in the first National Health and Nutrition Examination Survey, the Sokolow-

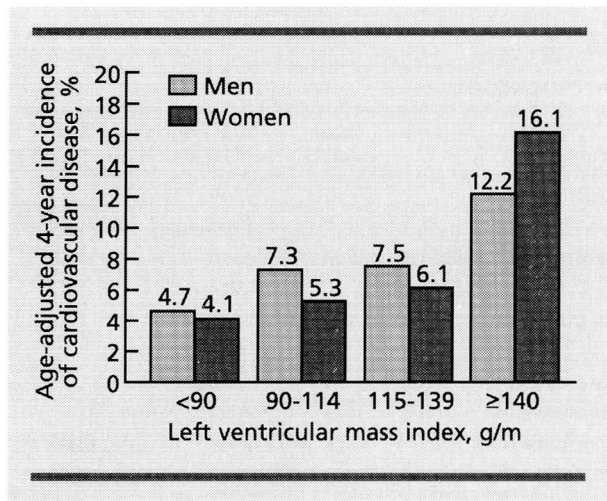


FIGURE 3. Risk of developing cardiovascular disease according to baseline echocardiographic left ventricular mass in the Framingham Heart Study. From Levy et al, reference 9.

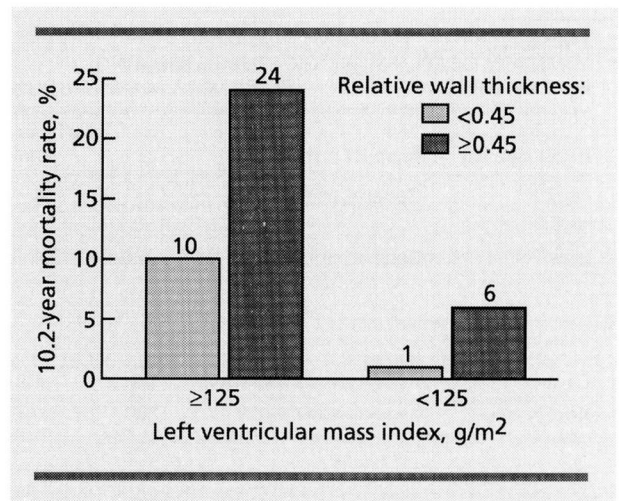


FIGURE 4. Risk of dying according to baseline echocardiographic left ventricular mass and relative wall thickness in a group of patients with uncomplicated hypertension. From Koren et al, reference 19.

Lyon criteria for LVH (R in $V_5 + S$ in $V_1 > 3.5$ mV) failed to predict cardiovascular mortality among all demographic subgroups. The Cornell voltage criteria (R in $aVL + S$ in $V_3 > 2.8$ mV) were predictive of events in black men (relative risk 3.10, 95% confidence interval [CI] 1.49 to 6.45) and in white women (relative risk 2.18, 95% CI 1.36 to 3.47). The electrocardiographic left ventricular mass index, estimated as described above, was predictive of cardiovascular mortality in all subgroups except black women. In multivariate Cox regression analyses adjusted for age, systolic blood pressure, and history of myocardial infarction, electrocardiographic left ventricular mass was independently predictive of cardiovascular mortality in all groups except black men.¹⁰

In the Charleston Heart Study,¹⁵ electrocardiographic LVH, defined according to the criteria of Romhilt and Estes,¹⁶ was noted in only 0.9% of the white men, but in 9.8% of the black men. Among white men, electrocardiographic LVH predicted all-cause mortality (relative risk 5.47, 95% CI 1.95 to 15.36) and coronary artery disease mortality (relative risk 5.61, 95% CI 1.25 to 25.22), but not among black men.

PROGNOSTIC IMPLICATIONS OF ECHOCARDIOGRAPHIC LVH

The major epidemiologic investigations of the association between echocardiographic left ven-

tricular mass and long-term prognosis are summarized in Table 2.^{9,17-20} In the Framingham cohort, the risk of developing coronary artery disease rose with increasing left ventricular mass,¹⁷ as did the risk of developing cardiovascular disease (Figure 3) or of dying of cardiovascular disease or of any cause.⁹ In two studies in hypertensive patients, LVH (defined as a left ventricular mass index of 125 g/m² or greater) was a powerful predictor of cardiovascular events,^{18,19} cardiovascular mortality, and all-cause mortality.¹⁹ Of note, wall thickening (the relative wall thickness, defined as the ratio of the posterior wall thickness to one half of the left ventricular dimension; a value of 0.45 or greater was considered abnormal) was also associated with an adverse prognosis (Figure 4).¹⁹ In a study of patients undergoing coronary angiography, LVH appeared to confer an increased risk of dying, whether or not coronary artery disease was present.²⁰

LVH and risk of congestive heart failure

Aronow and colleagues¹⁴ followed up 84 black and 326 white elderly hypertensive patients for 6 to 64 months. Congestive heart failure developed in 96 (52%) of 183 white patients with echocardiographic LVH, compared with only 22 (15%) of 143 without LVH ($P < .001$). Similar outcomes were found for the black patients.

WHAT CLINICAL RISK FACTORS PREDICT ECHOCARDIOGRAPHIC LVH?

In multivariate logistic regression analyses, independent predictors of echocardiographic LVH among Framingham subjects were age, systolic blood pressure, antihypertensive treatment, body mass index, history of myocardial infarction, angina (in men only), and valvular heart disease.⁵

Hypertension

The strength of association between left ventricular mass and blood pressure is remarkably weak; most studies report r values of 0.20 to 0.30.²¹⁻²⁴ Therefore, a number of investigators have looked at blood pressure parameters other than the casual resting blood pressure as potential determinants of increased left ventricular mass. The association is somewhat stronger for blood pressure measured during work²³ and for long-term average blood pressure,²⁴ especially for systolic blood pressure. Diastolic blood pressure during work also has a moderately strong association with relative wall thickness ($r = .59$).²³ Even in the range of systolic blood pressures considered normal (< 140 mm Hg) left ventricular mass steadily increased as long-term average systolic blood pressure increased (Figure 5).²⁴ Left ventricular mass had a moderately strong correlation with peak systolic blood pressure during exercise in one study ($r = .65$),²⁵ but only a weak correlation in a healthy Framingham cohort ($r = .21$ in men; $.29$ in women).²⁶

Pearson and colleagues²⁷ found patients with isolated systolic hypertension had markedly greater left ventricular mass than did age-matched normotensive subjects (103 vs 87 g/m² of body surface area, $P = .0014$). This was accompanied by a number of abnormalities of Doppler diastolic filling indices. Sagie and colleagues²⁸ at the Framingham Heart Study reported similar findings. Krumholz and colleagues²⁹ compared 79 Framingham subjects who had isolated systolic hypertension with 1282 normotensive subjects. After adjustment for age, diastolic blood pressure, and body mass index, isolated systolic hypertension was an independent predictor of echocardiographic LVH (in men, odds ratio 2.58, 95% CI 0.97 to 6.86; in women, odds ratio 5.94, 95% CI 3.06 to 11.53). Of note, women showed a pattern of hypertrophy in which increased wall thickness predominated, whereas men primarily had cavity dilatation.

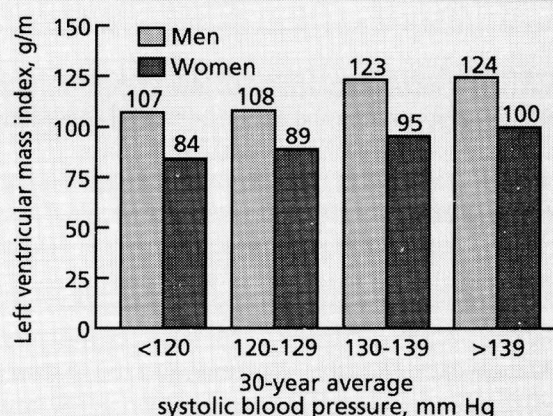


FIGURE 5. Left ventricular mass and 30-year average systolic blood pressure in a healthy subset of the Framingham Heart Study. Adapted from Lauer et al, reference 24.

Does LVH predict hypertension?

A study by de Simone and colleagues³⁰ involving 132 normotensive, employed adults found a greater echocardiographic left ventricular mass index at baseline among subjects who later developed hypertension (92 vs 77 g/m² of body surface area, $P < .005$). Subjects in the highest quartile of sex-adjusted left ventricular mass index had a 24% chance of developing hypertension during a mean follow-up of 4.7 years. In multivariate analyses, the echocardiographic left ventricular mass index was an independent predictor of subsequent hypertension ($P < .04$) but was a much weaker predictor than age or initial systolic blood pressure. Mahoney and colleagues³¹ followed up 274 children age 6 to 15 for a mean of 3.4 years. Initial systolic blood pressure did not predict subsequent left ventricular mass, but initial left ventricular mass predicted subsequent systolic blood pressure.

Obesity

The body mass index (weight divided by the square of the height, kg/m²) had a moderately strong association with left ventricular mass in healthy, normotensive Framingham subjects ($r = .41$ in men; $.52$ in women).⁶ Left ventricular mass was greater among subjects with even mild or moderate obesity ($P < .001$ compared with nonobese subjects for both groups). Obesity was also associated with increased left ventricular chamber diameter, left ventricular

wall thickness, and relative wall thickness. It is not clear how obesity may lead to increased left ventricular mass. Insulin resistance may play a role: in a particularly intriguing study in 40 obese, nondiabetic subjects, insulin resistance appeared to explain 50% of the variance of left ventricular mass.³²

Genetic factors

Harshfield and colleagues³³ found a much stronger correlation of left ventricular mass between monozygotic twins than between dizygotic twins ($r = .90$, $P < .01$ vs $r = .33$, P not significant). Verhaaren and colleagues³⁴ also noted that genetic factors appeared to significantly influence the relationship between body weight and left ventricular mass. Radice and colleagues³⁵ found adolescent children of hypertensive parents had a greater echocardiographic left ventricular mass than did sex-matched children of normotensive parents (125.0 vs 109.2 g/m², $P < .01$).

Other predictors of left ventricular mass

Physical activity. Left ventricular mass increases with physical activity, especially among athletes.³⁶ In Framingham subjects, leisure-time physical activity was found to have a weak association with left ventricular mass, but only in men younger than age 50.³⁷

Age. In a "very healthy" Framingham cohort, age predicted left ventricular mass only weakly in women and not at all in men.³⁸ The relationship between age and left ventricular mass was further questioned by an autopsy study of 67 subjects who died of noncardiovascular causes.³⁹ Regression analy-

ses demonstrated a decrease in the number of myocytes with age and a compensatory increase in myocyte volume; however, overall left ventricular mass actually fell with age. These age-related changes in cardiac structure may account for a decreased hypertrophic response to stress with aging and a decreased ability to withstand hemodynamic stress.^{40,41}

A few groups have reported other potential risk factors for LVH, including whole-blood viscosity⁴² and alcohol intake.⁴³ Further studies will be needed to confirm these reported associations.

IMPLICATIONS AND CONCLUSIONS

Electrocardiographic and echocardiographic LVH are both highly predictive of adverse cardiovascular events. While electrocardiography is less technically demanding, echocardiography is much more sensitive for detecting prognostically meaningful LVH.⁴ Important risk factors for echocardiographic LVH include hypertension and obesity. Both antihypertensive therapy and weight loss induce regression of echocardiographic LVH.^{44,45} However, a key unanswered question is whether treatment aimed specifically at reducing left ventricular mass will produce significant prognostic benefits. Future research will be needed to answer this and other related questions.

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