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Prognostic Significance of Increased Left Ventricular Mass Index to Mortality and Sudden Death in Patients with Stable Coronary Heart Disease (From the Heart & Soul Study)

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Abstract

There is limited data on the significance of LV hypertrophy or mass in coronary heart disease (CHD), particularly in the setting of normal ejection fraction (EF). We evaluated the association of LV mass index with all-cause mortality and sudden death in a cohort with CHD. Using transthoracic echocardiography, we measured LV mass, normalized to body surface area, in 1016 subjects with stable CHD. Cox proportional hazards models were used to examine the association of LV mass index and LV hypertrophy (LV mass index $> 95 \text{ g/m}^2$ in women and $> 115 \text{ g/m}^2$ in men) with time to death and time to sudden or arrhythmic death. The mean LV mass index was $101 \pm 27 \text{ g/m}^2$ in men and $88 \pm 23 \text{ g/m}^2$ in women. During a mean follow-up of 3.55 years, there were 146 deaths and 34 sudden or arrhythmic deaths. Total mortality was higher in subjects with LV hypertrophy (25% vs 11%, $p < 0.001$), as was mortality from sudden or arrhythmic death (6.7% vs. 2.2%, $p = 0.001$). After adjustment for age, sex, cardiovascular risk factors and medical therapy, LV hypertrophy was associated with both all-cause mortality (HR 2.0, $p < 0.001$) and sudden or arrhythmic death (HR 3.1, $p = 0.003$). Findings were similar in the subgroup with $\text{EF} \geq 55\%$ (mortality HR 1.8, $p = 0.02$; sudden and arrhythmic death HR 3.1, $p = 0.02$). When analyzed as a continuous variable, every 20-unit increase in LV mass index increased the adjusted hazard of death 22% ($p = 0.001$) and adjusted hazard of sudden or arrhythmic death 40% ($p = 0.004$). In conclusion, in patients with stable CHD, increased LV mass index is independently associated with all-cause mortality and sudden or arrhythmic death, even in the subjects with normal EF.

Population studies that have demonstrated an association between left ventricular (LV) hypertrophy and mortality have been performed in cohorts with a low prevalence of coronary heart disease (CHD).^{1–5} There is limited data on the significance of LV hypertrophy or mass in CHD, particularly in the setting of normal ejection fraction (EF). To determine if LV mass independently predicts all-cause mortality and SCD, we performed echocardiography in 1016 patients with CHD and assessed cardiovascular outcomes during 3.5 years of follow-up.

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Disclosures

None.

Methods

The Heart and Soul Study is a prospective cohort study investigating psychosocial factors and health outcomes in patients with coronary artery disease. Details regarding methods and study design have been previously published.⁶ Between September, 2000, and December, 2002, 1024 patients were recruited from two Veterans Affairs Medical Centers (San Francisco and Palo Alto, California), one university-based medical center (University of California, San Francisco), and 9 public health clinics in the Community Health Network in San Francisco. Eligible participants had at least one of the following: (1) history of myocardial infarction, (2) angiographic evidence of $\geq 50\%$ stenosis in ≥ 1 coronary vessels, (3) evidence of exercise-induced ischemia by treadmill electrocardiogram or stress nuclear perfusion imaging or (4) a history of coronary revascularization. Patients were excluded from the Heart and Soul Study if they were unable to walk one block, had an MI within the previous six months, or were planning to move from the local area within three years. Of the 1024 study participants, 1016 (99%) had complete echocardiographic measurements and are the subjects of this secondary analysis.

Baseline resting two-dimensional echocardiography with Doppler imaging was performed using a standardized protocol by 1 of 3 identical cardiac ultrasound systems (Siemens Medical, Malvern, PA). Left ventricular volumes were calculated using the truncated ellipse formula and Simpson's Rule by planimetry of standard parasternal short-axis and apical 2- and 4-chamber views.⁷ Ejection fraction was calculated as $[\text{end-diastolic volume} - \text{end-systolic volume}] / [\text{end-diastolic volume}]$. Left ventricular mass was derived from wall thickness measurements using truncated ellipsoid technique and indexed to body-surface area.⁸

Age, sex, race/ethnicity, medical history, and smoking status were determined by self-report. Weight and height were measured to calculate body surface area (m^2) and body mass index (kg/m^2). Participants were instructed to bring their medication bottles to the study appointment, and study personnel recorded all current medications.

The primary outcomes were time to death and time to either sudden or arrhythmic death. Outcomes were adjudicated by blinded study personnel. Death was ascertained by annual telephone interviews and hospital records. For any reported event, medical records, electrocardiogram, death certificates, and coroner's reports were retrieved and reviewed by two independent and blinded adjudicators. Sudden death was defined as unexpected, otherwise unexplained fatality within one hour of the onset of witnessed terminal symptoms or unexplained fatality during sleep. Arrhythmic death was defined as death from a cardiac rhythm disturbance requiring external defibrillation or pacing, documented ventricular fibrillation, or documented hemodynamically unstable cardiac arrhythmia. If the adjudicators agreed on the outcome classification, their classification was binding. In the event of disagreement, the adjudicators conferred, reconsidered their classification, and requested consultation from a third blinded adjudicator.

The primary predictor variable, LV mass, was normalized to body surface area to calculate the LV mass index, which had a normal distribution. LV mass index was analyzed as a continuous variable. LV hypertrophy was defined as LV mass index $> 95 \text{ g}/\text{m}^2$ in women and $> 115 \text{ g}/\text{m}^2$ in men using the most recent guidelines.⁸ We considered using an older definition based on LV mass index $> 110 \text{ g}/\text{m}^2$ in women and $> 134 \text{ g}/\text{m}^2$ in men^{4,9}, but these values were set at over two standard deviations above the mean (97% percentile) from one population study and may fail to capture risk at lower values of increased LV mass index due to reduced sensitivity.¹⁰

Differences in baseline characteristics stratified by LV hypertrophy were compared using chi-square tests for categorical variables and *t*-tests for continuous variables. Cumulative event-

free survival was measured by the method of Kaplan-Meier, and unadjusted differences were compared using the log-rank test. To assess the independent value of LV hypertrophy for predicting death and sudden/arrhythmic death, we performed Cox regression analysis and adjusted for baseline clinical variables, selected on the basis of face validity, that were associated with LV mass quartiles at a P value of ≤ 0.10 . The Cox model assumption of proportional hazards was found to be valid by using the log-minus-log curves and the Schoenfeld test.^{11,12} The analyses were repeated in the subgroup of patients with normal resting ejection fraction ($\geq 55\%$). Statistical analyses were performed using STATA 9.0 (College Station, TX). The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Among the 1016 participants, the mean LV mass index was 101 ± 27 gm/m² in men and 88 ± 23 gm/m² in women. LV hypertrophy was present in 23% of men and 27% of women ($p=NS$). The mean ejection fraction was $62 \pm 9.6\%$, and 82% of patients had a normal ejection fraction ($\geq 55\%$). Subjects with LV hypertrophy were older, more likely to be men, and had a higher prevalence of baseline diabetes mellitus, hypertension, previous myocardial infarction, and heart failure. Participants with LV hypertrophy were also more likely to be taking rennin-angiotensin inhibitors and beta-blockers. Higher LV mass was also associated with lower ejection fraction, greater septal and posterior LV wall thickness, and LV volumes (Table 1).

During a mean follow-up of 3.55 years, there were 146 deaths (14% of cohort). Mortality information was available for 1008 of 1016 participants (99%). Thirty-four deaths (23%) were due to sudden or arrhythmic death. Twenty of 34 (59%) sudden or arrhythmic deaths and 95 of 146 (65%) overall deaths were in subjects with normal baseline EF. Total mortality through the end of the follow-up period was higher in subjects with LV hypertrophy (25% vs 11%, $p < 0.001$). The mortality from sudden or arrhythmic death was also higher in subjects with LV hypertrophy (6.7% vs. 2.2%, $p = 0.001$).

Kaplan-Meier estimates for the outcomes of death (Figure 1) and sudden/arrhythmic death (Figure 2) demonstrated significantly lower survival for participants with LV hypertrophy. After adjustment for age, sex, hypertension, diabetes, heart failure, myocardial infarction, and use of angiotensin blocker, statin, or beta blocker, the LV hypertrophy was significantly associated with death and sudden/arrhythmic death (Table 2). When analyzed as a continuous variable, every 20-unit increase in LV mass index increased the adjusted hazard of death 22% ($p=0.001$) and adjusted hazard of sudden or arrhythmic death 40% ($p = 0.004$). Findings were similar in the subgroup of patients with normal ejection fraction (Table 2). Addition of LV mass index to the full multivariate clinical models significantly improved the clinical model for the outcomes or mortality (LR chi-square 14.0, $p < 0.001$) and sudden or arrhythmic death (LR chi-square 8.8, $p = 0.003$).

We also created a second multivariate model to assess the incremental prognostic value of LV mass index in addition to other significant echocardiographic structural parameters. After adjustment for left ventricular end-systolic volume, and EF, LV mass index was significantly associated with death and sudden or arrhythmic death (Table 3). Addition of LV mass index significantly improved the echocardiographic Cox regression models of death and sudden or arrhythmic death. (Table 3). For the outcome of death, the sensitivity of LV hypertrophy was 42%, specificity 78%, positive predictive value 25%, and negative predictive value 89%. For sudden or arrhythmic death, the sensitivity of LV hypertrophy was 49%, specificity 77%, positive predictive value 7%, and negative predictive value 98%.

Discussion

The principal finding of this observational study is that in patients with stable CHD, LV hypertrophy as determined by LV mass index is associated with all-cause mortality and sudden or arrhythmic death independent of other clinical covariates or echocardiographic parameters. These associations were also present in subjects with normal EF, which represented most of the cohort.

The strongest data demonstrating an association between LV mass index and sudden death comes from the Framingham study.³ However, in this study, the baseline prevalence of CHD and heart failure was low (9.3% combined), unlike in our cohort in which CHD was a criterion for enrollment (100% prevalence of CHD). In the Framingham study, the adjusted hazard ratio of LV hypertrophy for SCD was 2.16, which is similar to our own data. The similar risk ratios may be due to the use of a higher cutpoint to define LV hypertrophy in the Framingham study despite major baseline differences between cohorts.

A notable finding of our study is that LV mass index predicted sudden and arrhythmic deaths that would not have been captured by MADIT-II criteria ($EF \leq 30\%$) with reasonable specificity, although sensitivity was low. This may have implications for risk stratification for SCD in patient with CHD and normal EF, particularly since one-half of sudden death occurs in patients with normal EF¹³. Furthermore, in the MADIT-II trial that randomized patients with CHD and prior myocardial infarction with $EF \leq 30\%$ to implantable defibrillators, only 169 of 719 patients (23%) received any appropriate therapy from their implantable defibrillators, indicating poor specificity.¹⁴

LV hypertrophy may be causally related arrhythmic mortality through a number of mechanisms. Myocardial fibrosis in hypertrophied regions may facilitate reentrant ventricular arrhythmias^{15–18}, while prolonged or heterogeneous ventricular repolarization and reduced coronary flow reserve may increase susceptibility to ventricular fibrillation.¹⁹ Increased LV mass may contribute to diastolic dysfunction, leading to heart failure and associated neurohormonal changes and autonomic dysregulation that may directly predispose to arrhythmias. Finally, rather than being causally related, LV hypertrophy may be a marker for atherosclerosis, endothelial dysfunction, or ventricular remodeling in CHD patients that represents a phenotype associated with higher-arrhythmic risk. However, our findings were significant even after adjustment for prior MI, hypertension, and heart failure.

Limitations

This is an observational study and residual confounding may be present. Since the ability to walk one block was an inclusion criterion, subjects with poor functional status or low EF may be underrepresented. Since LV mass and ejection fraction were measured at baseline, and it is possible that ejection fraction could have declined between the time of the echo and time of death, although these types of findings represent mediators rather than confounders and would not bias results. Most subjects were enrolled at Veterans Affairs medical centers, which could limit generalizability. LV mass index was calculated by three skilled sonographers trained in measurement of LV mass index. If LV mass index measurements are performed by less experienced technicians, then increased measurement error and variability may attenuate the observed associations, thus limiting reproducibility. The endpoint of sudden or arrhythmic death should not be construed as a surrogate for deaths preventable by implantable defibrillators, since other causes of death such as pump failure may also be associated with increased LV mass. Since calculation of LV mass requires measurement septal and posterior wall thickness and since EF requires measurement of end-systolic and end-diastolic volumes, we limited the number of variables in our echocardiographic model to avoid overadjustment

from highly collinear variables. Finally, although there were relatively few sudden or arrhythmic deaths (34), no statistical assumptions were violated.

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Figure 1. Kaplan-Meier survival curves for all-cause mortality in 1016 participants with CHD, stratified by LV hypertrophy

Figure 2. Kaplan-Meier survival curves for sudden or arrhythmic death in 1016 participants with CHD, stratified by LV hypertrophy

Table 1

Baseline characteristics of 1016 participants with coronary heart disease by quartile of left ventricular (LV) mass index

Demographic	LV Hypertrophy*		P value
	No (n = 772)	Yes (n = 243)	
LV mass index range (g/m ²)	87 ± 15	134 ± 23	< 0.001
Age (years)	66±11	68±11	0.04
Men	83%	79%	0.24
Caucasian	61%	57%	0.18
African American	15%	22%	0.01
Body mass index (kg/m ²)	28 ± 5.0	29 ± 5.5	0.36
Current smoker	19%	22%	0.44
Hypertension	67%	80%	< 0.001
Diabetes Mellitus	24%	33%	0.006
Heart failure	13%	33%	< 0.001
Previous myocardial infarction	50%	63%	< 0.001
Prior coronary revascularization	58%	62%	0.34
Renin-angiotensin inhibitor	46%	67%	< 0.001
Statin therapy	63%	68%	0.11
Beta blocker therapy	55%	67%	0.001
Echocardiographic			
LV end systolic volume (cc)	34 ± 16	60 ± 38	< 0.0001
LV end diastolic volume (cc)	93 ± 27	127 ± 48	< 0.0001
Ejection fraction (%)	64 ± 7.7	55 ± 12.2	< 0.0001
Posterior wall thickness (mm)	11.5 ± 1.6	12.9 ± 2.5	< 0.0001
Septal thickness (mm)	11.9 ± 1.9	13.6 ± 3.3	< 0.0001

Values are mean ± SD or percentages.

LV hypertrophy defines as LV mass index >

95 g/m² in women and > 115 g/m² in men

Table 2
Association of left ventricular hypertrophy with all-cause mortality and sudden death

Variable	All-Cause Mortality EF $\geq$ 55% (n=835)			Sudden or arrhythmic death EF $\geq$ 55% (n=835)		
	Entire cohort (n=1016) HR (95% CI)	P	HR (95% CI)	Entire cohort (n=1016) HR (95% CI)	P	HR (95% CI)
Unadjusted	2.4 (1.8–3.4)	< 0.001	2.0 (1.3–3.2)	3.3 (1.7–6.5)	0.001	3.0 (1.2–7.6)
Adjusted for age and sex	2.3 (1.7–3.2)	< 0.001	2.0 (1.2–3.1)	3.1 (1.5–6.1)	0.001	2.8 (1.1–7.3)
Adjusted for age, sex, risk factors [*]	2.0 (1.4–2.8)	< 0.001	1.8 (1.1–2.8)	2.9 (1.4–6.0)	0.003	2.9 (1.1–7.6)
Adjusted for age, sex, risk factors [*] , and medical therapy [#]	2.0 (1.4–2.9)	< 0.001	1.8 (1.1–2.8)	3.1 (1.5–6.3)	0.003	3.1 (1.2–8.4)
Risk of LV mass index (per increase of 20 g/m ²), adjusted for age, sex, risk factors [*] , and medical therapy [#]	1.22 (1.09–1.37)	0.001	1.20 (1.01–1.4)	1.4 (1.1–1.8)	0.004	1.46 (1.01–2.1)

* Risk factors: body mass index, smoking, hypertension, diabetes, heart failure, prior myocardial infarction, prior revascularization

Medical therapy: angiotensin blockade, beta blockade, statin therapy

Table 3

Association of left ventricular mass index with all-cause mortality and sudden death, adjusted for left ventricular ejection fraction and end-systolic volume

Variable	All-cause mortality		Sudden or arrhythmic death	
	HR (95% CI)	P	HR (95% CI)	P
End-systolic volume (per 20 unit increase)	1.4 (0.96–1.4)	0.14	0.82 (0.55–1.2)	0.31
Ejection Fraction (per 5% decrease)	1.1 (0.94–1.2)	0.28	1.3 (1.05–1.7)	0.02
LV mass index (per 20 unit increase)	1.2 (1.1–1.4)	0.002	1.4 (1.1–1.7)	0.009
LR Chi-square for inclusion of LV mass index into model	9.25	0.002	6.23	0.01